



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

SUBJECT: Transmittal of Meeting Minutes and Final Report for the TSCA Science Advisory Committee on Chemicals Meeting via Phone and Webcast Held March 24 to 27, 2020

TO: Yvette T. Collazo
Director
Office of Pollution Prevention and Toxics

FROM: Todd Peterson, PhD
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Attached, please find the meeting minutes and final report for the TSCA Science Advisory Committee on Chemicals open meeting held via phone and webcast on March 24 to 27, 2020. This report addresses a set of scientific issues being considered by the Environmental Protection Agency regarding the Peer Review for the Draft Risk Evaluations for Trichloroethylene.

Attachment

cc:

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David Fischer
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OPPT Docket

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**TSCA Science Advisory Committee on Chemicals
Meeting Minutes and Final Report
No. 2020-4**

**Peer Review for EPA Draft Risk Evaluation for
Trichloroethylene (TCE)**

March 24–27, 2020

**TSCA Science Advisory Committee on Chemicals
Meeting,**

**Held via Phone and Webcast
(Virtual Meeting)**

NOTICE

The Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals (SACC) is an advisory Committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of TSCA as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The TSCA SACC provides independent advice and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) on the scientific basis for risk assessments, methodologies, and pollution prevention measures and approaches for chemicals regulated under TSCA. The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics (OPPT), and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency. Additional peer reviewers are considered and from time-to-time added on an *ad hoc* basis to assist in reviews conducted by the TSCA SACC. This document constitutes the meeting minutes and final report and is provided as part of the activities of the TSCA SACC.

The TSCA SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public. The minutes represent the views and recommendations of the TSCA SACC and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use.

The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the Agency or any party. The meeting minutes and final report of the March 24–27, 2020, TSCA SACC meeting represent the SACC’s consideration and review of scientific issues associated with the peer review for EPA’s Draft Risk Evaluation of Trichloroethylene. Steven Knott, MS, TSCA SACC Executive Secretary, reviewed the minutes and final report. Kenneth Portier, PhD, TSCA SACC Chair, and Todd Peterson, PhD, TSCA SACC Designated Federal Official, certified the minutes and final report. The report is publicly available on the SACC website (<https://www.epa.gov/tsca-peer-review>) under the heading of “Meetings” and in the public e-docket, Docket No. EPA-HQ-OPPT-2019-0500, accessible through the docket portal: <https://www.regulations.gov>. Further information about TSCA SACC reports and activities can be obtained from its website at: <https://www.epa.gov/tsca-peer-review>. Interested persons are invited to contact Todd Peterson, PhD, SACC Designated Federal Official, via e-mail at peterson.todd@epa.gov.

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**TSCA Science Advisory Committee on Chemicals
Meeting Minutes and Final Report
No. 2020-4**

**Peer Review for EPA Draft Risk Evaluation for
Trichloroethylene (TCE)**

March 24–27, 2020

**TSCA Science Advisory Committee on Chemicals
Meeting,**

**Held via Phone and Webcast
(Virtual Meeting)**



**Kenneth Portier, PhD
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Date: June 1, 2020

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**Toxic Substance Control Act
Science Advisory Committee on Chemicals Meeting
March 24–27, 2020**

**Peer Review for EPA Draft Risk Evaluation of
Trichloroethylene (TCE)**

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LIST OF ACRONYMS AND ABBREVIATIONS

ACS	American Chemical Society
AF	Assessment Factor
AFC	Antibody Forming Cells
ANA	Anti-Nuclear Antibodies
AOP	Adverse Outcome Pathway
ATSDR	Agency for Toxic Substances and Disease Registry
BIOWIN	The EPI Suite™ Module that Predicts Biodegradation Rates
BMD	Benchmark Dose
BMDL	Benchmark Dose Level
BMDS	Benchmark Dose Modeling Software
BMR	Benchmark Response
CAA	Clean Air Act
CARB	California Air Resources Board
CDR	Chemical Data Reporting
CEM	Consumer Exposure Model
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
ChV	Chronic Value
COC	Concentration of Concern
COU	Condition of Use
CPDat	Chemical and Products Database
CT	Central Tendency
CWA	Clean Water Act
CYP	Cytochrome P450
DBPs	Disinfection Byproducts
DCA	Dichloroacetic Acid
DCVC	S-dichlorovinyl-L-cysteine
DCVG	S-dichlorovinyl-glutathione
DHHS	Department of Health and Human Services
DMR	Discharge Monitoring Report
DNPL	Dense Non-Aqueous Phase Liquid
DQE	Data Quality Evaluation
DOD	Department of Defense
dsDNA	Double Stranded DNA
EC ₂₀	Effect Concentration at which 20% of test organisms exhibit an effect
EC ₅₀	Effect Concentration at which 50% of test organisms exhibit an effect
EDF	Environmental Defense Fund
E-FAST	Exposure and Fate Assessment Screening Tool
EPA	Environmental Protection Agency
EPI Suite™	Estimation Programs Interface Suite of models

FDA	Food and Drug Administration
GGT	γ -glutamyltransferase
GHS	Globally Harmonized System
GIS	Geographic Information Systems
GLP	Good Laboratory Practices
GSH	Glutathione
GST	Glutathione S Transferase
HAA5	Group of five Haloacetic Acids (dibromoacetic acid, dichloroacetic acid, monobromoacetic acid, monochloroacetic acid, and trichloroacetic acid)
HC ₀₅	Hazardous Concentration threshold for 5% of species in a Species Sensitivity Distribution
HE	High End
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
HHE	Health Hazard Evaluation
HUC	Hydrologic Unit Code
HSIA	Halogenated Solvents Industry Alliance
IUR	Inhalation Unit Risk
IWTF	Industrial Wastewater Treatment Facility
K _{oc}	Organic Water-Carbon Partition Coefficient
K _{oa}	Octanol-Air Partition Coefficient
K _{ow}	Octanol/Water Partition Coefficient
LCA	Life Cycle Analysis
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effects Level
LC ₅₀	Lethal Concentration at which 50% of test organisms die
LOEC	Lowest-Observable-Effect Concentration
LNT	Linear Non-Threshold
MCL	Maximum Contaminant Level
MOA	Mode of Action
MOE	Margin of Exposure
NAFLD	Nonalcoholic Fatty Liver Disease
NAS	National Academy of Sciences
NASH	Nonalcoholic Steatohepatitis
NCEA	National Center for Environmental Assessment (now: Center for Public Health and Environmental Assessment)
ND	Non-Detect
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's Lymphoma
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration

NOEL	No Observed Effect Level
NPDES	National Pollutant Discharge Elimination System
NR	Not Reported
NRC	National Research Council
NTP	National Toxicology Program
OCSP	Office of Chemical Safety and Pollution Prevention
OSF	Oral Cancer Slope Factor
OEL	Occupational Exposure Limits
OES	Occupational Exposure Scenario
ONU	Occupational Non-Users
OPPT	Office Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
OTVD	Open Top Vapor Degreasers
OU	Occupational User
PBPK	Physiologically Based Pharmacokinetic
PCI	Pneumotosis Cystoides Intestinalis
PDM	Probabilistic Dilution Model
PEL	Permissible Exposure Limit
PF	Protection Factors
PFC	Plaque-Forming Cell
PESS	Potentially Exposed and Susceptible Subpopulations
POD	Point of Departure
POTW	Publicly Owned Treatment Works
PPE	Personal Protective Equipment
PPAR α	Peroxisome Proliferator Activated Receptor alpha
RfC	Chronic Reference Concentration
RQ	Risk Quotients
SACC	Science Advisory Committee on Chemicals
SDS	Safety Data Sheets
SDWA	Safe Drinking Water Act
SIC	Standard Industrial Classification
SNUR	Significant New Use Rule
SRBC	Sheep Red Blood Cell
SSD	Species Sensitivity Distribution
ssDNA	Single Stranded DNA
STP model	Sewage Treatment Plant Model
SWC	Surface Water Concentration
TCA	Trichloroacetic Acid
TCE	Trichloroethylene
TCOH	Trichloroethanol
TNSSS	Targeted National Sewage Sludge Survey
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	Time-Weighted Average

UF	Uncertainty Factor
UF _A	UF Extrapolating from laboratory animals to humans
UF _H	UF Human (intraspecies) variability
UF _L	UF Uncertainty in extrapolating from LOAELs to NOAELs
UF _S	UF Uncertainty in extrapolating from subchronic to chronic exposures
VCR	Video Cassette Recorder
WOE	Weight of Evidence
WQX	Water Quality Exchange
WWTP	Wastewater Treatment Plant

INTRODUCTION

The Toxic Substances Control Act (TSCA) of 1976, as amended by The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016, Science Advisory Committee on Chemicals (SACC or Committee) completed its review of the set of scientific issues being considered by the U.S. Environmental Protection Agency (EPA) regarding the “Draft Risk Evaluation for Trichloroethylene.” The Draft Risk Evaluation, supplemental files, and related documents in support of the SACC peer review meeting are posted in the public e-docket at <https://www.regulations.gov> (ID: EPA-HQ-OPPT-2019-0500). The initial notice of availability of the Draft Risk Evaluation, opening the docket for comments, and notice of meeting was published in the *Federal Register* on February 26, 2020, (85 FR 11079) with an additional *Federal Register* notice for announcement of the change to virtual meeting format published March 20, 2020, (85 FR 16096). The review was conducted in an open Committee meeting held online by teleconference and Webex conferencing internet platform, on March 24–27, 2020. Dr. Kenneth Portier chaired the meeting. Dr. Todd Peterson served as the Designated Federal Official.

In preparing these meeting minutes and final report, the Committee carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. These meeting minutes and final report address the information provided and presented at the meeting, especially the Committee response to the Agency charge.

TSCA SACC Peer Review – Draft Risk Evaluation for Trichloroethylene

March 24 – 27, 2020: Summary of Meeting Agenda

Opening of Meeting – Todd Peterson, PhD, Designated Federal Official, EPA/Office of Science Coordination and Policy (OSCP)

Introduction and Identification of SACC Members – Kenneth Portier, PhD, Chair, TSCA Science Advisory Committee on Chemicals (SACC),

Introduction and Welcome – Mark Hartman, EPA/Office of Pollution Prevention and Toxics (OPPT), Immediate Office

Welcome and Introductory Comments - Alexandra Dapolito Dunn, Esq, Assistant Administrator, EPA/Office of Chemical Safety and Pollution Prevention (OCSPP)

OPPT Technical Presentation – Overview of Trichloroethylene Risk Evaluation – Keith Jacobs, PhD, and Heidi Bethel, PhD, EPA/OPPT/Risk Assessment Division (RAD)

Public Comments

Charge to Committee

Public Commenters:

Oral statements were presented as follows:

Jennifer McPartland, PhD, Environmental Defense Fund

Richard Denison, PhD, Environmental Defense Fund

Lindsay McCormick, MPH, Environmental Defense Fund

Eleni Kapatou, Elemar Marine Services

Nicholas Chartres, PhD, University of California San Francisco, Program on Reproductive Health and the Environment

Anthony Tweedale, R.I.S.K. Consultancy

Daniele Wikoff, PhD, ToxStrategies

Robert Sussman, JD, Sussman & Associates

Jennifer Sass, PhD, Natural Resources Defense Council

David Michaels, PhD, George Washington University School of Public Health

Jon Urban, PhD, ToxStrategies

John DeSesso, PhD, Exponent, Inc.

James Bus, PhD, Exponent, Inc., on behalf of Halogenated Solvents Industry Alliance

Written statements were provided to docket as follows:

Anonymous (multiple submissions)

Richard Denison, PhD, Lead Senior Scientist, Environmental Defense Fund

Exponent, Inc. on behalf of the American Chemistry Council and the Halogenated Solvents Industry Alliance

Suzanne Hartigan, PhD, Senior Director, Regulatory and Technical Affairs, American

Chemistry Council

Liz Hitchcock, Director, Safer Chemicals Healthy Families, et al.

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Jennifer McPartland, PhD, Senior Scientist, Environmental Defense Fund

Stephen P. Risotto, Senior Director, American Chemistry Council

Michelle Roos, Environmental Protection Network

Jennifer Sass, PhD, Senior Scientist, Natural Resources Defense Council

ToxStrategies on behalf of the American Chemistry Council

EXECUTIVE SUMMARY OF SACC REVIEW

The TSCA Science Advisory Committee on Chemicals (the Committee) responded to a series of questions on the Draft Risk Evaluation (the Evaluation) for Trichloroethylene (TCE) as follows:

Question 1 – Environmental Fate and Exposure

Overall, the Committee found the environmental fate evaluation for trichloroethylene to be very similar to the previous evaluations of methylene chloride and carbon tetrachloride, although this document may be less concise and more difficult to read than previous evaluations. The Committee recommended additional properties and estimate ranges be added to the table of physical-chemical properties.

The qualitative analysis is generally adequate, but the Committee recommended that a diagram that displays pathways and rates be included. There is a need to include more information on degradation products. The methods used to analyze the biosolids in these surveys are not suitable for trichloroethylene and the targeted analysis did not appear to specifically look for trichloroethylene. When considering exposure pathways, it is important to note that movement between compartments goes both ways based on equilibrium, and hence movement from water to air is only true in scenarios where air does not contain significant trichloroethylene. The Committee questioned the use of derived K_{OC} values when experimentally derived estimates are available.

The Committee suggested at a minimum adding confidence intervals and conducting a model sensitivity analysis for the environmental models to determine if variability associated with the physical-chemical properties would change the trichloroethylene fate assessment.

Question 2 – Environmental Exposure and Releases

The Committee recognized significant uncertainty results with using the E-FAST model to assess chemicals of high volatility. Uncertainties limit confidence in the analysis and estimates should be considered of low confidence. Concern with having only limited monitoring data resulted in recommendations to use other data sources, such as the National Pollutant Discharge Elimination System (NPDES). More measurements of trichloroethylene in sediments near release sites are needed to increase confidence. Issues with the limitations of the EPI SuiteTM tool and the Fugacity Level 3 model were discussed.

The mass balance approach recommended in previous reviews of TSCA chemical evaluations was further explained and approaches discussed. The Committee remains divided on the feasibility and utility of this approach.

Question 3 – Environmental Hazard

The Committee largely supported the approach used to characterize environmental hazards of trichloroethylene acute and chronic exposures in the aquatic environment. The development of species sensitivity distributions (SSDs) provides additional confidence in the toxicity benchmarks and its use is encouraged in subsequent risk assessments when data are available.

Specific recommendations are provided for magnitude of adjustment and safety factors and references are provided. The Committee wondered about the range in concentrations of concern (COCs) developed for algae that span several orders of magnitude. The Committee requested performing a more robust evaluation of the evidence supporting the low value that deviates significantly from the Hazardous Concentration (HC₀₅) value derived from the SSD for algae as it is likely an outlier and a result of chance rather than a species-specific sensitivity. An inadequate rationale is provided for not examining hazards to other organisms, including sediment-dwelling organisms, aquatic birds, and burrowing animals including mammals in functionally confined spaces exposed to trichloroethylene from vapor intrusion.

The Committee further supported the computational approach to creating the SSD and the Evaluation's interpretation. Diagrams illustrating the nature and spread of toxicity data relative to species, endpoint, and exposure duration support final conclusions. Other minor editorial recommendations are provided.

Question 4 – Occupational and Consumer Exposure

In general, estimation methods, models, and data used in the occupational exposure assessment are like those used in past TSCA chemical risk evaluations with some differences (e.g., comparison of data- and modeling-derived inhalation exposures). Some problems persist from past TSCA evaluations and there are areas that need further clarification or revision.

More detailed explanation is needed on the impact of regrouping use-case subcategories into different categories. Data and analysis demonstrating that indeed there is no impact on exposure estimates are needed.

The Committee noted Tables 2-12 to 2-16 are very useful summaries of occupational exposure evaluation findings. The level of overall confidence for dermal exposures should be added. Also, helpful would be adding links from cell entries to sections where estimates are discussed and links from discussion to the corresponding sections in appendices or supplemental documents where detailed calculations are provided.

The Evaluation should identify specifically those occupational exposure pathways that are not included because of competing areas of regulatory mandate (some cases are recognized: e.g., lace wig and hair extension glues are considered cosmetics (FDA), but hoof polish as a cosmetic remains under TSCA but not when used for veterinary or medicinal reasons (FDA)). There should be a table that lists specifically all the pathways for trichloroethylene exposure and whether alternative risk assessments have been done or not for these pathways.

The Committee was uncertain whether the Evaluation reflects current market uses of trichloroethylene including changes that have occurred since the trichloroethylene significant new use rule (SNUR) banning aerosol and vapor degreasing uses and the California Air Resource Board 2019 prohibition of trichloroethylene in spot removers. The Market and Use Report is dated 2017 but references the TSCA Work Plan for trichloroethylene, which has a 2014 date stamp. Of the 33 reported conditions of use (COU), 17 appear valid, 2 appear to no longer exist and current use of 13 are unclear. Some products, e.g., the hoof polish product, appears to have been reformulated, also some new products containing trichloroethylene are not discussed.

The Committee recommended EPA request more detailed product use information from manufacturers.

The Committee agreed with using the Consumer Exposure Model (CEM) to estimate consumer and dermal exposures since direct measurement data are not available. There is concern that the 33-year old Westat survey data (U.S. EPA, 1987), a key CEM input, may not reflect current consumer product use patterns, and that the assumption that bystanders are not present in the same room as the user needs additional justification. The permeability sub-model (P_DER2b) in the CEM raised concerns as did pairing of the aqueous phase permeability coefficient to the concentration of the neat liquid. The Committee offered alternatives for estimating the permeability coefficient. How the consumer COUs were identified is poorly described, which coupled with incomplete product formulation information and consumer use patterns may result in some scenarios not reflecting actual exposures.

The Committee disagreed with the decision not to characterize chronic risk for consumer exposures and considered the rationale supporting this decision not persuasive. Other sources of exposure to trichloroethylene were identified and recommended be incorporated in the risk characterization for consumers. The Committee was pleased to see more transparency in how levels of confidence in risk characterization are determined, but recommended even more effort is needed in this regard. It remains unclear how the results of the uncertainty analysis are used in characterizing consumer risk and the Committee again recommends more use of sensitivity analysis to inform the importance of uncertainty in different risk parameters.

Question 5 – Human Health Hazard

Non-Cancer Hazard:

Several on the Committee considered the issues identified with the Johnson et al. (2003) research protocol made it difficult for them to support this study's use in establishing a point of departure. The cardiac effects reported by Johnson et al., seen at trichloroethylene exposure levels that are orders of magnitude lower than no-effects levels of other studies, have not been seen even at much higher doses in other investigations of trichloroethylene where heart effects were also examined. Trichloroethylene inhalation studies, notably that of Carney et al. (2006), should receive greater attention. Epidemiological data suggest an association between maternal trichloroethylene exposure and cardiac effects, but several Committee members suggested down-weighting these results due to study design weaknesses that detract from the studies' reliability and relevance (e.g., exposures to multiple solvents, uncertainty of where pregnant women were residing during critical time period for fetal cardiac development). The mechanistic data are incomplete.

The scoring of evidence for cardiac defects was judged to be overly simplistic, difficult to understand, and problematic in its value judgments and net result. The Evaluation does not integrate available information into a coherent causal pathway or offer any mode of action (MOA) as more likely than another. The Committee recommended redoing the weight of evidence (WOE) assessment to account for the strengths and relevance of all *in vivo* animal experimental evidence, the weight and clarity of available mechanistic evidence, and the strength and relevance of the epidemiological results.

The Committee requested additional detail on the dose metrics used in establishing the non-cancer points of departure (PODs) including the process of selecting an appropriate benchmark response (BMR) for each non-cancer endpoint discussed. The reason why the PBPK model could not be used to examine a dose metric of total absorbed dose of parent trichloroethylene needs further discussion. Indicators of immune enhancement and immunosuppression need to be separated and how these reflect different modes of action should be discussed. The Evaluation should clarify that the acute immunosuppressive response is based on a single well-performed study that nevertheless has deficiencies that should be discussed further. There is uncertainty in the relevance of these results to humans that should also be further discussed, along with additional justification for the uncertainty factors used to derive the associated POD. The Evaluation should also incorporate into the WOE assessment the results of chronic trichloroethylene exposures in autoimmune-prone mice studies and immune hypersensitivity responses to trichloroethylene in humans. The Committee recommended references for both.

Cancer Hazard:

The Committee found the discussion on the meta-analysis for trichloroethylene induced cancer to be concise, clear, and, consistent with the IRIS trichloroethylene review conclusions. Issues with the association of trichloroethylene exposure and liver cancer were discussed, specifically that a high dose is needed to induce liver tumors in mice and that the mechanism whereby trichloroethylene induces liver tumors in mice is not relevant to humans.

A table summarizing what is known on the genotoxicity of trichloroethylene and metabolites should be added to the Evaluation. All possible modes of action for liver carcinogenesis due to trichloroethylene exposures should be discussed along with their relevance to humans.

Overall:

The Committee considered the liver and kidney toxicity potencies in laboratory animals and occupationally exposed humans as overstated. It was not clear whether an adaptive or a cytotoxic dose in the study by Kjellstrand et al. (1983) was used as a POD. There was concern with the use of the rat data of Maltoni et al. (1986) to establish the POD for nephrotoxicity, considering the relatively high metabolic activation of trichloroethylene in rats. Concern was also expressed by several Committee members about the lack of detailed discussion in the Evaluation on developmental toxicities, including neurotoxicity and immunotoxicity. While well-conducted developmental neuro- and immuno-toxicity studies are difficult to find, the Committee concluded that the TSCA program would be well-served to enhance its ability to assess neuro-developmental and immuno-developmental toxicity studies, and to integrate these study findings in its risk assessments.

Question 6 – Risk Characterization

The Committee recommended that the fundamental objectives for the environmental or human health risk characterization need to be more clearly and explicitly stated in the Evaluation.

Environmental Risk:

The Evaluation concludes that trichloroethylene uses and releases regulated under TSCA pose a

hazard to environmental aquatic receptors, with invertebrates and fish being the most sensitive taxa identified for aquatic exposures. Some Committee members recommended adding and discussing worst-case scenarios from wastewater contaminated streams. Data on the response on reproductive and developmental effects of trichloroethylene exposures to vertebrate receptors should be presented and discussed.

The justification for not assessing ambient air emission levels and impacts from commercial and stationary sources needs improvement. The Committee noted issues with the environmental risk characterization conclusions that are not adequately explained. There are estimated risks with risk quotients greater than one ($RQ > 1$) associated with some facilities and species, but this is not translated to a risk determination per condition of use (COU) and the Committee was unable to follow the data analysis that produced the days of exceedance.

Human Health Risk:

The Evaluation summarizes findings of human health risks in a set of clear and well-organized tables that list benchmark margins of exposure (MOEs) and worker MOEs with and without personal protective equipment (PPE), for each occupational exposure scenario, each health endpoint, and route of exposure. Determination of these values and conclusions about whether unreasonable risks exist for each use are clearly described and logically presented, although it is less clear how the assumptions and uncertainties are weighted to arrive at the overall confidence summaries. The Committee again recommended that this Evaluation base the risk characterization on aggregation of inhalation and dermal risks.

While the Committee was divided on reliance on fetal heart malformations for risk characterization, it recommended the Evaluation revise and expand the justification for not using it as the unreasonable risk driver, especially in light of the decision in the 2011 IRIS trichloroethylene evaluation to compute a POD for this health endpoint. The justification for using immunosuppression as the unreasonable risk driver for acute non-cancer risks needs to be improved.

Risks from oral exposures should be directly discussed and the exclusion of oral exposure should be justified in the Evaluation. The risk characterizations for occupational non-users (ONUs) should be identified as high-end exposures despite being based on central tendency exposure levels in workers.

The Evaluation needs to identify COUs having low expectations of appropriate PPE use among workers and incorporate this information into the risk characterization and final risk determination. The Committee noted that the discussion of PPE is too limited, and the Evaluation should incorporate a more complete discussion of the occupational exposure control hierarchy. Available data demonstrating adherence or non-adherence to these guidelines that impact exposures within COUs should be presented to help inform readers about which risk estimates, either with or without PPE, might be best to assume for a COU.

The Committee found the explanation of uncertainties too limited and recommended clarification. In general, limitations due to data gaps need to be presented in a more highlighted and obvious manner. Sensitivity to assumptions and data uncertainties need a more quantitative

assessment, and findings integrated into the broader uncertainty discussion. The uncertainty in consumer risks from high-end periodic exposures combined with exposures via background air and water concentrations should be better characterized. The Committee discussed ways the limited available and potentially biased monitoring data might be processed in a way that produces more representative exposure estimates. More discussion is needed on the uncertainties in the PBPK model including route-to-route extrapolation from oral to inhalation exposures.

The Evaluation should aggregate exposures with other factors for more accurate estimation of risk to potentially exposed and susceptible sub-populations (PESS, i.e. pregnant women and their developing fetuses, and people with kidney and liver illness) who might be more susceptible to trichloroethylene. The Committee suggested running the PBPK model to understand trichloroethylene exposure effects on individuals (workers, ONUs, consumers) with preexisting health conditions, such as obesity, hepatitis, and non-alcohol fatty liver disease, that change several significant model input parameters.

Question 7 – Overall Content and Organization

Committee members commented on areas that could be made easier to read and offered several suggestions to improve overall clarity. These include: 1) incorporating more information and explanation in the Evaluation instead of having the information in supplemental documents, 2) using similar formats as IRIS reviews, and 3) incorporating more links.

The Committee recommended including additional physical-chemical properties in Table 1-1 and including the variability in these properties and how they affect the Evaluation. There were several recommendations for improving the presentation of manufacturing, use, and disposal information that is currently in Table 1-2 and other locations. These include a mass balance approach to improve understanding and highlight incomplete estimates. The Committee also recommended using pie charts and other figures instead of tables to illustrate manufacturing and use percentages and trends.

The Committee recommended clearer explanations in specific places throughout the Evaluation, including summarizing previous hazard assessment and risk assessment findings, level of PPE use by COU, and a full and complete description of the issues surrounding fetal cardiac malformations and the decision to not use it as the unreasonable risk driver.

The Evaluation discusses uncertainty and sensitivity of data and assumptions, but the results of this discussion are not linked to corresponding risk determinations. The Committee recommended the Evaluation include a more complete explanation of how studies are selected for informing points of departure (PODs), including treatment of outliers, and how cancer risks are estimated. The Committee also recommended adding a summary of the critical endpoints, the critical studies identified for each endpoint, and those that were used to set POD values.

DETAILED COMMITTEE DISCUSSION AND RECOMMENDATIONS – TRICHLOROETHYLENE

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA or Agency) to conduct risk evaluation on existing chemicals. In response to this requirement, EPA has prepared and published a Draft Risk Evaluation for Trichloroethylene (Evaluation). The Draft Risk Evaluation for Trichloroethylene is the eighth of the first ten to undergo a peer review by the Science Advisory Committee on Chemicals (SACC). The Risk Evaluation process is the second step, following Prioritization and before Risk Management, in EPA's existing chemical process under TSCA. The purpose of risk evaluation is to determine whether a chemical substance presents an unreasonable risk to health or the environment, under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation. As part of this process, EPA must evaluate both hazard and exposure, exclude consideration of costs or other non-risk factors, use scientific information and approaches in a manner that is consistent with the requirements in TSCA for the best available science, and ensure decisions are based on the weight-of-scientific-evidence.

The SACC was requested to provide advice and recommendations on the following questions.

Question 1: Environmental Fate and Exposure:

EPA qualitatively analyzed the sediment, land application, and biosolids pathways based on Trichloroethylene's physical/chemical and fate properties. Exposure estimates to the environment were developed for the conditions of use for exposures to aquatic organisms.

<i>Q 1.1</i>	Please comment on EPA's qualitative analysis of pathways based on physical/chemical and fate properties (Section 2.1).
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Response to Q1.1: Qualitative analysis of pathways.

Overall, the Committee found the environmental fate evaluation for trichloroethylene to be very similar to the previous evaluations of methylene chloride and carbon tetrachloride and comments from those reviews are applicable here.

The Committee continued to be concerned about the potential impact of groundwater to surface water pathway to the evaluation. Members also mentioned that landfill releases to surface water should be included inasmuch as they derive from current uses of trichloroethylene. If the partitioning to sediments and soil is considered minimal, then the risk to groundwater, especially unregulated drinking water sources, must be objectively determined. Some Committee members previously commented for other SACC TSCA risk evaluation reviews that exclusion of groundwater on the basis of regulation under clean water or safe drinking water statutes is erroneous, indicating that private wells are not regulated under the Clean Water Act (CWA) or Safe Drinking Water Act (SDWA). Furthermore, trichloroethylene-contaminated storm water must have resulted from landfill and industrial use and should be assessed.

The Agency discounts the findings of their own 2014 TCE Work Plan (P158, C-1-3) according to one Committee member. For example, the environmental fate sections in that document state: “there are several factors that can limit the aerobic biodegradation of trichloroethylene, including trichloroethylene concentration, pH, and temperature. Toxicity of the degradation products (e.g., dichloroethylene, vinyl chloride, chloromethane) to the degrading microorganisms may also reduce the rates of biodegradation of trichloroethylene in aerobic soils.”

Recommendation 1: Include a diagram that displays pathway and rates (e.g., biodegradation, exchange, discharge).

Some members found this Evaluation document for trichloroethylene less concise and more difficult to read than previous evaluations. Members also commented that the qualitative analysis is generally adequate but recommended that a diagram that displays pathways and rates be included.

Recommendation 2: Include the range of physical-chemical properties where multiple values are available.

Compared to other evaluations reviewed by the Committee, there are many experimental physical-chemical properties for trichloroethylene. It is not clear in the Evaluation how the physical-chemical properties listed in Table 1-1 were selected over other values reported in the literature (many of which are listed in the supplemental data) or why a range of values is not provided. A range of physical-chemical properties should be reported and used in the environmental fate modeling to determine how sensitive the models are to the key chemical input properties.

Recommendation 3: Include information on degradation products.

The Committee discussed the need to include more information on degradation products and recommended that the Agency include available information on specific degradation/hydrolysis substances in the Evaluation.

Several sections of the Evaluation state that anaerobic biodegradation of trichloroethylene is rapid. The Committee noted that this is not always the case, and in many situations toxic biodegradation intermediates are formed, including dichloroethylene and vinyl chloride. Atmospheric photolysis via the hydroxyl radical (OH) also can result in the formation of chloroform and other chlorinated byproducts (Itoh et al. 1994).

Another Committee member commented that there is no mention of the influence that trichloroethylene density has on environmental fate. Trichloroethylene density and partitioning to suspended sediments means that trichloroethylene will deposit in bottom sediments, where it may form a dense non-aqueous phase liquid (DNAPL). Although the density dependent deposition to sediments is acknowledged in Section C-1-2 of the EPA 2014 Work Plan for Trichloroethylene (U.S. EPA, 2014), none of this is considered in the Evaluation.

Recommendation 4: Modify the discussion on the lack of trichloroethylene in biosolids based on the suitability of the analytical methods used in the cited surveys.

Page 276 of the Evaluation states that trichloroethylene is not anticipated to partition to biosolids during wastewater treatment. To further support this analysis, EPA states that trichloroethylene is not detected in the Targeted National Sewage Sludge Survey (TNSSS) nor is it reported in biosolids during EPA's Biennial Reviews for Biosolids, a robust biennial literature review conducted by EPA's Office of Water (U.S. EPA, 2019). The Committee noted, however, that the methods used to analyze the biosolids in these surveys are not suitable for trichloroethylene and that the targeted analysis did not appear to specifically look for trichloroethylene.

Recommendation 5: Include additional discussion on uncertainties for exposure based on the potential for persistent exposure.

The Agency used the Sewage Treatment Plant (STP) model within EPI Suite™ to predict fate of trichloroethylene during wastewater treatment. The model estimated 80% will be lost to the air and 1% remain in the aqueous effluent. Based on the log K_{OW} and predicted log K_{OC}, the Agency predicts limited partitioning into biosolids. The Agency states that this is confirmed with Targeted National Sewage Sludge Survey data (reference not provided in the Evaluation) which did not detect trichloroethylene. However, as previously mentioned, the Committee noted that the methods used to analyze the biosolids in these surveys are not suitable for trichloroethylene and the targeted analysis did not appear to look for trichloroethylene. While a similar argument is made for partitioning into sediments, there is no measured data to support this qualitative estimate. Additional text regarding uncertainties for the predictions is needed. For example, the Agency indicates that trichloroethylene would not bioaccumulate based upon a log K_{OW} of ~2. This value indicates that trichloroethylene would partition into the organic phase 100 times more than in the aqueous phase. If trichloroethylene is continuously discharged into aquatic systems, "pseudo-persistent" exposure would occur because there is limited aerobic biodegradation (according to BIOWIN module of EPI Suite™¹). While only 1% is predicted to be discharged into surface water from EPI Suite™, based on the production volume and multiple detections observed in surface waters across the United States, persistent exposure may be a possibility and should be addressed as an uncertainty.

As it has with previous evaluations, most of the Committee discussed the desire for a "mass balance" approach (see Recommendation 21, 27, and 123) particularly for environmental exposure. See additional discussion in the response to Question 2.

Several Committee members also emphasized that kinetics cannot be directly inferred from equilibrium properties. As mentioned in previous Committee reviews (e.g., methylene chloride, carbon tetrachloride), the rate of volatilization depends on environmental conditions more than equilibrium properties. K_{OC} values are assumed to reflect equilibrium. Sorption kinetics depend on the chemical and sorbent combination. When considering exposure pathways, it is important to note that movement between compartments goes both ways based on equilibrium. For

¹ The EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical-chemical properties and environmental fate estimation programs developed by EPA and Syracuse Research Corp. (SRC). Version 4.11 used.

instance, movement from water to air is only true in scenarios where air does not contain significant trichloroethylene concentrations.

Q 1.2	Please comment on the data, approaches, and/or methods used to characterize exposure to aquatic receptors (Section 2.2).
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Response to Q1.2: Characterization of exposure to aquatic receptors.

The Committee noted that there is significant overlap between Questions 1.2 and 2.2. See also responses to Question 2.2.

The EPA expects limited exposure to aquatic organisms due to a high volatilization rate. However, the Committee noted that trichloroethylene only slowly biodegrades under aerobic conditions and the predicted volatilization half-lives in river waters (1.2 hours) and lake waters (110 hours) are not negligible.

Recommendation 6: Include additional discussion and justification for the decision to not assess risk to sediment and terrestrial organisms.

The Committee questioned, as in previous SACC reviewed evaluations, EPA's decision not to evaluate risk to sediment and terrestrial organisms based on low sorption (low K_{oc} estimated by EPI Suite™) and rapid volatilization (based on Henry's law constant) even though trichloroethylene is one of the most widespread groundwater and soil gas contaminants in the United States.

Recommendation 7: Explain why estimated K_{oc} values are used in place of measured values.

A calculated log K_{oc} value is used to rationalize low sorption and justify not assessing risks to sediment and terrestrial organisms. However, there are many experimentally derived estimates of trichloroethylene's sorption coefficient that are available in the literature that show values ranging as high as a log K_{oc} of 4.2 (e.g., see Allen-King et al., 1997). Committee members questioned why a predicted value of log K_{oc} is used when there are experimentally derived values available. The Committee also noted that acute exposures to terrestrial organisms that may spend significant time at the soil/air or water/air interface where volatilization may produce inhalation exposures cannot be ruled out (see also Recommendation 124).

Recommendation 8: Add confidence intervals and conduct a model sensitivity analysis to determine if variability associated with the physical-chemical properties would change the EPA's fate assessment.

The Evaluation states that the STP model in EPI Suite™ predicts 81% removal via volatilization and 1% removal via sorption. It is further stated that trichloroethylene is not reported in EPA's Biennial Review for Biosolids. The 81% removal is used in subsequent modeling efforts without considering any variability as is the 1% removal via sorption. The Committee recommended adding confidence intervals to the estimate of proportional removal and conducting a sensitivity analysis to determine if variability associated with the chemical-physical properties input to the

model would change the EPA's fate assessment. The human exposure modeling efforts are far more extensive and detailed than those used for environmental exposures.

Recommendation 9: Clarify why E-FAST, considered inappropriate for VOCs, is relied on for evaluating environmental exposures.

Committee members questioned why a comparison is performed between E-FAST modeled and measured data when, according to EPA documentation, the model is not appropriate for trichloroethylene, and stream flow data are not current. The Committee was uncertain on which data should be used to assess environmental exposures, since modeled data seemed inappropriate for the task and monitoring data is limited. A Committee member questioned whether it is even appropriate to make the comparison between the two datasets.

One Committee member noted that the Probabilistic Dilution Model (PDM) portion of the E-FAST 2014 model was specifically written to handle surface runoff from nonpoint sources. It is used in this evaluation for determining the number of days exceeding the concentration of concern (COC) in free-flowing water bodies (Evaluation, Section 2.2.3.2) from a point source. The use of this model for evaluating a source with continuous point source releases needs justification because inputs to the model represent nonpoint source releases, not necessarily appropriate for point source releases. The Evaluation has explicitly omitted non-point source releases in this and previous evaluations. In using this model, it remains unclear what assumptions are being made related to the upstream and initial downstream concentrations. Without further clarification, it is not possible for the Committee to comment on the appropriateness of this model in this evaluation.

A Committee member questioned whether the search for Superfund sites, described in Section 2.2.5, used five river miles or a simple five-mile radius from the water sampling point. Since there are no Superfund sites near sampling points, it probably does not influence this evaluation. However, if a Superfund site was within five miles, would Superfund site information be queried to determine that trichloroethylene exceeded a COC?

Recommendation 10: Modify Tables 2-7, 2-8, and 2-9 to make it clear they refer to estimated concentrations.

Recommendation 11: Modify Table 2-2 to clarify it applies to water releases.

A Committee member had difficulty finding an estimate of the total pounds of trichloroethylene released to waterways. The problem formulation lists 52 pounds for 2015 (Problem Formulation, page 31 Table 2-7, U.S. EPA, 2018). Later in that document there is a release value from Discharge Monitoring Report (DMR) data of 1,564 pounds (Page 34, Section 2.3.4).

The Committee recommended that EPA make it clear that Table 2-7, 2-8, and 2-9 present *estimated* aqueous concentrations. Table titles and figure captions should “stand alone.” The captions should better distinguish between estimated and measured aqueous concentrations. Similarly, it is not clear that Table 2-2 refers to water releases.

Additional comments on Table 2-2 and associated text noted by members:

- Estimated daily releases per COU depend heavily on Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) data for 2016 and assumes 260 days of operation per year.
- Impact on Toxics Release Inventory (TRI) data comes only from those manufacturers/processors having 10 full-time employees, and that handle greater than 25,000 pounds (manufacturers) or 10,000 pounds (processors).
- Impact on Discharge Monitoring Report (DMR) data of requirement to load major discharger data, but optional to load minor discharger data, and the fact that distinction between major/minor is set independently by each state.
- If release is to lake waters (110-hour half-life), is daily averaging an appropriate measure of average water concentrations (there is an issue of carry-over of the undegraded fraction from day one added to new releases on day two)?
- Wipe cleaning – uses towels, rags, paper – may end up in landfills. What impact would there be, if any, from this slow release of trichloroethylene to the environment?
- ‘Footnote a’ to Table 2-2 assumes 260 days of operation per year in assessing annual releases from TRI and DMR data. But Appendix I, where there is a discussion of the approach to estimating water releases from manufacturing sites using effluent guidelines, apparently assumes and justifies the use of 350 operating days per year (see ‘footnote c’ to Table Apx I-2). The number of operating days that form the basis for the range of manufacturing estimated daily releases reported in Table 2-2 is not reported and is not clear in the associated text. Appendix I discusses the approach to estimating water releases from manufacturing sites using effluent guidelines in the situation where TRI and DMR data were not available or where TRI and DMR data did not sufficiently represent releases of trichloroethylene to water for a COU. It would be useful to know what fraction of manufacturing sites had water releases that were estimated by this approach and what fraction used monitoring data directly. Similarly, it would be useful to know what fraction of processing facilities under each COU were represented by estimates and which by monitoring data. This has direct relevance on the uncertainty that would be assigned to the range of estimates reported in Table 2-2 (this table should refer to Table 2-4 for clearer description of assumption on release days).
- Difficulty justifying pounds per day values in Table 2-2 with kg/site-day estimates presented in Appendix I.
- ‘Footnote a’ to Table 2-2 justifies using the Open Top Vapor Degreasers (OTVD) range of water releases for multiple other degreasing, cleaning and metalworking applications because “releases were estimated using TRI and DMR data.” This sounds less like a justification than an acknowledgement that there are only reliable water release data for larger OTVD operations.

Recommendation 12: Clarify the use of ranges in number of facilities in Table 2-3.

Estimates of Number of Facilities (Evaluation, Section 2.2.2.2.2): A Committee member questioned the use of ranges in number of facilities in Table 2-3. For example, line 2 of the table reports 5 to 440 facilities that are in the scenario “Processing as a Reactant.” Is one to assume this means EPA acknowledges that they are not sure of the number of facilities? Does this mean something like “we know of 5, and there could be as many as 435 or more facilities that do this?”

A Committee member commented that the estimates of release days (Evaluation, Section 2.2.2.2.3) are really assumptions, not estimates. There are no data on exactly how these facilities operate. (See also responses to Question 2)

Recommendation 13: Clarify how confidence is assessed on overall release estimates.

The Committee noted everything is assessed as having “medium” confidence in the summary of overall confidence in release estimates. It was not clear to the Committee that there are any rules as to what qualifies as “high” or “low.” There seems to be a lot of uncertain components that go into a “medium” confidence assessment. Specifically, the Committee thought that the “medium” confidence for Commercial Printing and Copying is unjustified based as it is on one facility that is likely not representative of the whole industry. This should be an example of a “low” confidence occupational exposure scenario (OES) water release estimate.

A Committee member recommended that the Not Reported (NR) values in Evaluation Table 2-11 be replaced with values calculated using the data in the source publications as shown in Table 1, below. These publications contain ambient air data that show significant concentrations near manufacturing facilities. Extracted data from U.S. EPA 1977 are used to compute statistics as shown in Table 2. The same should be able to be done for data from other sources, especially federal documents, or publications from researchers at federal laboratories.

One Committee member commented that the Evaluation does not adequately explain why historical measured concentrations of trichloroethylene are not considered representative of current releases (Page 95, lines 671-675, and page 99, line 787-792). Another Committee member noted that the reduction in trichloroethylene use and process modifications over the last four decades make use of historical concentrations in the risk evaluation problematic.

Modeling of trichloroethylene concentrations in river water is highly problematic without downstream monitoring data to parameterize modeling efforts. This would require both near and intermediate distances from facilities. A Committee member noted that the Evaluation does not use Physiologically Based Pharmacokinetic (PBPK) models for fetal transfers and suggested that this may reflect a lack of data to parameterize those models. The same criteria should be used here, and if there are no data for model parameterization, conservative assumptions should be used throughout the Evaluation. According to the Committee member, these conservative assumptions include the 1977 data, the use of high centile concentrations and inclusion of lower centile of degradation. None of these conservative considerations have been included in the Evaluation.

Table 1: U. S. Production of Trichloroethylene from 1952 to 1987, from Bakke et al, 2007 and U. S. EPA, 2015.

Year	TCE *10 ⁶ kg	Reference
1952	123	Hardle, 1964
1953	147	Hardle, 1964
1954	178	Hardle, 1964
1955	143	Hardle, 1964
1958	134	Hardle, 1964
1960	160	Hardle, 1964
1961	140	Hardle, 1964
1962	162	Hardle, 1964
1965	198	Mertens, 1993
1970	277	Page and Arthur, 1978
1971	234	Page and Arthur, 1978
1972	194	Page and Arthur, 1978
1973	205	Page and Arthur, 1978
1974	176	Mertens, 1993
1975	133	Page and Arthur, 1978
1976	138	Page and Arthur, 1978
1977	117	Page and Arthur, 1978
1979	145	Waterhouse and Miller, 1985
1980	121	Mertens, 1993
1983	91	Waterhouse and Miller, 1985
1985	80	Mertens, 1993
1986	77	Mertens, 1993
1987	89	Mertens, 1993
2015	78 ^a	EPA, 2020

^a Reported as 172 pounds/year

Table 2: TCE concentrations in surface water and sediments (from USEPA, 1977).

Trichloroethylene						
Matrix	DOW	Vulcan	Ethyl	PPG	Boeing	Background
Water	µg/L	µg/L	µg/L	µg/L	µg/L	µg/L
	126	5	128	353	30	0.025
	122	74	0.4	447	17	
	5	24	37	179	8	
	13	360	10	403	5	
	0.9	4300		29	26	
	2					
Mean	44.8	952.6	43.9	282.2	17.20	NC
Geo Mean	11.0	106.6	11.7	201.2	13.96	NC
92nd centile for all sites		447		76th centile for all sites		179
Sediment	µg/kg	µg/kg	µg/kg	µg/kg	µg/kg	µg/kg
	0.21	0.25	0.02	146	0.42	2.2
	0.036	3.2	116	15	0.02	0.45
	0.02					
Mean	0.1	1.7	58.0	80.5	0.22	1.33
Geo Mean	0.1	0.9	1.5	46.8	0.09	0.99
92nd centile for all sites		146		77th centile for all sites		3.2
Carbon Tetrachloride						
Matrix	DOW	Vulcan	Ethyl	PPG	Boeing	background
Water	µg/L	µg/L	µg/L	µg/L	µg/L	µg/L
	116	2	67	29	0.6	0.2
	32	193	0.1	40	0.4	0.05
	5	92	23	12	0.4	
	7	629	12	38	0.2	
	0.3	9060		0.05	0.05	
	0.3					
Mean	26.8	1995.2	25.5	23.8	0.33	0.13
Geo Mean	4.8	182.5	6.6	7.7	0.25	0.10
92nd centile for all sites		629		76th centile for all sites		67

Other Committee members commented that volume or use patterns do not consider any handling procedures, process, or engineering changes that may have taken place over the intervening years, particularly after regulatory limits were enacted.

<i>Q 1.3</i>	Please comment on EPA’s assumption that TCE concentrations in sediment pore water are expected to be similar to the concentrations in the overlying water or lower in the deeper part of sediment, in which anaerobic conditions prevail. Thus, the TCE detected in sediments is likely from the pore (Section 4.1.3).
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Response to Q1.3: TCE detected in sediments is likely from the pore water.

The Committee noted that it appears likely that trichloroethylene pore-water concentrations are similar to overlying water. The movement from sediment is dependent upon the organic carbon content of the sediment. With a predicted log K_{OC} of ~2, there is 100 times greater likelihood that trichloroethylene will be in organic carbon. However, the lack of detected trichloroethylene in sewage sludge, which has high concentrations of organic carbon, suggests partitioning into pore water does occur even with this log K_{OC} .

Recommendation 14: Consider obtaining measurements of trichloroethylene in sediments near release sites.

The Evaluation does not consider the fact that a K_{OC} of between 60 and 126 demonstrates higher trichloroethylene concentrations in sediment than in water for all situations where sediment organic carbon (OC) is 0.8 to 1.6% of the water mass. Sediments most often have OC content much higher than 1.6%. These values are relatively simple to obtain from the U.S. Geological Survey or from direct measurements in sediments near discharging facilities. The Evaluation seems to assume that all systems are at thermodynamic equilibrium and that kinetics do not exist. Not all Committee members agreed with this assumption. Water in sediment (i.e., pore water) and overlying water can only be at equilibrium with high turbulence and at significant distance downriver from inflow. In sediments of rivers with low turbulence, only the first few centimeters of sediment are in equilibrium with overlying water. There is virtually no advection between stationary sediment and water. So, once trichloroethylene-laden sediments are deposited, the trichloroethylene is less likely to partition back into water than might be predicted in ideal situations. Measurements of trichloroethylene in sediments near commercial releases are needed.

A Committee member noted that the partition coefficient from measured data (U.S. EPA, 1977) shows field measured partition coefficients of 0.076 and 0.32 when using geometric mean and arithmetic mean concentrations in water and sediment media, respectively. The Evaluation should justify that 0.32 (32%) represents low partitioning to sediments.

The review of available data raised questions regarding the extent to which trichloroethylene may be present in sediments, yet no monitoring studies have been conducted to refute the available data. This means that the Evaluation erroneously states that “review and evaluation of reasonably available information on TCE confirmed” problem formulation conclusions (Page 56, line 1827).

Question 2: Environmental Exposure and Releases

EPA evaluated releases to water and aquatic exposures for conditions of use in industrial and commercial settings. EPA used Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) data to provide a basis for estimating releases. EPA used these releases and associated inputs within EFAST 2014 to estimate instream chemical concentrations and days of exceedance. EPA also evaluated monitored values of TCE in surface water and where possible compared those values to estimated release concentrations.

<i>Q2.1</i>	Please comment on the approaches, models, and data used in the water release assessment including comparison of modeled data to monitored data (Section 2.2).
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Response to Q2.1: Water release assessment and comparisons of modeled and monitored data.

Recommendation 15: Compare model estimates with values from municipal wastewater or National Pollutant Discharge Elimination System (NPDES) discharge data from industrial wastewater treatment facilities to determine model sensitivity.

Modeling estimates were obtained from E-FAST using data compiled from the Toxics Release Inventory (TRI), Discharge Monitoring Report (DMR) and Chemical Data Reporting (CDR). A probabilistic dilution module is then used to estimate surface water concentrations in freshwater streams and still water systems. Several Committee members indicated that it is unclear how these data are used in the model. For example, it is uncertain how NPDES data from DMR are used. Based upon the Evaluation, it seems the only data compiled from DMR is dilution data. It is unclear why monitoring data for trichloroethylene in wastewater effluent was not obtained from NPDES. It seems that only the 10th percentile value of stream dilution is used from DMR and is considered a conservative estimate. However, the Committee found it unclear why the upper end conservative (i.e., 90th percentile) of E-FAST values are not used; or why effluent values are not used. In fact, it appears that municipal wastewater measurements are excluded from the water quality exchange (WQX) measured data.

Concerns were expressed on the use of a model that is specifically designed for runoff scenarios, but spills and runoff are excluded from the trichloroethylene risk evaluation.

There is a lack of clarity regarding references to concentrations. For example, the range of measured surface water concentrations near facilities reported as 0.4 to 477 parts per billion (ppb) (Page 259, line 19) is not the observed concentration range. The observed range is ~0.05 µg/L to 9090 µg/L. As such, the text is misleading as written.

In contrast, one Committee member thought the approaches followed by EPA to assess water releases seemed adequate. This member thought that sections 2.2.2.3, 2.2.6.3, and 2.2.6.4 in the Evaluation did a good job in highlighting the limitations and uncertainties of the assessment. For instance, the TRI data is probably the best source for mass flows, but given its inherent limitations (e.g., excluding companies with less than 10 full-time employees, minimum thresholds, potential underreporting) the Committee suggested this is likely to be an

underestimation of loading.

Recommendation 16: Add a few explanatory paragraphs immediately after the concept of “cleansed data set.”

Several Committee members pointed out that in the beginning of section 2.2.6.2.2, it was unclear what ‘cleansed data sets’ means. The Committee recommended enhancing the clarity with a quick reminder of the definition, given the length of the overall report.

One Committee member thought that Table 2-10, although not a full uncertainty assessment, provides a good sense of the potential uncertainty through presenting data ranges and standard deviations.

Recommendation 17: Compare E-FAST advantages and disadvantages with other models.

In the first paragraph in Section 2.2.3 the advantages of using EPA’s E-FAST are listed. Several Committee members thought to be fair to readers, at least one disadvantage to using this tool for everything should be listed. For example, using a model that does not consider the fate of the chemical is problematic. Members wondered if other models could be compared to the E-FAST results.

Recommendation 18: Discuss the potential uncertainties of other wastewater treatment processes (e.g., aeration), particularly with volatile chemicals.

The estimated percent removal from wastewater treatment (WWR%) is based on a specific kind of industrial wastewater treatment facility (IWTF). Variation in types of IWTFs (sludge [dewatering], chemical, biological [aerobic, anaerobic, composting], physical [screening, sedimentation, skimming]) that manufacture, or process trichloroethylene should be discussed. This is particularly important because aeration is typically used in secondary treatment. At a minimum, a range of estimated removal percentages (or a confidence interval around the estimate of percent removal) should be provided.

Several Committee members expressed concerns about the Geospatial Analysis Approach. If the geospatial analysis finds a Superfund site within 1 to 5 miles of the facility, then the Evaluation indicated that those monitoring sites were excluded. One Committee member was uncertain how Department of Defense (DOD) facilities that use trichloroethylene are treated. Of additional concern would be the possibility that the DOD facility also included a Superfund site. This member also had concerns for situations where the monitoring site is downstream (down slope) of the trichloroethylene use facility but upstream (up slope) from the Superfund site.

Page 90, Geographic Coordinates: One Committee member thought that location of release points is needed rather than the “address” of the facility or the “front door” of the Superfund site. This member thought that the geographic analysis sounded quite cursory even though it is a screening analysis. This member thought that incorporating land slope, Superfund site boundaries and facility discharge points would not be that much extra work.

On Table 2-7 to 2-9: Several Committee members thought that the aqueous concentrations

should be consistently expressed as micrograms per liter.

Pages 92 and 93: One Committee member thought that the state of active facility releases and release characteristics should be reported in Section 2.2.2.2.2, or that Section 2.2.2.2.2 text should be moved or cross-referenced to pages 92 and 93.

Table 2-10: One Committee member indicated that with such a high fraction of non-detect (ND) levels, the average is likely an overestimate of central tendency while standard deviation is likely an underestimate of variability. The member noted that in all years, the average of detections is less than the average of all data, suggesting that there are a lot of NDs from sites where the detection level (DL) is closer to 5 than to 0.022.

E-FAST does not estimate stream concentrations based on the potential for downstream transport and dilution. This implies that E-FAST is acceptable for near-field environmental concentration estimation but not acceptable for estimating downstream concentrations, which are the bulk of environmental measurements.

- E-FAST stream flow data are 15 to 30 years old. Evaluation needs more recent data (last 10 years) to significantly decrease uncertainty.
- Geographic Information Systems (GIS) work has not been validated through ground truthing.

Recommendation 19: More detailed GIS modeling is needed to raise confidence to moderate.

Confidence in Aquatic Exposure Scenarios: The draft assessment concludes overall moderate confidence. Many on the Committee concluded that despite a lot of work and best intentions, confidence in exposure scenarios is low, primarily due to high propagation of uncertainties. More detailed GIS modeling is needed to raise confidence to moderate.

Using notes from Supplemental Document 10 Environmental Data Extraction, one Committee member noted that data from the Lake Charles PPG Facility released trichloroethylene that produced mean surface water concentrations of 282 µg/L and median of 353 µg/L (U.S. EPA, 1977). Surface water concentrations at the DOW plant in Freeport, TX, ranged from 0.9 to 126 µg/L. The table of environmental monitoring studies in Supplemental Document 10 reports ranges and standard deviations. In reporting the number of samples and detection frequencies in column 4 of the table, a value of 1 indicates that all the samples had detectable concentrations. This is not completely clear, because it could also be read as there being only one sample with a detectable concentration in the sample.

Recommendation 20: Incorporate an estimate for releases from all facilities that are likely to use trichloroethylene but that do not report TRI data.

Several Committee members recommended the Agency should incorporate an estimate for releases (via maximum likelihood, censored regression, or equivalent, see Helsel, 1990 and Helsel, 2005) from approximately 68,400 facilities that are likely to use trichloroethylene but

that do not report TRI data. This approach uses the distribution of known observations to predict the unknown observations (non-detects). The Evaluation lists 68,600 potential or likely users (Evaluation Table 2-3: Summary of EPA's estimates for the number of facilities for each Occupational Exposure Scenario (OES)). The Agency that reports are available from 183 facilities and 8 wastewater treatment plants (WWTPs). Data from these locations could be used to develop a population distribution that could be used to estimate total releases from all facilities.

Recommendation 21: Provide better mass balance analysis to determine whether unaccounted trichloroethylene should be considered an environmental release.

The Problem Formulation document (U.S. EPA, 2018) indicated that recycling and disposal at 172 reporting facilities totaled 91,000,000 pounds. Yet the Evaluation assesses only 52 pounds of releases. It is scientifically indefensible to disregard 91,000,000 pounds of reported emissions from reporting facilities and base a nationwide environmental risk assessment on 0.003% of the known releases. Similarly, the TRI reported 91,000,000 pounds released is a fraction of the 172,000,000 pounds used in commerce (Problem Formulation: Table 2-4). Much of the remainder is unaccounted for. Some Committee members noted the difficulty of assigning any "unaccounted TCE" to a condition of use. Other Committee members emphasized that 83.6% of trichloroethylene manufactured/imported is known to be consumed in the production of refrigerant 134a (Section 1.2.2).

The Committee noted that Section 2.2.6.2, lines 567-572 has no mention of Appendix P, suggesting there is no way to determine the adequacy of the underlying information upon which surface water concentrations are based (Tables 2-7, 2-8, and 2-9). The Committee concluded that Appendix P contains assumptions that are not conservative and are improper for use in the absence of measured data for releases from commercial operations.

Recommendation 22: To be conservative, high percentile estimates of releases should be used anytime monitoring data are not available.

Several Committee members indicated the exclusion of spills in the trichloroethylene Evaluation is inappropriate as spills result from trichloroethylene uses in commerce. One Committee member indicated this omission stems from a decision to omit hazardous spills in the problem formulation (Page 33: EPA-740-R1-7014; U.S. EPA, 2018). One Committee member expressed concern that this decision is unprotective (e.g., not appropriately conservative).

The impact of spills needs to be discussed. Several of the NIOSH Health Hazard Evaluations (HHE) report workers concerned about the impact of spills and cleanup and that those are reported as associated with headaches, dizziness and other symptoms.

Recommendation 23: The Agency should consider the impact on discharge estimates of multiple facilities discharging to a single Publicly Owned Treatment Works.

In evaluating Appendix P, one Committee member concluded that releases from degreasing operations were estimated based on "best practices" for Open Top Vapor Degreasers (OTVDs). Under this approach, 80% of wastewater is released to a water treatment facility (Page 708. line 3041). If this assumption is made, the Committee member concluded that aggregates from all

commercial users within a water treatment district could discharge to a single Publicly Owned Treatment Works (POTW). Data presented in the Evaluation did not allow determination of the extent to which multiple facilities were discharging to a single facility and if the magnitude of any such discharges would be essential to estimate high centile releases from POTWs receiving trichloroethylene from multiple commercial users.

Recommendation 24: The Committee restated the need for robust monitoring data to be used in exposure assessments.

One Committee member concluded that the hydrologic unit code (HUC) approach can be valuable *if and only if* assessments can show that measurements at downstream monitoring sites are predictive of discharges from upstream facilities. Otherwise the Committee member expressed concern that the approach is likely to underreport trichloroethylene concentrations downstream of manufacturing facilities.

The American Chemical Society (ACS) has publicly available statements regarding the need for robust monitoring data sets and biomonitoring in regulatory risk assessment/risk determination frameworks (ACS, 2019). These documents clearly state that ACS supports better understanding of critical risk assessment science in specific areas:

- Exposure assessment, which uses best practices for modeling and assessment, including robust exposure data ... [NRC, 2012].
 - Biomonitoring, which measures a wide range of chemicals and transformation products... [NRC, 2006].
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Q 2.2	Please provide any specific suggestions or recommendations for alternative data or estimation methods, including modeling approaches, that could be considered by EPA for conducting or refining the water release assessment and relation to monitored data (Section 2.2).
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Response to Q2.2: Refining the water release assessment.

Recommendation 25: Use NPDES data to confirm E-Fast outputs for trichloroethylene.

NPDES measurements of trichloroethylene from permit-required sampling results and notifications to state/EPA of compliance or noncompliance should be obtained. These data would allow a much more robust method of comparison of modeled E-FAST data versus measured data to be performed. While measured data are obtained from the Water Quality Exchange (WQX)², these data are primarily surface water measurements that are rarely obtained from discharge sites where TRI or other input data are used in E-FAST.

The Committee expressed concern that available monitoring data could not be used to corroborate the monitoring approach given the downstream distance, which may represent an opportunity for EPA to implement a program of monitoring that can provide more data with greater confidence.

Recommendation 26: Range estimates or a statement of uncertainty should be provided on the number of facilities for each OES.

In Table 2-3 where the summary of estimates for the number of facilities for each Occupational Exposure Scenario (OES) are provided, one Committee member thought that the estimation of the number of facilities could be enhanced by adding a sense of uncertainty $\pm$ X percent or X facilities. This member thought that these data are evidently needed, as one sees the number of facilities for “processing as reactant” estimated at “5 to 440,” which is quite a range, whereas the rest of the estimations are left without any measure of uncertainty.

One Committee member could not find the surface water concentration maps mentioned in section 2.2.5. This member was concerned that the color coding is provided but not certain the maps were found in Section 4 of the Evaluation. If so, this member could not see the immediate reference.

In Figure 2-4, one Committee member thought the choice of a tornado graph is not the best one to promote clarity and suggested that a set of pie charts or a sectioned bar graph may better illustrate the point.

Recommendation 27: Perform a sensitivity assessment for environmental exposures.

Given the uncertainties and medium confidence ranking for the environmental exposure and releases, a sensitivity assessment is needed to better understand the impact of key assumptions

² Data were downloaded from the Water Quality Portal (www.waterqualitydata.us) on 10/3/2018

and limitations in the final conclusions. The Committee noted the inclusion of a sensitivity assessment performed on species (species sensitivity distribution in Section 3), which is a good step forward. Some Committee members recommended including an evaluation of how sensitive the environmental exposure estimations are to the assumptions, or at least provide a semiquantitative assessment.

Several Committee members noted that the Evaluation indicates that when it is not possible to confidently assign a facility to a specific COU based on TRI or DMR reporting information, it is assigned to its “most likely” or “primary” COU. It is not clear why the facilities were not asked for more information on how trichloroethylene is used on site. This seems reasonable, for example, for the manufacturing sites, where only three or maybe five are identified. One member suggested that this approach be used to reduce uncertainty by obtaining information on the days of manufacture versus assuming 350 days/yr for all.

Recommendation 28: Link the National Hydrological Dataset to E-FAST.

Several Committee members noted that material flows are not the same as in the E-FAST database. The Committee recommended that a mass balance approach would be helpful to address some issues in comparing trichloroethylene production and releases. Several Committee members recommended that the Agency link the National Hydrological Dataset to E-FAST.

Recommendation 29: Provide separate Supplement for EPI Suite™ data or change the title of the current supplement.

The supplemental PDF document, “5_TCE-Data Extraction for Environmental Fate and Transport Studies Public” (U.S. EPA, 2020) discusses results and assigns data quality for studies from which the input parameters used in EPI Suite™ are obtained. It also presents some EPI Suite™ model output. This is not clear from the document title, yet this is key information for Evaluation readers.

Recommendation 30: The implications of the Fugacity Level 3 modeling needs to be better explained.

EPI Suite™ consists of several models. Some are used to predict physical-chemical properties, one is used to predict removal from wastewater treatment plants (WWTPs), and another is the Fugacity Level 3 model. In some cases, they are linked, in others they are not. For example, physical-chemical properties can be manually added or estimated within EPI Suite™, then used in the STP model or fugacity models.

One Committee member concluded that the fugacity model encoded in the EPI Suite™ tool and presented in the Evaluation predicts trichloroethylene movement from air to water, not water to air (Page 30; U.S. EPA, 2020b). The member noted that any consideration of trichloroethylene degradation in wastewater will only lower the initial concentration released to water and increase the predicted air-to-water flux. Several Committee members thought this was a serious flaw in the Evaluation’s assessment of environmental fate data (Table SACC 2-1). The Committee suggested this pertains to all chlorinated solvent TSCA risk assessments.

Several Committee members suggested the ratios and mass loadings assumed in the default Fugacity Level 3 (fugacity model) within EPI Suite™ do not represent the Evaluation's estimates of environmental releases (Problem Formulation Table 2-7). Default assumptions are 1000 kg/hr release of the chemical being evaluated into the compartments of air, water, and soil. More refinement of fugacity model within EPI Suite™ estimates can be done by using data from Problem Formulation Table 2-7 (U.S. EPA, 2018).

The Draft Evaluation for trichloroethylene did not list estimates for total trichloroethylene releases to water or any other media. Therefore, the Problem Formulation contains the most comprehensive summary of the data available to estimate trichloroethylene releases to the environment. Data from Problem Formulation Table 2.7 (U.S. EPA, 2018) show annual trichloroethylene releases to air, water, and soil of 1,881,000 pounds, 52 pounds, and 50,000 pounds, respectively (Note: For this purpose, the SACC only lists the higher mass numbers to the nearest 1000 lb). There are also 2016 DMR data that show 1,564 pounds of trichloroethylene released from the top ten trichloroethylene producers (Problem Formulation 2.3.4 page 34, last line).

Table 3 shows six scenarios to demonstrate using environmentally realistic release ratios of trichloroethylene to air, water, and soil that multimedia models such as EPI Suite™ show trichloroethylene moving from AIR TO WATER, not from water to air.

- Scenario 1 (Default): The Agency's default case which shows equilibrium trichloroethylene concentrations in water that exceed releases to water by 63%.
- Scenario 2 (Scaled Default): Retains the equal ratios of the default case but scaled to the total releases to all compartments (Problem Formulation Table 2-7). This scenario is provided to show that as long as the ratios released into the three compartments are the same, the relative distributions are predicted to be the same.
- Scenario 3 (Problem Formulation): Shows the release rates to each compartment as calculated from Problem Formulation Table 2-7 (U.S. EPA, 2018). This scenario estimates aqueous trichloroethylene concentrations that are 13,100% (131 times) above those estimated from TRI data. This would represent 6,812 pounds released to water by industrial uses.
- Scenario 4 (Problem Formulation High): Used to determine if using the higher 2016 DMR aqueous release estimates of 1,560 pounds (Problem Formulation 2.3.4 page 34, last line) would lower the flux to water. Using this higher annual aqueous release (Problem Formulation 2.3.4 page 34, last line) rather than the 52 lb release (Table 2-7) produced an EPI Suite™ fugacity model output of 792% trichloroethylene increase in water over the concentration released to water. That represents 12,350 pounds of trichloroethylene released to water from industrial uses. So, a 30X increase in release to water only increases modeled surface water concentrations by 2X because the flux from other compartments is the dominant contributor to aqueous concentrations.
- Scenarios 5 (Water Low + Air) and 6 (Water High + Air): Use the trichloroethylene releases to air and water from Scenarios 3 and 4 but assume that there is no release to surface soils and that there is no hydraulic connectivity from soils to surface water (both

of which are not protective assumptions). Scenario 5 shows a 10,900% increase in trichloroethylene over the 52 pounds in table 2-7, and

- Scenario 6 (Water High + Air): Shows a 732% increase over the 1,560 pounds from 2016 DMR data, clearly demonstrating partitioning from AIR to Water.

One Committee member noted that overall, these EPI Suite™ fugacity outputs show that trichloroethylene releases to other abiotic media must be considered if aquatic receptors are to be protected. This fugacity evaluation also clearly demonstrates why the Agency cannot pretend that discharges to non-aqueous media can be assessed separately. All biotic and abiotic compartments are interconnected through phase boundaries and material transport across those boundaries does not behave as any policy or regulatory nexus dictates.

Recommendation 31: Link monitoring data to upstream sources.

The Committee recommended that monitoring data must have some downstream hydraulic connection to the source. The Committee suggested the simplest way to incorporate these data would be to identify which ones are indeed downstream with transit time of no more than 3 days and to situate another monitoring station downstream from the source, approximately 1/3 of the way (transit time) to the current monitoring station.

Table 3: EPI SUITE Estimations of Trichloroethylene in Environmental Compartments Using Release Data from the EPA Problem Formulation Document (U.S. EPA, 2018)

INPUTS	Fugacity inputs (kg/hour)			OUTPUTS Percent Distribution				Persist (hrs)	Mass Fraction of Input		
	Air	Water	Soil	Air	Water	Soil	Sediment		Air	Water	Soil
Default ^a	1000	1000	1000	35.4	54.2	10.1	0.26	147	1.06	1.63	0.30
Scaled Default ^b	73.4	73.4	73.4	35.4	54.2	10.1	0.26	147	1.06	1.63	0.30
Problem Formulation ^c	214.5	0.0059	5.7	97.7	0.35	1.93	0.0017	62.4	1.00	131	0.75
Prob Formulation High ^d	214.5	0.183	5.7	97.4	0.658	1.92	0.003	62.6	1.00	7.92	0.74
Water Low + Air ^e	214.5	0.006		99.6	0.3	0.08	0.001	61.2	0.996	109	
Water High + Air ^f	214.5	0.183		99.3	0.62	0.081	0.002	61.4	0.994	7.27	

a- Data inputs directly from USEPA Systematic Review Supplemental File: Data extraction Tables for Environmental Fate and Transport Studies for TCE.

b- Input data represent equal distribution of TCE releases to all compartments based on total releases (220.2 lb/hr) in Scenario below

c- Input values based on data in Table 2-7 of the Problem Formulation

d- Input values based on DMR data on page 69 of the Problem Formulation

e- Input values based on data in Table 2-7 of the Problem Formulation but excluding releases to soils.

f- Input values based on DMR data from the Problem Formulation, but excluding releases to soils

Question 3: Environmental Hazard:

EPA evaluated environmental hazards for aquatic species from acute and chronic exposure scenarios.

<i>Q 3.1</i>	Please comment on EPA’s approach for characterizing environmental hazard for each risk scenario (e.g., acute aquatic, chronic aquatic). What other additional information, if any, should be considered (Section 3.1)
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Response to Q3.1: Approach for characterizing environmental hazard by risk scenario.

The Committee supports the EPA’s development and use of species sensitivity distributions (SSDs) in the development of values intended to be protective of all aquatic receptors. It was encouraging that an SSD is used in conjunction with most sensitive species data for concentration of concern (COC) determinations. With one potential exception, values that were derived for acute and chronic exposures to aquatic organisms are reasonable, although there was not agreement on the magnitude of assessment factors (AFs) used; however, appropriate references are provided. It was also encouraging that sublethal endpoints of growth and reproduction were used to determine chronic values (ChV) for aquatic invertebrates.

Recommendation 32: Discuss reasons for the 4-fold difference in acute algal COC estimates based on the EC₂₀ versus the SSD HC₀₅ values.

The Evaluation computes two COCs for acute algal effects, one using the EC₂₀ for the most sensitive species and one using the SSD HC₀₅ value (Evaluation, page 199, lines 368-380). These values vary by more than four orders of magnitude, yet no explanation is provided for why this might be reasonable. When values differ by such a large extent, further investigation is warranted. There could be study quality issues or simply false positive outcomes that may help explain these results. Was this study repeated? The Committee recommended a more robust assessment of the Labra et al. (2010) study to evaluate its potential as outlier data and further justify the use of these data over the HC₀₅ designed to protect 95% of the species. Further, it is not clear why the Labra et al. (2010) quality metric is downgraded to medium while most individual quality components are rated high.

While a fish 32-day growth value is used for COC determination (7.88 mg/L), it is unclear why the lower 4 mg/L tadpole survival No Observed Effect Concentration (NOEC) is neglected. Since the values are on the same order of magnitude, it does not appear to affect overall COC estimates.

It is typically inappropriate to treat median lethal and median sub-lethal values equally (Evaluation, page 198). However, if the mode of action or endpoints are consistent with those that could reasonably be assumed to result in mortality (e.g., narcosis, terata) values would largely be

equivalent and hence appropriate to treat equally. The Evaluation needs to specify the endpoints for the EC₅₀ values used. If not, use the lowest biologically relevant endpoint value and apply an AF, then carry this value through the risk assessment.

Recommendation 33: Justify the use of the geometric mean in calculating lethal and non-lethal acute effects for invertebrates.

That the geometric mean is used to calculate a COC from both lethal and non-lethal data for acute invertebrate effects also requires further justification. What justifies the mean value when endpoints are different? Are all studies otherwise equivalent (see previous comment)? What data justifies the geometric and not the arithmetic mean? Precisely, why is the HC₀₅ not used as a point of departure (POD) for acute exposures to aquatic invertebrates (9.9 mg/L)?

Recommendation 34: Distinguish between study quality and study relevance in WOE considerations.

There is a difference between data quality and data relevance (see page 197, lines 287-315). Some very high quality toxicity data are not relevant to derive toxicity values from (e.g., mechanistic, *in vitro* data, population data, lack of dose response); however, they still have utility in addressing questions regarding biological plausibility and addressing issues associated with extrapolation of effects across species and populations. The Committee recommended that the EPA make this distinction between quality and relevance in judging total weight of evidence (WOE) in the development of toxicity reference values. Here, data relevance would directly refer to dose response information that could be used to develop a POD or COC.

Recommendation 35: Consider taxonomic representativeness of data and MOA information in setting AFs.

Several Committee members found that the use of assessment factors (AFs) of 10 and 5 to adjust the PODs for chronic and acute COCs appropriate and consistent with the scientific literature that have evaluated sensitivities of aquatic organisms using SSDs and NOECs; however, it is stressed that NOECs are often artifacts of study design and recommended that the Agency consider taxonomic representativeness of the data and any available mode of action or mechanistic data when deciding on the magnitude of AFs (see Belanger and Carr, 2019). One Committee member proposed that the lack of an aquatic vertebrate reproduction endpoint may suggest an uncertainty factor of 100 rather than 10 be used; however, if retained, the sensitivity of algae seems to allow conservatism in other COC calculations (Keinzler et al., 2017). The lack of reproductive data should also be discussed as an uncertainty.

Recommendation 36: Summarize environmental hazard conclusions in a table.

The Committee encouraged the creation of a table, such as below (Table 4), for summarizing environmental hazard findings.

Table 4: Example table for displaying environmental hazard findings.

Organism	Exposure Duration	Value (ppm)	SSD	AF	Method
<i>Algae</i>	acute	0.003	no	10	Geometric mean between LOEC and NOEC
<i>Algae</i>	acute	52	yes	0	SSD
<i>Aquatic other (inverts)</i>	acute	3.2	no	5	Geometric mean for LC and EC ₅₀ s combined
<i>Aquatic other (inverts)</i>	acute	9.9	yes	-	Not used
<i>Fish</i>	chronic	0.8	no	10	EC ₂₀ (growth)

Recommendation 37: Better justify exclusion in the exposure assessment of soil invertebrates and burrowing mammals in functionally confined spaces.

Section 3.1.5 (Evaluation page 278, lines 381-388) should be modified to include the comments above. In that section, volatilization rates are assumed to not contribute to exposure for terrestrial organisms (Evaluation page 275, lines 329-333). However, several Committee members expressed concern regarding exposures to soil invertebrates and burrowing mammals in functionally confined spaces exposed to trichloroethylene through vapor intrusion from contaminated underground sources. Certainly, this is considered in other Agency regulations (e.g. the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)) for human health concerns. A more robust justification or assessment is needed to dismiss such exposures for these organisms. Another acceptable response may include appropriate jurisdiction by other laws or regulation.

<i>Q 3.2</i>	Please comment on the use and interpretation of Species Sensitivity Distributions (SSDs) and hazardous concentrations (HC₀₅s) for ecological risk characterization and provide any specific suggestions or recommendations for how this information could inform EPA's risk assessment for TCE or other solvents (Section 3.1).
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Response to Q3.2: Use and interpretation of SSDs.

The Committee supports the Agency's development and use of Species Sensitivity Distributions (SDSs) in the development of a value intended to be protective of 95% of aquatic species. The SSDs are used to assess overall eukaryotic (invertebrate and vertebrate) and algal toxicity. Acute lethality is used for each assessment. The benefit of SSDs is that all species are compared using

the same toxicity endpoint (usually acute lethality), allowing for a transparent overview of the available data for the search for patterns and reasonableness of the COC. This benefit is also based upon the mode of action being narcosis, which is conserved between invertebrates and vertebrates for compounds such as trichloroethylene and other solvents. The inclusion of most sensitive species estimates of toxicity are warranted as often there is not enough sublethal endpoint data (e.g., reproduction data) to support SSD calculations. Thus, the Committee considered a combination of both processes for development and further support of the COC as an appropriate exercise.

Recommendation 38: Describe how the HC₀₅ is computed and what it represents.

It is unclear how to interpret an HC₀₅ comprised of both EC₅₀ and LC₅₀ data. The Committee recommended that the EPA provide a precise explanation of what the HC₀₅ represents. More description is needed on the methods used to derive those values and how they would be valuable in advance. Note that Section E1 only describes the tool used to compute the values, provides no additional justifications, and cites Etterson (2019), which does not provide a description of the methods used.

Recommendation 39: Use EC₅₀ or EC₂₀ values in computing the SSD.

Recommendation 40: If computing an SSD is not possible, use the EC₂₀ of the most sensitive species as the POD.

The SSDs are a good visualization tool for determining the potential relative impact to different species and may inform actions depending on the dynamics of trichloroethylene in an aquatic environment. However, specifically for trichloroethylene, given data gaps for the development of the curves, one Committee member asserted that no definitive conclusions can be made for algae. In addition, one limitation of SSDs is that outputs do not include the lowest toxicity values reported (including Lowest Observable Effect Concentrations (LOECs) and No Observed Effect Concentrations (NOECs)). Adding the values may provide additional visualization of the data that may help in supporting COC derivation.

The Committee recommended that SSDs be developed using EC₅₀ (or optimally EC₂₀) values exclusively to develop a sublethal value that is expected to be protective for 95% of the species. If sufficient data are not available for an SSD derivation, then the use of the EC₂₀ for the most sensitive species as a POD from which to apply an AF to derive a COC is reasonable.

Aqueous concentrations should be consistently expressed as µg/L or mg/L in the main text, to avoid confusion. In fact, the information in Appendix E (Evaluation page 528, line 321 of the Appendix) shows the average of HC₀₅ is 9,900 µg/L and a safety factor of 5 places that value at 1,959 µg/L. To further illustrate this, Figure Apx E7 (Evaluation page 529, Gumbel distribution) shows three closely agreeing fits for HC₀₅ and one outlier. Thus, the acute COC should exclude the Gumbel fit and thus the HC₀₅ would be ~6.3 mg/L or 6,300 µg/L. A safety factor for not having over 20 species (i.e., the SSD computation is extrapolating beyond the range of the data)

would then provide a concentration that is lower than currently estimated by the Agency.

Recommendation 41: Correct issues with Figure 3-1.

Comments on Figure 3-1

- The green algae *Raphidocelis subcapitata* is formally called *Pseudokirchneriella subcapitata*. In the Environmental Hazard Data Extraction Table for Trichloroethylene (U.S. EPA, 2020b) the label *Pseudokirchneriella subcapitata* is used. In Figure 3-1, the newer name *Raphidocelis subcapitata* is used. The Committee suggested using the most recent taxonomic nomenclature consistently throughout.
- The green algae (*Raphidocelis subcapitata*) has a toxicity value from the Data Extraction Table of $\log_{10}(411.5) = 2.61$ [Medium quality (Lubra et al., 2010) and high quality (Tsai and Chen, 2007)] whereas in Figure 3-1, the toxicity value for *Raphidocelis subcapitata* is shown at a value below 2.
- Value for the Diatom (*Skeletonema costatum*) in Figure 3-1 is below 2, whereas the value should be $\log_{10}(122.5) = 2.088$ [Medium quality (Ward et al., 1986)].
- The value for green algae (*Parachlorella kessleri*) in Figure 3-1 at toxicity value of $\log_{10}(640) = 2.8$ [Medium quality (Lukavsky et al., 2011)] is not included in the figure.
- The value for the green algae (*Chlamydomonas reinhardtii*) in Figure 3-1 at a toxicity value of $\log_{10}(24.4) = 1.39$ [High quality 72-hour (Brack and Rottler, 1994)] is not included in the figure.

Other specific comments: Genus previously *Rana* is now *Lithobates* (Evaluation page 190, lines 9293 and throughout).

Also note that developmental effects could result in premature mortality in these aquatic organisms (Page 191, lines 98-102).

Please be specific regarding the term “mild intoxication.” If this is narcosis or lethargy, please state as such (Evaluation page 192, line 144).

One Committee member suggested that the mantra that only toxic endpoints of mortality, growth, and reproduction are “populationally relevant” is fundamentally flawed (Evaluation page 192, lines 136-138; 148-161). Since there is no direct knowledge regarding the criteria important in regulating the populations of any of the aquatic communities from where there are releases, it is improper to characterize any toxic endpoint necessarily of having “direct population level effects.” Many populations are regulated by predator activity that makes narcosis or lethargy very important. In many natural systems, r-selected organisms (i.e., ones that produce many eggs/individuals) lose a large proportion to events resulting in mortality or otherwise removing individuals from the population in pristine ecosystems. The member suggested that the priority of using mortality, growth, and reproduction are legacy endpoints supported during a time when

only such data could be collected from aquatic toxicity tests. They recommended selecting endpoints by thinking in terms of any adverse effects that are potentially relevant to maintaining population size; such endpoints would include those such as lethargy (which is the result of narcosis and results in slow movement making individuals more susceptible to predation) and developmental affects that could ultimately result in mortality or otherwise removing individuals from of the reproduction pool. However, in this paragraph, many of these described mechanistic effects could be characterized as endpoints of uncertain biological significance or those of an adaptive response, which would not fit this definition. Two other Committee members mentioned that there are regulatory requirements associated with mortality, growth and reproduction and recommended EPA consider those criteria when choosing endpoints.

Question 4. Occupational and Consumer Exposure:

Occupational Exposure

EPA evaluated acute and chronic exposures to employee users (workers) and occupational nonusers (ONUs) for conditions of use in occupational settings. For exposure via the inhalation pathway, EPA quantified occupational exposures for both workers and occupational non-users based on a combination of monitoring data and modeled exposure concentrations. For exposure via the dermal route, EPA modeled exposure for workers, accounting for the effect of volatilization. EPA assumed dermal contact with liquids would not occur for occupational non-users. EPA assumed that workers and occupational non-users, exposed via the inhalation and/or dermal pathways, would be adolescents and adults of both sexes (≥16 and older, including males and females of reproductive age, and pregnant women and their developing embryo and fetus).

<i>Q 4.1</i>	Please comment on the approaches and estimation methods, models, and data used in the occupational exposure assessment (Section 2.3.1).
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Response to Q4.1: Approaches and methods used in occupational exposure assessment.

Most of the problematic occupational health issues in this Evaluation are the same ones that have been identified and discussed in most of the previous reviews completed by the SACC. These issues include: use of Personal Protective Equipment (PPE) and Protection Factors (PFs); not describing the data available from the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) and comparing these data to the very limited monitoring data sets used to arrive at exposures; not considering aggregate exposure of inhalation and dermal exposures; and not addressing the role of spills.

Recommendation 42: Consider breathing rates, alcohol consumption and other models for vapor generation in the inhalation assessment.

EPA needs to consider breathing rates in their inhalation assessments. The rate used is basically a resting rate; EPA should also include a calculation using a strenuous rate of exercise breathing.

The Committee considered how heavy alcohol consumption is known to interact and aggravate some of the symptoms of trichloroethylene exposure. Workers who consume alcohol on a regular basis, before or after they're exposed to trichloroethylene constitute a vulnerable sub-population.

Recommendation 43: Explore alternatives to the box model of Nicas (2009).

This Evaluation, as others previously reviewed by the SACC, uses the Nicas (2009) two-zone box model for estimating occupational inhalation exposures. The Committee recommended that EPA explore other models available in the research literature for estimating vapor generation.

Recommendation 44: Provide a rationale for not estimating the separate vapor and particle-bound fractions of trichloroethylene-containing aerosols in the near field.

It is not clear whether the literature on liquid aerosol modeling has been examined to see if it would be possible to estimate the vapor phase/particle bound fraction of trichloroethylene in aerosols generated in close proximity to the worker applying the product. Despite the rapid volatilization of trichloroethylene from droplets, it is likely that a sizable portion of the trichloroethylene is in the particle-bound phase close to the worker, not completely in the vapor phase.

Recommendation 45: Specifically identify all occupational exposure pathways with their associated regulatory authority.

The Evaluation should address more specifically those occupational exposure pathways that are not included because of competing areas of regulatory mandate. For example, lace wig and hair extension glues are excluded because they are considered cosmetics (FDA regulation), but hoof polish, used for cosmetic purposes and not considered a veterinary medicine under FDA regulations, remains under TSCA. A table should be included that specifically lists all the excluded pathways, and which indicates whether risk assessments are available for these pathways from other regulatory programs.

Recommendation 46: Improve the discussion of the exposure control hierarchy.

The Evaluation's discussion of the exposure control hierarchy should be more complete, specifically noting the PPE is the third stage of protection after establishment of proper engineering and administrative controls. The Agency should also present data demonstrating relatively poor adherence to guidelines and supporting recommendations for worker protection, not just provide a reference (as is done more explicitly for the carbon tetrachloride evaluation). At a minimum, the discussion should provide a table summarizing the type of gloves recommended for trichloroethylene by NIOSH, OSHA, and product manufacturers, both for handling neat trichloroethylene and trichloroethylene-containing mixtures.

Although at the start of Section 4.1 it is mentioned that PPE and PFs have been discussed at length in all previous Evaluations reviewed by the SACC, one Committee member raised a new concern that the factor that had the greatest impact on the final risk determination is PPE Protection Factors (PFs) as categorical constants in risk determination calculations. This reviewer cited the comments by the Environmental Defense Fund (EDF) and their analysis on pages 61-65, which indicates that the factor that had the greatest impact on the risk determination was the application of PPE PFs for respirators and gloves. This reviewer also indicated that it is distressing that the factor which impacts the risk determination the most has only one page of text dedicated to discussion. EPA must provide an expanded justification for applying various PFs to reduce the risk determination as constants applied to whole populations in the equations. It was hard to discern on page 120 of the Evaluation that OSHA only requires respiratory PPE be used when the Permissible Exposure Limit (PEL) continues to be exceeded after implementing the

higher priority controls (engineering and administrative) in the exposure control strategy. Assuming that PPE is required for all workers and used continuously is, therefore, not likely to be correct. This leads to the conclusion that application of PFs in risk determination for trichloroethylene is inappropriate unless the entire worker group is exposed at levels above the PEL. EPA's use of these various PFs thus serve only to inappropriately and systematically reduce the calculated risk. There is a lack of substantial discussion about exposure controls and use of PPE in actual practice. EPA references some of the NIOSH Health Hazard Evaluations (HHEs) and should review those to see what was being done in the businesses inspected by NIOSH and the corresponding exposure levels. Nearly all were below the PEL. Modification of risk estimates by applying PFs for PPE seemed to many on the Committee as inappropriate when there is no regulatory reason to compel the use of such PPE.

Recommendation 47: Consider the potential for dermal exposure to trichloroethylene vapor.

At a minimum, there should be mention and discussion of the vapor through the skin pathway of exposure, including the potential for vapor penetration through non-impermeable clothing.

Recommendation 48: Discuss the implications of using monitoring data from surrogate scenarios that can differ in the level and extent of exposure controls.

For manufacturing and processing as a reactant, EPA uses monitoring data from a subcategory/ Occupational Exposure Scenario (OES) (i.e., Halogenated Solvents Industry Alliance (HSIA) data) that could be under better controlled exposures compared to scenarios in other subcategories. This should be discussed. In addition, some reviewers reported difficulty in accessing the HSIA exposure monitoring data. The link provided in the Evaluation is to the HSIA response on the Johnson et al. (2003) and Charles River studies (Charles River Laboratories, 2019), not the exposure monitoring data.

Recommendation 49: Improve the discussion on aggregate exposure and justification for it not being performed.

The issue of aggregate exposure combining inhalation and dermal routes is inadequately discussed and ignored. Individuals will be exposed via both routes and the combined exposure will certainly be greater than each individually. These may be reasonably treated as additive exposures.

Q 4.2	Please provide any specific suggestions or recommendations for alternative data (modeling or monitoring) or estimation methods that could be considered by the Agency for conducting the occupational exposure assessment. If so, please provide specific literature, reports, or data that would help us refine the exposure assessment (Section 2.3.1).
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Response to Q4.2: Alternative data or methods for conducting the occupational exposure assessment.

EPA should attempt to get information on use of products directly (from distributors, retailers, etc.) as an alternative means to obtain market penetration information. For some uses (e.g., dry cleaning, metal working fluids, and others) the number of vendors to these trades is not overwhelming. Contacting these vendors for information would more fully inform the risk evaluation.

The Committee suggested that EPA identify the drivers for model exposure estimates (from the Monte Carlo simulations), and how changing values in these drivers affect differentially the central tendency (CT) and high-end (HE) model-based exposure estimates in comparison to estimates based on measurements. This exercise could provide insights into the assumptions that need refinement or improved data.

Q 4.3	Please comment on assumptions used in the absence of specific exposure information (e.g., dermal surface area assumptions: [high-end values, which represents two full hands in contact with a liquid: 890 cm² (mean for females), 1070 cm² (mean for males)] and [central tendency values, which is half of two full hands (equivalent to one full hand) in contact with a liquid and represents only the palm-side of both hands exposed to a liquid: 445 cm² (females), 535 cm² (males)]). Please also consider these values in the context of different lifestages and body weights (Section 2.3.1.2).
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Response to Q4.3: Dermal assumptions used in absence of specific exposure information.

The Committee expressed that these estimates are valid, or at least are reasonable as a means of calculating potential dermal exposure. These are mean surface areas as described in the Exposure Factors Handbook (U.S.EPA, 2011), which in turn use data from National Health and Nutrition Examination Survey (NHANES). The Handbook presents dermal surface area central tendency estimates for males and females over 21, children 11-16 years, and children 16 to 21 years as a percentage of body surface area. The Handbook also provides central tendency estimates of body surface area for different age groups. Body surface area can also be calculated from body weight, so using body weight data from NHANES it would be possible to construct a distribution of

dermal surface areas for each age category in addition to central tendency values.

Q 4.4	Please comment on EPA's approach to characterizing the strengths, limitations and overall confidence for each occupational exposure scenarios presented in Section 2.3.1. Please comment on the appropriateness of these confidence ratings for each scenario. Please also comment on EPA's approach to characterizing the uncertainties summarized in Section 2.3.1.3.
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Response to Q4.4: Characterizing occupational exposure scenarios strengths, limitation and confidence.

Recommendation 50: Discuss all parameters that drive all human exposure estimates based on modeling.

The Committee recommended providing a clear, specific discussion about the parameters involved in calculating exposure estimates based on modeling (see Table 6 for dermal parameters recommended by the SACC for inclusion in the current and future TSCA risk evaluations) and further consider a limited sensitivity analysis to identify those parameters that most influence (drive) the exposure estimates.

Related to Recommendation 49: Other issues that continue in this Evaluation and prior evaluations are non-consideration of aggregate exposures (e.g., workers who are also consumer users; workers that may be exposed in more than one scenario). This will be a standing problem unless EPA places their estimates in the context of risks from sources and pathways not included in the TSCA evaluation.

To estimate occupational non-user (ONU) inhalation exposure, EPA reviewed personal monitoring data, area monitoring data and modeled far-field exposure concentrations. When EPA did not identify personal or area data or parameters for modeling potential ONU inhalation exposures, EPA assumed ONU inhalation exposures could be lower than occupational user inhalation exposures; however, relative exposure of ONUs to workers could not be quantified. When exposures to ONUs were not quantified, EPA considered the central tendency from occupational user personal breathing zones to estimate ONU exposures.

Q 4.5	Please comment on the adequacy, appropriateness, and transparency of EPA's approach and the assumptions EPA used to characterize ONU exposure via this approach (Section 2.3.1).
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Response to Q4.5: Characterization of ONU exposure.

Recommendation 51: Clarify the distinction between workers and ONUs for all COCs.

The Evaluation should clarify the distinction between workers and occupational non-users (ONUs) in some instances. For example, in Table 2-23 (Evaluation, page 121) it is not clear why chemists are considered ONUs (even analytical chemists?), as are engineering technicians, or shoe and leather workers. In small commercial operations, the same person can be both a retail worker (ONU) and worker-operator.

Recommendation 52: Discuss all the biases and uncertainties inherent in OSHA and non-OSHA, and foreign monitoring data for exposure estimation.

For aerosol and non-aerosol products and for repacking, the Evaluation uses a surrogate condition (unloading in repacking) and monitoring data from a semi-closed production manufacturing facility in Germany (same source is used for degreasing). The Occupational Exposure Limit (OEL) for Germany may have been 30 ppm Time Weighted Average (TWA) at the time, although it is likely that the EU Commission OEL of 10 ppm TWA was already adopted at the time these data were collected. Both are lower than the OSHA's Permissible Exposure Limit (PEL) of 100 ppm TWA. There is potential for exposures in Germany to be lower because of tighter controls in response to the stricter occupational exposure regulations. This issue and corresponding limitation of using the German data should be specifically discussed.

The Evaluation indicates it does not use the wealth of OSHA data because it may not be representative (potential for bias). These OSHA data are unlikely to be any less representative than using monitoring results from a single plant with a small number of measurements as is used for the exposure derivation in this Evaluation. TSCA Evaluations should be using a composite approach to understanding exposure. The Evaluation uses summary central tendency and high-end descriptors, so compiling all the data would provide a broader base.

Q 4.6	Are there other approaches or methods for assessing ONU exposure for the specific condition of use (Section 2.3.1)?
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Response to Q4.6: Other approaches to assessing ONU exposures.

Recommendation 53: Explore the use of area monitoring samples and estimates of far field modeling concentrations for deriving ONU exposure estimates.

Monitoring data reports frequently have area samples (also called static samples) collected away from the worker's location. These data could be explored as potential indicators of ONU's exposures. Similarly, modeling estimates of far-field concentrations could be considered as indicators of ONU's exposures.

Consumer Exposure

Consumer exposure estimates were developed for the conditions of use for inhalation and dermal exposures to consumers. EPA performed systematic review, collected data from available sources and conducted modeling for estimating consumer inhalation and dermal exposures using the Consumer Exposure Model (CEM) Version 2.1.

Product specific consumer monitoring information was not identified during the systematic review process, therefore, model inputs related to consumer use patterns (duration of use, mass of product used, room of use, and similar inputs) are based on a data from a comprehensive national survey 1987 as described and referenced within the TCE draft risk evaluation. The age, reliability, representativeness, and uncertainty of this survey is discussed in Sections 2.3.2.4.1, 2.3.2.5, 2.3.2.5.1, 2.3.2.6.1, 2.3.2.6.2, 2.3.2.7.1, 2.3.2.7.2, and 2.3.2.8. Weight fractions of chemical within products are based on product-specific safety data sheets (SDS). Default values utilized within the models are based on literature reviewed as part of model development as well as EPA's Exposure Factors Handbook.

<i>Q 4.7</i>	<i>Please comment on the appropriateness of the approaches, models, exposure or use information and overall characterization of consumer inhalation and dermal exposures for users and bystanders for each of the identified conditions of use. What other additional information, or approaches, if any, should be considered (Section 2.3.2)?</i>
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Response to Q4.7: Characterization of consumer inhalation and user and bystander dermal exposures by COU.

Recommendation 54: Include a more detailed description of the process used for identifying consumer COUs and trichloroethylene-containing products.

The Committee concluded that there is insufficient description about the process used for identifying consumer COUs and products containing trichloroethylene. One member of the Committee noted that the Evaluation is clear in explaining differences between COU categories and products identified in the Evaluation and those identified in the Problem Formulation (U.S. EPA, 2018). The Evaluation references the Use and Market Report and Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: TCE (U.S. EPA, 2017c), but the report does not describe how specific consumer products were identified. The Evaluation does not describe in enough detail and specificity how comprehensive and systematic the search was for this information. On page 142, lines 1862-1864, the Evaluation states: "Additional online research was undertaken following Problem Formulation to confirm trichloroethylene concentrations and compile a comprehensive list of products that may be available to consumers for household use." What kind of "online research" was performed? Similarly, on page 179 (Evaluation, lines 2960-2962) the statement: "Additional sources of product information were evaluated, including the

NIH Household Product Survey and EPA's Chemical and Products Database (CPDat), as well as available product labels and safety data sheets (SDSs)" does not provide enough details to know how comprehensive and systematic the search was. It should also be noted that the NIH Household Product Survey is no longer maintained by the NIH.

Recommendation 55: Review current uses of the 33 reported commercial, industrial, and consumer COUs and identify all the trichloroethylene-containing products for each of the consumer use scenarios.

Recommendation 56: Clarify whether consumer paints and coatings no longer contain trichloroethylene.

As mentioned previously, it is not clear when the Use and Market Report and Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: TCE was updated. U.S. EPA (2017c) refers to the U.S. EPA, 2014, but is also not clear if U.S. EPA (2014) is reflective of likely market changes since the significant new use rule³ (SNUR) on consumer uses for trichloroethylene was implemented as well as the proposed rules for the ban of aerosol and vapor degreasing. For example, the hoof polish product appears to have been reformulated and is now listed as being extremely flammable on the manufacturer's website.

Based upon a review of the 33 reported commercial, industrial, and, consumer products listed in the Market and Use Report, 17 appear valid, 2 appear to no longer exist, and 13 are unclear as to current status. In addition, there are products that have not been discussed (captured) in the Evaluation. For example, the previously cited hoof polish product now is labeled as 'extremely flammable' and has likely been reformulated, and Berryman Products appears to have products formulated with trichloroethylene (www.berrymanproducts.com).

It is unclear if the IRTA (2007) report is a good proxy for trichloroethylene-based spot remover, as the trichloroethylene product was prohibited by California Air Resources Board (CARB 2019) for that use in 2012.⁴ Additional products may have also been reformulated in part due to California Proposition 65. Another Committee member noted that a surrogate product is used for film cleaner and toner aid use scenarios, but a simple Google internet search reveals the commercial availability of trichloroethylene-containing film cleaners (i.e., brands such as Edwal, Tetenal, etc.) both in liquid and spray forms, and toner aid (e.g., brand Sprayway; SDS on line; see example: <http://www.spraywayinc.com/content/toner-aide>).

Another Committee member indicated that there should be a clarification on whether consumer paints and coatings, unlike industrial paints and coatings, no longer contain trichloroethylene to justify the exclusion of painting scenarios for consumers.

³ See <https://www.federalregister.gov/documents/2016/04/08/2016-08152/trichloroethylene-significant-new-use-rule>

⁴ See ww3.arb.ca.gov/consprod/regs/2019/regs-all_final_5_2019.pdf (Table 94509(m)(1) Product Categories in which Use of Methylene Chloride, Perchloroethylene, and Trichloroethylene is Prohibited)

A Committee member noted that the NIH Household Product Survey is no longer maintained by the NIH, and wondered what steps are being taken going forward to ensure that products are identified in a systematic and comprehensive manner.

The Committee agreed that the use of modeling for characterizing consumer inhalation and dermal exposures is appropriate because exposure measurement data for consumer products use are lacking. However, the Committee noted several areas that require additional consideration and clarification in order to support the characterization of trichloroethylene risk to consumers.

Recommendation 57: Consider developing CEM exposure estimates for bystanders present in Zone 1 for scenarios where it is likely that the bystander could be in the same room as the user.

Reservations were expressed about the consumer exposure model (CEM). Most of the concerns expressed by the Committee were about the inputs (e.g., product emissions, other parameters, etc.) to the CEM, while only a couple of issues related to the conceptual model itself were raised.

With respect to model structure, members of the Committee were concerned about the assumption that bystanders remain in Zone 2 while the product is in use, without providing adequate justification for this assumption, which could result in underestimation of bystander exposures. This concern has been raised in prior chemical reviews by this Committee. One Committee member suggested that bystanders should be treated similarly to how ONUs are treated in the occupational exposure scenarios. This Committee member was unclear why “near-field” and “far-field” zone assumptions could not be applied to consumer users and bystanders in the same room (i.e., in addition to the alternative of assuming the zones correspond to two separate rooms).

Recommendation 58: Consider updating the Westat survey data (U.S. EPA, 1987) to verify that use patterns and building-related parameters reflect current consumer use patterns and housing construction.

With respect to model inputs, the Committee was unanimous in their opinion that at least some consumer use patterns are likely to have changed since the Westat survey (U.S. EPA, 1987) data were collected, about 30 years ago from the present time. The Committee has made this same comment in prior TSCA chemical reviews. The size of homes has also changed in the last few decades with a trend to larger homes and more open floor designs, as well as a trend to increasingly tighter structures that may affect air exchange rates.

Recommendation 59: Reexamine the pepper spray use scenario.

Committee members indicated that it is unclear whether any of the pepper spray products remain available in the consumer market. The Evaluation (Page 148, footnote 12 in Table 2-28) notes that “Based on EPA/Economic and Policy Analysis Branch research that found one spray from the most common civilian canister is estimated to be approximately 0.0216-0.108 ounces (based on a pepper spray manufacturer’s website). Spraying occurred between 3 and 5 seconds (converted to minutes for use in modeling) before obtaining desired effect.” It is not clear what efforts were

taken to ensure the scenario is reflective of actual usage. EPA needs to verify and/or determine the concentration of the existing pepper spray products, and review if this and other product use patterns appear reasonable.

Another Committee member considered the assumption of only one gun in the gun scrubber use scenario not well justified and not sufficiently conservative.

Recommendation 60: Characterize trichloroethylene chronic risk for consumers.

The Committee disagreed with EPA's decision not to characterize chronic risks for consumers on the basis that (Evaluation, page 279, lines 393-401):

“In general, the frequency of product use was considered to be too low to create chronic risk concerns. Although Westat (U.S. EPA, 1987) survey data indicate that use frequencies for high-end product users (i.e., those reflecting 95th percentile annual use frequencies) may use products up to 50 times per year, available toxicological data is based on either single or continuous trichloroethylene exposure and it is unknown whether these use patterns are expected to be clustered or intermittent (e.g. one time per week). There is uncertainty regarding the extrapolation from continuous studies in animals to the case of repeated intermittent human exposures.”

Several Committee members suggested that some consumers are likely to be exposed more frequently and more pervasively to emissions from these products than indicated by the Westat survey data (U.S. EPA, 1987). Firstly, certain high-exposed consumers (hobbyists, home businesses, etc.) are likely to use more than one trichloroethylene-containing product on the same day and/or multiple and consecutive days. Secondly, the Westat survey was unlikely to capture the true distribution of use frequency for high-end users (i.e., oversampling these subpopulations would have been required to obtain a reliable estimate of use patterns for these individuals). Thirdly, it is likely that contributions to indoor air concentrations (and, therefore, exposures) persist for longer periods of time than assumed by EPA from sources such as carpet spot cleaners and fabric sprays (see also, for example, Doucette et al., 2018; Gorder and Dettenmaier, 2011).

Recommendation 61: Use other trichloroethylene exposure sources in addition to those from trichloroethylene-containing products to characterize consumer risks.

Not including exposures from sources such as drinking water results in underestimates of risk. Trichloroethylene is a well-known groundwater contaminant and many homes rely on well water, which may not be adequately or routinely tested for trichloroethylene presence. EPA mentions exclusion of other contributors to trichloroethylene indoor concentrations as a source of uncertainty in the risk characterization for consumers, but this is an uncertainty that could be addressed. One Committee member suggested that the Evaluation could better characterize consumer risks by using an upper percentile of the residential exposures reported in the general population studies cited in the Evaluation.

Recommendation 62: Consider aggregating dermal and inhalation exposures for consumer users when simultaneous exposures by both routes are expected. (See also Recommendation 49)

There were different opinions expressed by Committee members about aggregation of dermal and inhalation exposures. Some Committee members noted that exposures by both routes should be aggregated in all scenarios. One member noted that aggregating dermal and inhalation exposure in all cases is not warranted because if there is dermal exposure, there is almost certainly inhalation exposure, but the converse is not necessarily always true.

Recommendation 63: Clarify how the results of uncertainty analysis are used in the characterization of consumer risk, and consider performing a more comprehensive uncertainty analysis (i.e., varying parameters instead of using defaults, for example).

The Committee was unclear about how the results of the limited (i.e., only some inputs were varied) uncertainty analysis were incorporated into the risk characterization. It is also unclear why a more comprehensive uncertainty analysis was not performed.

Q 4.8	Please recommend any additional data sources or studies that may be more reflective of current consumer use patterns for specific conditions of use (Section 2.3.2).
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Response to Q4.8: Additional data on consumer use patterns by COU.

Recommendation 64: Consider exploring the wealth of information available in the internet on DIY, hobbies, and home-based production of items for sale to get more data on products used by consumers who are likely high-frequency users.

The Committee could not identify additional sources of data for specific conditions of use and was not aware of any specific databases. However, it is likely that the Evaluation underestimates risk for the fraction of the population engaged in do-it-yourself (DIY) activities, hobbies, and small scale, home-based production of items for sale, which have expanded over time. It is also possible some of these activities involve use of industrial products. Although the Committee is not aware of specific databases, there is a trove of information on these types of activities on the internet that could be mined to obtain information about the products being used. Some of the large general population exposure assessment studies that are cited in the Evaluation also administered questionnaires about residential activity patterns and the use of some types of products. This literature could be explored to obtain information on product type use, though not specific products.

Recommendation 65: Scrutinize the products included in the ATSDR (2019) ToxProfile for trichloroethylene content or reformulation.

A member of the Committee indicated that the Agency for Toxic Substances and Disease Registry (ATSDR) ToxProfile for trichloroethylene (ATSDR, 2019) includes more trichloroethylene-containing household products, such as typewriter correction fluid. People are not using typewriters very often now, but students still use similar fluids to correct printed or handwritten text. ATSDR also includes drain cleaners, spray paint and paint strippers as uses, and they should be considered. Some of the uses included by ATSDR may have been consolidated for this Evaluation into fewer COUs or may not be used anymore, like VCR cleaners, which may either have not been included in this Evaluation or have been included with other electronics cleaners. Some of these uses are probably obsolete, since trichloroethylene has been included on California's Proposition 65 list since 1988. Since then, many products have been reformulated with other solvents; for example, Liquid Paper reformulated correction fluids some time ago to avoid labeling for Proposition 65. Nonetheless, it is not clear in the Evaluation whether all products included in the ToxProfile underwent careful scrutiny (revalidation) by EPA.

One Committee member suggested including trichloroethylene inhalant as a consumer exposure. However, other members indicated that intentional misuse of products is not considered a COU under TSCA.

Q 4.9	Dermal exposure was evaluated using the permeability sub-model (P_DER2b) within CEM Version 2.1. Please comment on the suitability and use of this modeling approach for this evaluation. Please provide any suggestions or recommendations for alternative approaches, dermal methods, models or other information which may guide EPA in developing and refining the dermal exposure estimates (Section 2.3.2.4.1).
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Response to Q4.9: Suitability and use of permeability sub-model in dermal exposure estimation.

Recommendation 66: Discuss skin damage from contact with trichloroethylene and how it affects skin permeability to trichloroethylene.

The Committee expressed concerns about the suitability of the permeability sub-model (P_DER2b). For consumer exposure to liquid trichloroethylene, EPA is using a permeability coefficient approach. EPA has selected a permeability coefficient published by Poet et al. (2000) and derived from fitting of a PBPK model. Two issues arise with respect to this modeling approach. The first is that PBPK models typically treat skin as a well-mixed compartment rather than as a membrane. Because the underlying mathematics is different, the numerical value of the coefficient can be affected (see Norman et al., 2008). The second issue with a PBPK approach is that such models represent multi-variable fitting exercises. Due to compensating errors, good fits can be achieved by poor estimates of more than one parameter. For these reasons, parameter values obtained from PBPK fitting should be checked against values obtained by other means. In this case, the permeability coefficient obtained from Poet et al. (2000) does not appear unreasonable for absorption from aqueous media.

However, the Evaluation pairs an aqueous phase permeability coefficient with the concentration of the neat liquid. This approach is invalid. The maximum concentration that can legitimately be paired with an aqueous phase permeability coefficient is that of the saturation concentration in water. Barring skin damage by the pure solvent, this should result in an overestimate of the maximum flux (and hence absorbed dermal dose).

Recommendation 67: Estimate dermal exposure to neat liquid trichloroethylene using experimental *in vivo* human data described in Table 5.

Since trichloroethylene is known to cause dermatitis (Hudson and Dotson (2017) cited in the Evaluation), which implies skin barrier damage, data that reflect exposure to neat trichloroethylene are needed. Morgan et al. (1991) have published *in vivo* rat data describing dermal absorption of both saturated aqueous solution and neat trichloroethylene. Based on peak blood concentration at 2 hours, rat skin appears to be about 25 times more permeable when challenged with neat trichloroethylene than with saturated aqueous solution. This is evidence that trichloroethylene does damage the skin barrier in mammals. *In vivo* exposures of humans to neat trichloroethylene have been reported by Stewart and Dodd (1964), Sato and Nakajima (1978) and Kezic et al. (2001). These results are summarized in Table 5. Maximum flux observed in these experiments does substantially exceed the maximum flux estimable from the Poet et al. (2000) permeability coefficient. This is consistent with the interpretation of the Morgan et al. (1991) rat study. The conclusion that should be drawn is that the best estimate of permeation expected from direct human exposure to neat trichloroethylene would be an approximation based on the results described in Table 5.

Table 5. Selected human *in vivo* experiments in which skin was challenged with neat TCE.

Reference	Date	Skin location	Estimated skin area exposed cm ²	Exposure duration min	Estimated average flux µg/cm ² ·h
Stewart & Dodd ^a	1964	thumb	40	30	>150
Sato & Nakajima ^b	1978	hand	500	30	900
Kezic et al. ^c	2001	volar forearm	3	1	3400

^a Based on graphical interpretation of tabulated (5 h) breath series only. Urinary metabolites not reported.

^b Based on tabulated cumulative (180 h) urinary excretion plus graphical interpretation of tabulated (10 h) breath series.

^c Flux estimate reported by authors based on fitting breath data only.

Recommendation 68: Provide a justification for the assumption that 10% of the skin surface will be exposed for consumer product users.

A member of the Committee mentioned that there is no justification provided for the assumption that 10% of the hand skin will be exposed in the consumer use scenarios.

<i>Q 4.10</i>	Please comment on EPA’s approach to characterizing the strengths, limitations and overall confidence for each consumer exposure scenario presented in Section 2.3.2. Please comment on the appropriateness of the confidence ratings for each scenario. Please also comment on EPA’s approach for characterizing the uncertainties summarized in Section 2.3.2.7.
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Response to Q4.10: Characterization of strengths, limitations, confidence of consumer exposures by scenario.

Recommendation 69: Provide more detail on the confidence ratings used in the tables for inhalation and dermal exposures.

Committee members liked the framework of variability and uncertainty for presenting strengths and limitations in risk characterization estimates for consumers. However, as with risk characterizations in previous TSCA chemical evaluations, it is unclear how the final confidence levels are derived. The confidence summaries presented in Tables 2-71 and 2-72 are useful and a step forward in the transparent display of confidence ratings for the major components of the risk characterization (i.e., confidence in the model, confidence in default and other parameters, etc.) and overall confidence. However, the footnotes in these tables are not enough to clarify the process that leads to a high, moderate or low confidence for each specific component of the risk characterization and consumer use in these tables. The footnotes do not provide enough detail in this regard.

One Committee member also noted that statements such as:

“The exposure durations modeled could exceed the duration of such dermal contact, therefore, the higher-end durations may result in an overestimation of dermal exposure”
(Evaluation page 153, lines 2145-2146)

should acknowledge the possibility of underestimation unless a specific reason is provided for why the potential error is one-sided.

Question 5: Human Health Hazard:

For hazard identification and dose-response, EPA reviewed the evidence for TCE toxicity and selected liver toxicity, kidney toxicity, reproductive toxicity, developmental toxicity, neurotoxicity, immunotoxicity, and cancer, that taken as a whole, demonstrated the most robust, sensitive and consistent adverse human health effects for risk characterization. EPA used benchmark dose (BMD) modeling where practicable and, when BMD values were adequate, they were used to generate the Point of Departure (POD) for characterizing acute and chronic exposure scenarios.

Non-Cancer

<i>Q 5.1</i>	<i>EPA performed a weight of evidence assessment for the endpoint of developmental cardiac defects based on available epidemiological, <i>in vivo</i> animal, and mechanistic data. EPA concluded that the available literature supported positive overall evidence that TCE may produce cardiac effects in humans (Section 3.2.4.1.6 and Appendix G.2); however cardiac defects after developmental exposure were not observed consistently across the available <i>in vivo</i> animal studies. The Charles River dissection methodology differed from Johnson et. al. (2003), resulting in reduced sensitivity to the full range of cardiac defects compared to Johnson et al. (2003) and other studies. Therefore, EPA concluded that the Charles River study did not adequately recapitulate the methodology of the Johnson et al. (2003) study. Please comment on EPA’s Weight of Evidence (WOE) analysis approach and conclusions for this endpoint, including EPA’s analysis of the Charles River (2019) and Dawson (1993)/Johnson (2003) studies.</i>
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Response to Q5.1: WOE analysis approach and conclusions for cardiac effects in humans.

There was a lengthy discussion of the cardiac effects studies and differences of opinion expressed by Committee members concerning the adequacy of the Dawson/Johnson and the Charles Rivers studies. It was apparent to the Committee that the EPA places significant weight on the Dawson et al. (1990, 1993) and Johnson et al. (2003) studies in its weight of evidence (WOE) analysis, even though these studies have several significant problems in their design and execution despite being scored as of medium quality. Johnson et al. (2003) reports results using pooled data for controls and treatment groups from the multiple studies conducted over six years. Johnson et al. (2003) has inadequate reporting of methods used. Use of non-concurrent, pooled controls per the TSCA scoring definition for this metric meets the TSCA definition of “Unacceptable for Risk Assessment.” The earlier studies from this laboratory also met the definition of unacceptable. Having even one study quality metric rating of “Unacceptable for Risk Assessment” meets TSCA definition for overall rating of “Unacceptable for Risk Assessment.” Some of the Committee members felt the Johnson et al. (2003) study lacked credibility and should not be relied upon by the EPA.

Members of the Committee recognized that the results of the Dawson/Johnson experiments were obtained in one laboratory and have not been replicated in another *in vivo* mammalian study. Dr. Paula Johnson participated in a subsequent investigation by Fisher et al. (2001) to score slides and assure the same cardiac dissection technique was used as in the prior studies. No anomalies were found in the heart of offspring of these rats given multiple high doses of trichloroethylene, trichloroacetic acid (TCA) or dichloroacetic acid (DCA) during pregnancy. The negative findings of this oral bolus assay were supported by the GLP drinking water study by Charles River Laboratories (2019). These results were published by DeSesso et al. (2019). EPA discounts these findings by saying in lines 1298-1300 that they failed to describe defects “though many other published reports have identified valve defects following administration of TCE.” What are the other reports beyond those from the laboratory of Dawson/Johnson? DeSesso et al. (2019) followed EPA guidelines for dissection methods and was scored as high quality. Even so, it was downgraded to a medium quality study based on the conclusion that the dissection methodology was insufficiently sensitive to identify all possible cardiac defects. Thus, the pooled Dawson et al. (1990, 1993) and Johnson et al. (2003) experiments conducted over six years and meeting TSCA criteria as unacceptable for risk assessment was scored as medium quality, as was the GLP study with large sample sizes by DeSesso et al. (2019).

Recommendation 70: Multiple *in vivo* animal trichloroethylene inhalation studies reporting no heart defects need more consideration in the WOE analysis of animal data.

Cardiac developmental anomalies have not been described in any of six trichloroethylene inhalation studies in rodents. Patterns in available developmental inhalation studies should be searched/assessed for specific endpoints to determine coherence. Particular attention should be paid to the study by Carney et al. (2006) that reported no evidence of heart defects in progeny of dams exposed to as high as 600 ppm trichloroethylene vapor 6 hours/day, 7 days/week during gestation. Several Committee members opined that the Evaluation needs to consider the findings in this focused investigation in its WOE analysis, as well as others by Beliles et al. (1980), Cosby and Dukelow (1992), and Narotsky et al. (1995). As there is no explanation for omission of negative results of inhalation studies, this may have been an oversight or possibly a result of bias.

Watson et al. (2006) published an analysis of information pertinent to induction of cardiac defects by trichloroethylene. They concluded there was not a causal association between trichloroethylene exposure at environmentally relevant concentrations and congenital heart defects.

Committee members concurred that the search for patterns in the toxicological literature for specific endpoints is useful in determining coherence. Pathway of exposure is relevant for combining factors of absorption, disposition, metabolism, and excretion, which affect target tissue dose of parent compound and metabolites. When PODs are markedly different for the same endpoint, it is useful to search for possible explanations. Often there are sound biological reasons for discrepancies (differences in study design, evidence of a specific endpoint not investigated by others), though sometimes they are due to chance (e.g., outliers due to Type I or Type II error). For this Evaluation, it appears data for the inhalation route would be preferred because inhalation exposures are most relevant to COUs. As a result, findings from studies based on the inhalation

route of exposure offer less uncertainty on POD estimates. PBPK models are useful; however, they do add uncertainty when conducting route-to-route extrapolation; hence, data from inhalation exposures and oral exposures are not equivalent. There are several high-quality developmental studies conducted with inhalation exposures. It is recommended that the Evaluation focus on these (but not ignore the oral studies).

Recommendation 71: Reconsider the scores assigned to the epidemiological evidence for trichloroethylene-induced cardiac anomalies.

Epidemiological data, showing suggestive evidence of an association between trichloroethylene exposure and cardiac effects in offspring, were judged to be weak by several Committee members. None of the three studies (Brender et al., 2014; Forand et al., 2012; Wright et al., 2017) utilized by the EPA accounted for the residential location of the mothers during the critical period for cardiac development (3rd to 8th week of pregnancy) or had trichloroethylene exposure data for the study population. The Evaluation states that together the studies show suggestive evidence for an association between maternal trichloroethylene exposure and cardiac effects in offspring (a summary score of '+'). Because the investigators in the three studies did not know the residential location of the subject women during the critical time period for cardiac effects (3rd to the 8th week of pregnancy, page 216) or had trichloroethylene exposure concentration data, the associations were not persuasive. Instead, they all used the maternal location at the time of birth. Forand et al. (2012) stated that other studies have shown 22-32% of women move between conception and delivery. Brender et al. (2014) used air emission data (not ambient air monitoring concentrations) for 14 solvents (including trichloroethylene) to estimate chemical exposures at maternal addresses at the time of delivery from 1996-2008. This study received '+' for reliability, '+' for strength, and '++' for relevance by EPA, however, the Committee judged these ratings as exceeding the merits of the study. Forand et al. (2012) looked at an area with presumed trichloroethylene and tetrachloroethylene vapor intrusion exposure for residences at birth. This was a small study with only 15 cases of all cardiac defects combined. Wright et al. (2017) examined cardiac birth defects and exposure to disinfection byproducts (DBPs) in water. The authors averaged first-trimester disinfection byproducts (DBP) exposure across all sample locations within a public water system based on zip code of residence at time of birth. Section G.2.2 states that the study scored only '+' for relevance, because the DBPs may also have originated from a different source. The degradants in the study originated from the disinfection of drinking water. DCA and TCA are DBPs regulated by EPA in drinking water as part of the haloacetic acid (HAA5⁵) maximum contaminant level (MCL). This study received '++' for reliability, '+' for strength, and '+' for relevance.

Relevance, as used in this WOE Ecological Assessment, was a measure of the degree of extrapolation that would be needed to use the data in question for developing a toxicity value. The Evaluation states that all usable studies (except Wright et al., 2017) were rated '++' for relevance, because they examined exposure of humans to trichloroethylene, although via indirect

⁵ Group of five haloacetic acids (dibromoacetic acid, dichloroacetic acid, monobromoacetic acid, monochloroacetic acid, and trichloroacetic acid)

quantitation. To some Committee members, the automatic ‘++’ scores for relevance of studies appeared to be too high. They felt that it would be difficult to use the data from any of the three studies in question to develop a toxicity value, even though animal to human extrapolation is not needed.

Recommendation 72: Improve the discussion on the MOA for trichloroethylene-induced fetal cardiac defects and identify gaps in the AOP that need to be filled.

The EPA’s WOE approach in scoring evidence for cardiac defects was judged by the Committee to be overly simplistic and problematic, in that it gave more weight to incomplete mechanistic data than to *in vivo* animal evidence. Mechanistic data are valuable in understanding modes of action and assessing biological plausibility. These data, however, are limited for trichloroethylene in that they primarily involve enzymes and gene induction. Metabolomic and proteomic evidence was not described. The evaluation did not integrate and organize the mechanistic data into a coherent causal pathway from initial exposure to adverse outcome. The mode of action (MOA) narrative in the risk evaluation proposes several hypotheses for potential modes of action but concludes that the evidence to date does not identify a specific MOA. Why then are mechanistic studies assign a score of ‘++’ in view of limited information and no apparent/likely mechanism? The use of high-dose experiments in *in vitro* and avian systems limit their relevance to assessing risks of environmental trichloroethylene exposures.

Recommendation 73: Revise the WOE to integrate strength and relevance of all *in vivo* animal and epidemiological study findings with available mechanistic evidence.

It appeared to the Committee that the WOE assessment and the systematic review process used two different rating systems, despite having overlap in their goals and methods. Figure 3.3, which is the same in all the TSCA chemical evaluation documents the Committee has reviewed to date, explains that data interpretation is part of the systematic review process. This suggests that the Evaluation should not need a separate WOE method and the WOE discussion should be considered part of the scoring and integration components of the systematic review. The systematic review appropriate for dose-response would be included.

The Committee discussed the issues with the Johnson et al. (2003) investigation that the Evaluation uses to preclude reliance on it in the current risk assessment. The Committee recognized that no systematic review or WOE analysis can definitively answer the question of whether the issues with this study are severe enough to disallow its use in setting a non-cancer POD. Reasonable scientists have differed on this, and two reviews came to opposite conclusions. Wikoff et al (2018) reviewed Johnson et al. and determined it was “not sufficiently reliable for the development of toxicity reference values.” Makris et al. (2016) reviewed all the evidence for developmental cardiac effects and determined that Johnson et al. (2003) is “suitable for hazard characterization and reference value derivation.”

Several Committee members commented that Johnson et al. (2003) reported adverse cardiac effects at trichloroethylene exposure levels that were orders of magnitude lower than no-effect

levels of other investigators. One Committee member observed that the lowest dose of thalidomide known to induce birth defects is 1 mg/kg, far higher than the Johnson et al. (2003) Lowest Observed Adverse Effects Level (LOAEL). Other Committee members expressed their opinion that it seems premature to completely dismiss Johnson et al., given that there are cardiac malformations (1-2 per 1,000) in humans that are of unknown etiology. The chemical lead was offered as an example where relatively high levels can be deposited in maternal bone during pregnancy, yet nanogram concentrations reaching the fetal brain can be impactful. Another Committee member opined that EPA came to an appropriate conclusion after assessing the strengths and weaknesses of the Dawson/Johnson studies. Another member felt that it might not be possible to reach consensus, and that it may be more practical instead to use immunotoxicity results to select acute and chronic non-cancer PODs.

Q 5.2	Please comment on the assumptions, strengths and weaknesses of the dose-response approaches used to estimate the non-cancer risks to workers, occupational non-users, and consumers. Please also comment on whether EPA sufficiently justified its selections of BMRs for BMD modeling results and uncertainty factor values in deriving the PODs and benchmark margin of exposures (MOEs) (Sections 3.2.5.3.2 and 3.2.5.3.3). As part of this discussion, please comment on EPA’s justification for selecting a 1% BMR for the cardiac malformation endpoint based on the severity of the endpoint (i.e. potential mortality).
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Response to Q5.2: Characteristics of dose response approaches in estimating non-cancer risks to workers, ONUs and consumers.

Other than specific comments on fetal cardiac defects (covered in Charge Question 5.1) and immunotoxicity (covered in Charge Question 5.3), the Committee was generally in agreement that the assumptions and approaches used to evaluate non-cancer endpoints were sound and appropriate.

Several studies are used to calculate BMDL₁₀ or BMDL_{0.5} values for kidney toxicity, using either nephropathy or increased kidney weight as indices of adverse effect. BMDL₁₀ values are all within approximately a twofold range of each other (16 – 40 ppm), demonstrating good consistency. The BMDL_{0.5} is calculated for the study measuring nephropathy as the adverse effect rather than increased relative kidney weight. The rationale for this relates to the more serious nature of the nephropathy effect, which represents sound and standard reasoning. The Committee was unclear of the meaning of the justification of “confounding mortality” used to score the NCI (1976) female study on kidney endpoint as unacceptable (Page 211, lines 775-6).

Multiple studies are used to calculate POD values based on LOAELs from neurotoxicity. A rat and a human study gave almost identical LOAEL values (12 and 14 ppm, respectively). Similarly, POD values based on LOAELs are calculated for immunotoxicity, using thymus effects,

autoimmunity, and immunosuppression. A BMDL₁₀ value of 24.9 ppm is also calculated for immunosuppression based on data in female Sprague Dawley rats in Woolhiser et al. (2006).

POD or BMDL₁₀ values were calculated for reproductive effects, considering those in males and females separately. While one of the lowest BMDL₁₀ values (1.4 ppm) is derived for effects on sperm morphology and numbers from a human study, considerably higher values are calculated from studies in rats.

For female reproductive effects, only two studies are cited, and one reported a LOAEL value. However, several studies are missing; this will be discussed in response to Question 5.7.

Recommendation 74: Provide better justification or reference policy to support the choice of BMR used in computing the BMDL.

Selecting a Benchmark Response (BMR) level and computing the associated Benchmark Dose (BMD) value is a multistep process starting with the selection of critical studies. For the most part, the current document simply recapitulated the selections made in the 2011 EPA IRIS report (U.S. EPA, 2011e). There is always a judgment call relative to how much information to provide directly in a document versus how much to provide simply by reference to the earlier document. With respect to selection of the critical effect and study, the selections themselves were appropriate and the text supporting the selection is adequate.

The critical judgment relative to this process is to select which BMR level (Evaluation page 239) to use as the POD – 10%, 5% or 1%. For liver, kidney and male reproductive effects, 10% levels are used; the 1% level is used for the congenital heart defect and immunotoxicity. The extent to which this is driven by EPA policy should be explained in the document. In previous experience on TSCA Committees, 5% and 10% response levels are often selected. Is this consistent with EPA policy? Is this simply selected because the effect is potentially lethal? One could note that liver and/or kidney toxicity are also potentially lethal. A 1% response level could be supported, but more explanation is needed to ensure full transparency for the basis for this selection. It certainly is conservative and health-protective, as is the use of 99th percentile estimates of the Human Equivalent Concentration (HEC₉₉) or Human Equivalent Dose (HED₉₉). Critically important, is a clear and transparent substantiation of the use of a 1% response level and a cumulative acute uncertainty factor of 10 (interspecies uncertainty factor, UF_A=3 (i.e., extrapolating from laboratory animals to humans) and intraspecies uncertainty factor, UF_H=3 (i.e., human (intraspecies) variability)). Should not one of these be reduced to 1.0 based on the highly conservative nature inherent in use of a BMDL-0.01 level? These decisions are based on scientific judgment but require more comprehensive justification.

Other than these issues (relative to 1% response levels and a subchronic to chronic UF_S of 3), the MOE selections and the discussion of same are adequate. It appears that standard processes are used to select the specific uncertainty factors that are used to calculate the ultimate MOE and the text describing their selection is clear, consistent with the state of the art, and are transparent.

Recommendation 75: Better discuss/justify the selection of each selected dose metric.

Conversion of the animal POD to HEC or HED requires multiple assumptions. A fundamental decision, however, in the HEC and HED calculations is the selection of the appropriate dose metric. The text lacks transparency relative to the basis for selection of dose metrics, and a number of questions remain to be answered. For example, how strong is the evidence that liver effects are driven by a metabolite? Is it merely that early studies show diminution of hepatic effect with a Cytochrome P450 (CYP) inhibitor and enhancement with CYP inducers? Is this evidence particularly strong? Does this evidence clearly indicate it is an oxidative CYP metabolite versus some other pathway? This might be a relatively straightforward discussion relative to the liver. However, the basis for this assumption relative to neurotoxicity, male reproductive toxicity, or congenital heart defects (only oxidative, not total metabolism?) is not clear. The short, vague statements in the text such as evidence suggests a metabolite important or the like, lacks detail and, therefore, lacks adequate transparency. An enhanced discussion should be provided in the text and in the uncertainty discussions. For example, if a single metabolite is responsible for an effect, is it truly best to use total metabolite as the dose metric? Would that not introduce more uncertainty than using parent compound, for example? What if the critical metabolite is a minor metabolite and the TotMetabBW34 (PBPK parameter measuring total amount of trichloroethylene metabolized per unit adjusted bodyweight; Evaluation, page 238, line 2035) is overwhelmed by non-relevant metabolites? In estimating exposure, one Committee member suggested that the Evaluation might look to using the PBPK model as a more scientific approach to extrapolating long-term (chronic) exposures from short-term (acute) exposure data than extrapolating using Haber's Law that simply multiplies the exposure concentration (c) by the duration time (t) of exposure.

There was more concern, however, for the evaluation of liver toxicity. For increased liver weight, the Evaluation summarizes three studies, and a BMDL₁₀ value is calculated from each study. Two of the studies (Kjellstrand et al., 1983 and Buben and O'Flaherty, 1985) in two strains of male mice yielded BMDL₁₀ values of 21.6 ppm and 82 mg/kg, bw/day, respectively. A third study in female rats (Woolhiser et al., 2006) gave a BMDL₁₀ value of 25 ppm. The Evaluation excluded the Woolhiser et al. study from further consideration because increased liver weight is observed, but no other indications of toxicity. This decision is made despite an almost identical BMDL₁₀ value between it and the Kjellstrand et al. study. The rationale that the Kjellstrand et al. study encompassed a wider range of doses, and is thus a higher quality study, is reasonable, but the conclusion that the increased liver weight observed in Woolhiser et al. is an adaptive response rather than an indicator of toxicity, needs better support and seems speculative. On line 2110, page 240: "kidney" needs to be changed to "liver."

What inhaled concentration in the study by Kjellstrand et al. (1983) is used in the Evaluation to calculate its POD? It is difficult to tell from the publication what the No Observed Adverse Effect Level (NOAEL) and/or LOAEL were for increased liver weight. It appears that 75 ppm is the LOAEL for liver weight, but 150 ppm is required to cause cytoplasmic vacuolation. It is not clear whether the vacuolation is due to lipid, glycogen or water accumulation. Any of these could contribute to increased liver weight, which is said in line 2115 to be "merely adaptive," as

opposed to cytotoxic. The fine vacuolation is shown to be reversible by the researchers.

Finally, even if the human health hazard with liver as an endpoint is correctly described, it is important to consider susceptible populations for liver endpoints, especially individuals with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH) because a large proportion (>30%) of the general population is obese or overweight.⁶ This may change the toxicokinetics of trichloroethylene, as large amounts of fat will be present in the liver.

For cardiac malformations as a developmental effect of trichloroethylene exposure, a BMDL₀₁ value is calculated based on the seriousness of this adverse effect. While the explanation for using a 1% level is clear and agrees with standard practice, the use of these data from the Johnson et al. (2003) raised concerns (see above) due to issues with the experimental design and replication problems.

EPA determined that the immune effects from Selgrade and Gilmour (2010) represent the best representative dataset to use for evaluating acute effects and the autoimmunity effects from Keil et al (2009) represent the best data set to use for evaluating chronic non-cancer effects (Section 3.2.6.4).

Q 5.3 a	Please comment on EPA's selection of these studies as the best representative endpoints, including consideration of the POD derivation and benchmark MOEs.
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Response to Q5.3a: POD derivation and benchmark MOEs for non-cancer effects.

Recommendation 76: Consider separating indicators of immune-enhancement and immunosuppression and discuss how these indicators reflect different modes of action.

In general, the Committee agreed with the selection of these studies, with caveats to follow. Despite its quality, it was pointed out that Selgrade and Gilmour (2010) has not been validated, and that there is a suggestion of support given that the chronic endpoint is also immunotoxicity. Based on the difference in mechanisms between these acute and chronic effects, the Evaluation should be especially careful not to suggest some false equivalence. The Evaluation states that in general, immunotoxic effects in animals and humans were associated with an enhanced immune response rather than an immunosuppressive effect (Evaluation, page 212, lines 839-840). However, the first paragraph on animal data (Evaluation, page 213, lines 872-880) suggest support for immunotoxicity is provided by decreased thymus weight and cellularity in mice, although the cellularity effect is not significant (Keil et al. 2009). The Committee recommended

⁶ According to NIH/NIDDK web page 2 of 3 US adults are overweight or obese. <http://niddk.nih.gov/health-information/health-statistics/overweight-obesity>

the Evaluation not put indicators of immune-enhancement and immunosuppression in the same category and think more about mode of action where these processes and indicators are different.

Selgrade and Gilmour (2010) demonstrated induced immunosuppression through susceptibility to infection, which is a functional endpoint with clinical significance. In the context of supportive studies showing induction of autoimmunity, this study provides dose-response data that serve as a robust basis of POD derivation. Selgrade and Gilmour (2010) tested whether a single 3-hour inhalation exposure to trichloroethylene (or chloroform) would suppress the immune response of mice to aerosolized *Streptococcus zooepidemicus*. There is a dose-dependent increase in mortality by day 10 when the mice were exposed to trichloroethylene at concentrations of 50 ppm and above. The increase in trichloroethylene-induced mortality roughly corresponded with a decrease in lung clearance of the bacteria by 72 hours post-infection. The results generated a No Observed Effect Level (NOEL) of 25 ppm for increased mortality to infection. This study is very well conducted and using the response to infection as an endpoint to study acute immunotoxicity is especially powerful as it adds real-world relevance. Thus, this study represents an appropriate choice for evaluating the acute effects of trichloroethylene on the immune system.

Recommendation 77: Highlight the uncertainty inherent in relying on one study to establish the immune end point.

The Selgrade and Gilmour 2010 study is not discussed in the EPA IRIS 2011 (U.S. EPA, 2011e) document (due to an oversight); the text in the current document adequately describes the appropriateness of using that study for benchmark dosing evaluation.

The Evaluation must make clear that acute immunosuppressive response is based on a single, albeit well-performed study (Selgrade and Gilmour, 2010) or as stated in the text “a single acute inhalation study in rats that identified a novel endpoint for impaired response to infection.” It should be acknowledged that while the Selgrade and Gilmour (2010) study is novel with respect to trichloroethylene, it is by no means a novel response or study design in the inhalation toxicology literature. This type of study has been performed for 50 years, and there is a huge database on the relevance and predictability of this approach. That being said, there are no human data to indicate the consistency or coherence of this response across species. While this in no way invalidates the Selgrade and Gilmour (2010) study, the text might better highlight the higher uncertainty inherent in relying upon a single study in isolation to evaluate the most sensitive response. In addition, while six valid criteria were listed in justification of utilizing the Selgrade and Gilmour data, none of these points really address whether this endpoint is the most representative or most sensitive and, therefore, the most protective. This conclusion should be more directly stated.

With respect to POD derivation from the Selgrade and Gilmour study, the description in the text and Appendix F is for the most part transparent and straightforward. Selection of a 1% BMR due to lethality is consistent with other POD derivation in the document (e.g., congenital heart defects), but it is not clear whether this is consistent with EPA policy or is fully a professional judgment call by the authors. For the sake of transparency, this should be explained. As a

judgment call, it is acceptable, and certainly health protective. The benchmark MOE based on UFs is clearly described; however, a more detailed description would be preferable relative to the choice of UF_A and UF_H based on the fact that such a conservative POD (based on 1% BMR) is selected.

However, to several of the Committee, the fit of the data is unclear in the BMDS Figure (Appendix F, page 599, Table-Apx F-5) and the model fit is questionable. The data from Selgrade and Gilmour (2010; i.e., the doses presented) do not match up with those described in the text (i.e., 0, 80, 100, 200 ppm presented; 0, 5, 10, 25, 50, 100, 200 ppm, but not found in Benchmark Dose Software (BMDS) model); moreover, measures of variance are not provided in the paper. The data used to generate I-bars in the BMDS model were not clear to some of the Committee. Some on the Committee recommended not trying to fit those data, instead, but suggested using the NOEL of 100 ppm as a POD instead.

Finally, while as stated above, the use of mortality as an endpoint is both clinically relevant and unequivocal, it brings into question whether this is effective as a protective POD, because one would expect other functional effects that precede mortality to occur at even lower doses. The Evaluation should consider reducing the POD based on the extrapolation of a reasonable sublethal effect.

Recommendation 78: Add and discuss autoimmunity studies performed in different rodent models and with humans.

The selection of the Keil et al. (2009) paper is useful for evaluating the effects of chronic trichloroethylene exposure on the development of autoimmune disease in non-autoimmune-prone mice. The selection of the anti-single stranded and anti-double stranded DNA antibodies as an endpoint seems appropriate with the relative consistency of the results in B6C3F1 mice. However, the Evaluation should also include at least one study that examined the effects of chronic trichloroethylene exposure on disease progression in autoimmune-prone mice. Because such mice can represent the human population most susceptible to the autoimmune-promoting effects of trichloroethylene, this inclusion is important. There are several studies that use models other than the NZBWF1 mice used in the Keil et al. (2009) study. Studies suggested by the Committee included different models: Griffin et al. (2000), Gilbert et al. (2009), and Wang et al. (2012).

Additionally, Human Equivalent Concentrations (HECs) from other studies are markedly different from these calculated from the Keil et al. study. How does the EPA explain the large differences in HECs compared with other data investigating the immunological endpoint? The Committee suggested that the EPA consider as high-quality inhalation studies only those that provide analytical chemistry results confirming exposure.

The autoimmune response study in rodents is supported by data in humans suggesting there are potential immune hypersensitivity responses to trichloroethylene. Suggested human studies include: Bond (1996), Chittasobhaktra et al. (1997), Nakajima et al. (2003), Xu et al. (2009), Liu (2009) and Kang et al. (2018).

Recommendation 79: Reevaluate the quality ratings of the four immunotoxicity studies.

As explained by a Committee member at the meeting when describing the limitations of one of the immunology papers, key studies should provide adequate information about statistics, clear documentation of dosage, explanations concerning animal group randomization, and evidence of use of standardized methodology. Although these criteria are extremely useful in evaluating every study, other considerations, not so easily quantified, need to be included for immunotoxicity studies in particular, these include: 1) decisions as to whether the choice of animal model and methodology are optimal for the scientific question being asked, 2) whether the proper controls were used, such that the reader can determine whether the immune assay actually worked, and 3) whether the data are properly evaluated and the conclusions reached were legitimate. These criteria need to be incorporated into the study rating.

In terms of the analysis for the immunotoxicity risk, the Evaluation identifies only four animal studies as suitable: Keil et al. (2009), Kaneko et al. (2000), Sanders et al. (1982) and Woolhiser et al. (2006). Each study scored as Medium or High in EPA's data quality evaluation (see Evaluation Table 3-11). Each of these studies has significant limitations that should affect their quality rating.

The Keil et al. (2009) study is ultimately selected for deriving a POD for chronic trichloroethylene exposure, and the associated outcome selected, namely autoantibody production, is appropriate. The dose levels in the Keil et al. (2009) study are misreported in the Evaluation. They were 0.001, 0.4, or 14 ppm (0, 1, 400, or 14,000 ppb) trichloroethylene in water. Neither purity, stability, nor homogeneity of trichloroethylene concentration is reported. However, it is noted that water concentrations (actual dose applied) were analyzed, though those data are not provided (only nominal dose levels reported). Exposures were static three-day renewal. It is not clear how this study was assigned a "high" quality rating when critical information regarding exposure is not provided and calibration of the biomarker is not discussed.

Based on the Keil et al. (2009) study, the Evaluation considered using the trichloroethylene-induced (1.4 or 14 ppm) decrease in thymus weight in B6C3F1 mice after 36 weeks as an endpoint for non-cancer effects. However, a decrease in thymus mass is not normally found following exposure of adult mice to trichloroethylene. The authors mention that 14 ppm exposure correspondingly decreased thymus cellularity (data not shown), but do not say that the 1.4 ppm exposure caused a similar decrease in cellularity even though both doses decreased thymus mass. If there is no decrease in thymus cellularity at the lower dose, the reported decrease in mass becomes less convincing. As it turns out, the Evaluation concludes to not use the thymus data for assessing risk because it is not sufficiently adverse compared to other endpoints. However, at least the Keil et al. study can be used to examine the impact of trichloroethylene on the generation of autoantibodies to double- (dsDNA) and single-stranded DNA (ssDNA) in non-autoimmune-prone mice.

While the Sanders et al. (1982) study did use four doses of trichloroethylene to treat CD-1 mice, it

offers only very brief descriptions of methodology and statistics that are supposedly required for an adequate rating. The study used a variety of assays to examine multiple immune parameters. However, only some of the results were consistent, and/or associated with adequate controls. A four-month drinking water exposure to trichloroethylene at 2.5 or 5.0 mg/ml suppressed anti-Sheep Red Blood Cell (SRBC) antibody-forming cells (AFC) in the spleens of female mice when measured 4 days after immunization, but not 5 days after immunization. This suppression of the anti-SRBC response is not observed if the trichloroethylene exposure is extended to six months. Trichloroethylene also inhibited cell-mediated immune response to SRBC as measured in a footpad assay after 4 months of exposure, but less so after 6 months of exposure. Trichloroethylene has no effect on mitogen-induced T cell and B cell proliferation, and inconsistent effects on macrophage activity. Overall, it is difficult to pick a consistent targeted effect on the immune system from the Sanders et al. study.

The Woolhiser et al. (2006) study used three concentrations of trichloroethylene administered via inhalation. The study is presented as a report conducted by Dow Chemical at the behest of the Halogenated Solvents Industry Alliance (HSIA). The results were later published again in an article by Boverhof et al. (2013), which by the way, should not be considered a separate evaluation of immunosuppression. In terms of the limited number of immunological outcomes tested Woolhiser et al. showed that trichloroethylene at 1000 ppm for 4 weeks suppressed the generation of anti-SRBC plaque-forming cell (PFC) in the spleen. It is not clear why this study, which only showed an effect at one concentration of trichloroethylene, should be chosen as a key study.

The Kaneko et al. (2000) study is chosen as a key study to illustrate how chronic trichloroethylene exposure causes immunotoxicity in an autoimmune-prone mouse model. Kaneko et al. apparently wanted to test whether trichloroethylene exposure promoted *pneumatois cystoides intestinalis* (PCI) in MRL lpr/lpr mice⁷. PCI is not an autoimmune disease, it is not found in MRL lpr/lpr mice, and MRL lpr/lpr mice are not a good model to examine chemically induced autoimmunity. It is not clear why this paper was selected over several other papers using superior animal models that have examined how chronic trichloroethylene exposure impacts autoimmune disease (suggested references provided above). A number of these studies use female MRL+/+⁸ mice, which develop a mild form of lupus late in life. Their ill-defined autoimmune proneness mimics the ill-defined increased susceptibility thought to be important for autoimmune disease development in humans. Thus, under one year of age before their spontaneous lupus begins to develop, female MRL+/+ mice represent a good model to test the autoimmune-promoting effects of different chemicals. This contrasts with MRL lpr/lpr mice, which start to develop spontaneous and fulminant lupus by 2-3 months of age, which makes it difficult to detect the additional autoimmune-promoting effects of a chemical.

In addition to the results concerning the ability of trichloroethylene to promote autoimmunity in non-autoimmune-prone mice, the Evaluation should also include similar results in autoimmune-

⁷ MRL lpr/lpr mice are a well-studied mouse model of systemic autoimmunity.

⁸ MRL +/+ mice are another mouse model of systemic autoimmunity which does not carry the lpr mutation.

prone mice. References to studies that have demonstrated the ability of trichloroethylene to promote autoimmunity in autoimmune-prone mouse models superior to MRL lpr/lpr were provided at the end of the discussion for Recommendation 78.

Recommendation 80: Use and define more precise terms in discussing immunotoxicity.

The Evaluation uses imprecise language to discuss immunotoxicity. For example, the use of terms such as “allergic respiratory sensitization” and “sensitization/hypersensitivity” need to be better defined. Although such vague terms are often found in the literature, they can and should be replaced by more precise and informative terms (e.g., one Committee member suggested using more precise designations such as Type I, II, III or IV hypersensitivity).

Recommendation 81: Provide the scientific rationale for selecting the Keil et al. (2009) study for evaluating chronic non-cancer effects given its deficiencies.

Several members of the Committee voiced other concerns over the use of Keil et al. (2009) study. The data from Keil et al. (2009) are outside the range of doses used in other immunotoxicity studies. One Committee member commented that the data are of questionable significance because there seems to be a lack of dose response (although Table APX F-3 does show a dose response; table source: Selgrade and Gilmour (2010)). In addition, normal humans are not well represented by a genetically-prone strain, the data were generated from another pathway of exposure (oral) than is considered in the human COU, and only nominal concentrations were reported (though the authors suggest doses were analytically confirmed). In the Risk Characterization section, Keil et al. (2009) is cited in Table 3-14, mentioning differences in anti-dsDNA and -ssDNA antibodies (a marker of systemic lupus erythematosus) in genetically prone and non-genetically prone mice as the endpoint. No explanation for the selection of this endpoint is given, and the levels of anti-dsDNA antibodies at 14,000 ppb in both normal and genetically prone mice are nearly identical to controls at 36 weeks. This is also the case for anti-ssDNA antibody (Ab) of genetically prone mice, but not normal mice. Qualification of this biomarker (along with a lack of justification) suggests these data are not appropriate for use in this manner. The Evaluation suggests that trichloroethylene has both immunosuppressive and autoimmunity properties. A biologically plausible explanation for how this might happen should be provided. Further, the authors also state that there is no statistically significant difference in thymic cellularity (Page 244, lines 2251-2257). This equivocal cellularity issue is a recurring problem.

Another problem with the Keil et al. (2009) study is that the thymus mass effects measured may not be reliable, given the subjective nature of the assay, and because the thymus must be removed and trimmed, which unavoidably introduces technique related variability in weight determination. This is a very small organ and very prone to trimming artifacts. In addition, inconsistent trichloroethylene-induced changes were observed between the two mouse strains. Decreased thymus weight changes were observed in the B6C3F1 non-sensitive mouse model. Thymus weights in the NZBWF1 autoimmune susceptible mouse model seem to increase, but the increase was not statistically significant.

The Committee discussed autoantibody findings for dsDNA and ssDNA analyses. One Committee member pointed out that with the exception of the 26-week age dsDNA autoantibodies in the B6C3F1 mice, all statistically significant observations in both strains were observed only for the low-dose groups, but not for the high-dose groups. One Committee member noted that in all cases the high-dose groups exhibits a lower (average) response than the low dose groups, suggesting that the LOAEL should be the high dose group, not the low dose group.

In addition, age-dependent differences in responses were observed in NZBWF1 mice, but not in B6C3F1 mice. The control and treatment group response levels measured in the B6C3F1 mice were 10- to 20-fold lower for the same age/treatment groups in NZBWF1 mice. Thus, it was not clear to some Committee members whether the inconsistent minimal effects observed in the B6C3F1 non-sensitive mouse have any clinical relevance. Other Committee members disagreed and pointed to multiple figures in the Keil et al. paper that show legitimate levels of toxicant-induced increases in antibodies. While dose responses are not very evident, trichloroethylene effects are evident.

Recommendation 82: Consider using Sanders et al. (1982) to set the immunotoxicity POD.

Some Committee members suggested that EPA consider using an immunotoxicity study with a clearer dose-response for evaluating chronic non-cancer effects. One Committee member suggested using the study by Sanders et al. (1982) that observed trichloroethylene at concentrations of 2.5-5 mg/mL (in drinking water for 4 or 6 months) that resulted in suppression of humoral and cell-mediated immunity in female CD1 mice. Another Committee member disagreed, finding the Keil study superior to the Sanders study and hence that it is appropriate to use the Keil study in establishing the POD for immunotoxicity.

One Committee member concluded that the TSCA program is struggling to integrate immunotoxicity into its chemical risk evaluations. This is evidenced by the poor discussion and justification applied to inclusion/exclusion criteria used to identify key immunotoxicity studies and by the imprecision of terms used to discuss immunotoxicity in this Evaluation.

EPA determined that the immune effects from Selgrade and Gilmour (2010) represent the best representative dataset to use for evaluating acute effects and the autoimmunity effects from Keil et al (2009) represent the best data set to use for evaluating chronic non-cancer effects (Section 3.2.6.4).

Q 5.3 b	EPA did not input the data on response to pulmonary infection from Selgrade and Gilmour (2010) into the TCE PBPK model due to uncertainty over the proper dose metric to be used. Therefore, EPA relied on standard methods for cross-species scaling (i.e., blood:air partition coefficient for HEC, allometric scaling for HED) and accordingly reduced the default 10X UF_A uncertainty factor to 3 (see Section 3.2.5.3.2). Please comment on whether this approach is appropriate and whether the UF is sufficient.
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Response to Q5.3b: Reliance on standard methods for cross-species scaling.

Recommendation 83: Discuss why the PBPK model could not be used to examine a dose metric of total absorbed dose of parent trichloroethylene.

The PBPK model is not used for the Selgrade and Gilmour (2010) model because of uncertainty over the proper dose metric. Certainly, there is no basis upon which to determine if a metabolite (or which metabolite) is responsible for the effects observed in this study, so that precludes the selection of most possible dose metrics. However, it was not clear to some Committee members why a PBPK model could not be used with a dose metric of total absorbed dose of parent trichloroethylene. If the toxicity is due to the parent compound, then this is the most appropriate dose metric (although this is not the conclusion of most studies). Moreover, because the level of any metabolite must be in some way proportional to the delivery of parent compound then this would still be a potentially valuable dose metric. The decision to not use this or similar dose metric should be described.

Although it is not stated in the text, presumably the HEC determination is based on the RfC methodology assuming trichloroethylene is a category 3 gas. This should be explicitly stated. This process is based on the inherent assumption that parent compound dosimetry is critical. It is not particularly soluble (partition coefficient of 9-25), but it is “reactive” because it is metabolized in the respiratory tract. Because a PBPK model is available and validated (according to the document) it is unclear why simulations are not performed to determine if the category 3 assumption is valid. The exposure duration is critical here. Based on the partition coefficient of trichloroethylene, it is not clear whether in short-term exposure the whole body is in steady state (likely not) and it is not clear the extent to which trichloroethylene is recirculated in the venous blood (thus limiting respiratory tract uptake). Thus, it is not clear that the standard chronic reference concentration (RfC) category 3 assumption is valid. As noted above, this could easily be

confirmed by running the PBPK model to verify the validity of this approach. Because the RfC methodology assumes that delivery of the parent compound is critical, the most appropriate thing would be to rely upon the PBPK model to assess delivery of the parent compound rather than rely on default assumptions.

The use of standard methods for cross-species scaling due to uncertainty regarding uncertainties in the dose metric for pulmonary infection follows standard practice. However, this issue seems to only be addressed in a pair of footnotes to Table 3-13 (Evaluation page 252):

“1. Data from (Selgrade and Gilmour, 2010) was not subject to PBPK modeling due to uncertainty concerning the most appropriate dose metric. The BMDL value adjusted for a 24hr exposure will be used as the POD for occupational risk estimates, while the 3hr value will be used for consumer risk estimates. This value is presented in the HEC99 column but does not represent any particular percentile since it was not PBPK-modeled.”

“2. A dermal HED was obtained through route-to-route extrapolation using breathing rate and body weight data on male CD-1 mice (insufficient female data was reasonably available) from (U.S. EPA, 1988) and allometric scaling based on (U.S. EPA, 2011d) using a dosimetric adjustment factor of 0.14 for mice.”

This important point should be more prominent in the text rather than in the footnotes of a table.

EPA determined that the immune effects from Selgrade and Gilmour (2010) represent the best representative dataset to use for evaluating acute effects and the autoimmunity effects from Keil et al (2009) represent the best data set to use for evaluating chronic non-cancer effects (Section 3.2.6.4).

Q 5.3 c	EPA acknowledges that in using the Keil et al (2009) study, EPA is relying upon an early clinical marker to account for susceptibilities, and the endpoint is a precursor to adverse effects for autoimmunity. This LOAEL was considered in this context and the LOAEL to NOAEL uncertainty factor was reduced from 10 to 3X. In light of this, please comment on EPA's use of a 3x Uncertainty Factor for human variability and LOAEL to NOAEL extrapolation.
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Response to Q5.3c: Use of 3x UF_H for autoimmunity effects.

Recommendation 84: Consider increasing the autoimmunity effect UF_L to account for uncertainties in the clinical significance of autoantibodies.

The Committee was comfortable with using a UF_L (LOAEL-to-NOAEL uncertainty factor) of 3 for the Keil et al. (2009) study because the LOAEL is based on an early clinical marker. However, the clinical significance of autoantibodies was subjected to a vigorous discussion during the meeting. Autoimmune diseases are notoriously difficult to diagnose. The one parameter that is most often used as a biomarker in the diagnostic process is the presence of autoantibodies. Different autoimmune diseases are associated with different autoantibodies that vary in their specificity and sensitivity for the particular disease. Anti-DNA autoantibodies, which are one type of anti-nuclear antibodies (ANA), are among the least specific and sensitive. However, they are also among the most commonly tested-for and are used to help diagnose a variety of autoimmune diseases. For example, 98% of people with systemic lupus erythematosus make ANA. ANA are also used to diagnose rheumatoid arthritis and scleroderma. However, low levels of non-pathological ANA can also be found in older adults. Bottom line: although not always associated with tissue pathology, the development of ANA such as anti-DNA autoantibodies represent an adverse effect, a sign of some level of immunotoxicity.

Because anti-DNA autoantibodies are often the precursors for actual autoimmune disease, some Committee members suggested that a UF_L=10 should be assigned to their detection. Not all Committee members agreed with this increase, depending upon their confidence in the significance of this pre-clinical endpoint.

Cancer

Q 5.4	EPA performed a meta-analysis on the published database for liver cancer, kidney cancer, and non-Hodgkin's lymphoma (NHL), concluding that there was a statistically significant association between TCE exposure and all three cancers when accounting for various sensitivity analyses. Please comment on EPA's methodology and conclusions (Sections 3.2.4.2.1 and Appendix H).
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Response to Q5.4: Cancer methodology and conclusions.

With two exceptions, members of the Committee indicated that the short subsection on the meta-analysis for trichloroethylene-induced cancer is concise and clearly explains the interpretation of the conclusions of an association with kidney cancer, liver cancer, and non-Hodgkin's lymphoma (NHL). More detail on this analysis is presented in Appendix H. As the document notes, this conclusion is consistent with both the EPA IRIS review (U.S. EPA, 2011b) and other risk assessments. This section and the analysis are clear and appropriate. Differences between this and a previous analysis seemed to be largely driven by the results of the Vlaanderen et al. (2013) study, and this study is ultimately excluded based on a weak association with trichloroethylene exposure. This exclusion is well discussed and justified.

One member of the Committee had reservations about the association of trichloroethylene with liver cancer. Because the POD is derived from the more definitive kidney cancer data and modified to account for additional cancer types (liver and non-Hodgkin's lymphoma (NHL)), the other members of the Committee did not see this as an issue. The basis of this Committee member's lack of confidence in the association of trichloroethylene exposure with liver cancer can be summarized as follows:

Animal studies provide conflicting evidence on liver tumors, although multiple studies have reported increased liver tumors, predominantly in male mice. However, even among susceptible strains of mice, relatively high doses (hundreds of ppm (inhaled) and thousands of mg/kg (oral)) are required to induce liver tumors. This is compounded by the possibility that the actual mechanism of trichloroethylene action in rodent liver is not relevant to humans (see next section).

Q 5.5	For the cancer dose-response assessment, EPA derived an inhalation unit risk (IUR) and oral cancer slope factor (OSF) based on epidemiological kidney cancer data from Charbotel et al, 2006, adjusted upward to also account for the relative contribution of NHL and liver cancer. Per EPA Guidelines for Carcinogen Risk Assessment, overall, the totality of the available data/information and the WOE analysis for the cancer endpoint was sufficient to support a linear non-threshold model (Section 3.2.4.2.2). Please comment whether the cancer hazard assessment has adequately described the methodology and justification for the cancer dose-response approach, including the use of a linear model and the adjustments made for the other tumor sites (Section 3.2.5.3.4).
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Response to Q5.5: Cancer hazard assessment and dose-response approach.

Recommendation 85: Include a table summarizing what is known on the genotoxicity of trichloroethylene and metabolites.

The Committee noted that the MOA for trichloroethylene carcinogenicity is not well addressed in the Evaluation, because it essentially relies on the conclusions from the IRIS assessment. The Evaluation should include a table of data addressing the genotoxicity (for both *in vivo* and *in vitro* studies) of trichloroethylene and metabolites. Because kidney cancer is the most important driver of the conclusions, the data germane to that tissue should be prioritized.

Regarding the use of a linear non-threshold (LNT) model for the cancer hazard dose-response, the Evaluation follows the standards set forth in the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005). Specifically, when a genotoxic mode of action (MOA) is concluded to be involved, as is the case for trichloroethylene-induced kidney cancer, an LNT dose-response model is assumed. There are two caveats here that should be considered. First, while the penultimate metabolite of trichloroethylene, S-(1,2-dichlorovinyl)-L-cysteine (DCVC—known to cause nephrotoxicity and kidney cancer) is clearly mutagenic, it is a relatively weak mutagen. Second, while there is evidence that mutagenicity does play a role, it is clearly not the only MOA. Moreover, its relative contribution as compared to cytotoxicity and proliferation is unclear. Thus, although following an LNT dose-response model for cancer assessment would seem to follow standard practice, support for it remains weak.

Some Committee members suggested that alternative MOAs for trichloroethylene in liver carcinogenesis have not been adequately discussed.

Multiple modes of action have been proposed for the carcinogenic action of trichloroethylene and its metabolites in rodents, including activation of peroxisome proliferator activated receptor alpha (PPAR α). The human relevance of PPAR α agonism has been the subject of debate due to the substantial species differences in response to peroxisome proliferator receptor activation between rodents and primates, with rodents, especially mice, showing greater sensitivity than primates.

The National Research council (NRC, 2006) reported that:

“a significant lack of concordance in the sensitivity of human and rodent hepatocytes to peroxisome proliferators and early events associated with liver tumor promotion has been noted, with humans being much less sensitive. In addition, there is no supporting epidemiologic evidence of enhanced occurrence of liver tumors in humans administered potent rodent peroxisome proliferators. The weak carcinogenic activity of chloral hydrate in the liver of male B6C3F1 mice combined with lower rates of oxidation and higher rates of conjugation in humans compared with mice indicate that the mode of action for mice is not relevant to humans.”

The NRC also concluded that “exposure to trichloroethylene at concentrations relevant to the general public is not likely to induce liver cancer in humans.” Thus, based on the inconclusive epidemiologic evidence and questionable relevance of the liver tumors observed in mice, how can EPA defend quantifying liver cancer risk?

A Committee member suggested that other, non-PPAR α mechanisms, such as cytotoxicity and activation of other nuclear receptors had not been adequately discussed. These events occur in short-term acute and subchronic scenarios but are potential mechanisms of liver cancer pathogenesis. Changes induced by trichloroethylene include increased DNA synthesis, hypertrophy and cell proliferation, which occur in response to either liver injury (compensatory changes) or activation of mitogenic nuclear receptors (constitutive active/androstane receptor (CAR) or inactivation of anti-proliferative receptors (HNF4 α)).

Overall, the Committee noted that a genotoxic mechanism (supportive of using an LNT model) had been assumed for trichloroethylene. There is some support for this due to the mutagenic potential of the metabolites DCVC and S-(1,2-dichlorovinyl) glutathione (DCVG). While this evidence is greatest with regard to kidney toxicity and is further supported by relevant data from female reproductive toxicity, it is far from definitive. Committee members were concerned with both the low mutagenic potential of these metabolites and the doses that would be achievable *in vivo*. It is probably best to consider the presence of these compounds as providing “biological plausibility” for a genotoxic mechanism and consistent with an LNT model rather than conclusive proof. However, there is also no compelling evidence for the other mechanisms discussed above, so no reason to specifically reject a genotoxic mechanism.

Q 5.6	Please comment on EPA’s application of the PBPK model to the dose-response analysis for all endpoints. Was the selection of dose metrics and percentile output selection appropriate when considering the sensitivity, uncertainty, and variability of the data (Sections 3.2.2 and 3.2.5)?
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Response to Q5.6: Application of PBPK model to dose response analysis.

Recommendation 86: Expand the discussion on the PBPK model including results of sensitivity analyses to identify key inputs.

The discussion of PBPK modeling and its use in dose-response assessments is too limited and lacks sufficient clarity for most readers to understand what this model is and how it can be used to reduce uncertainty relating external chemical exposure to internal (i.e., blood and target tissue) doses, and in turn to the extent of injury. Only two references (U.S. EPA 2006a, 2011e) are provided. Both are lengthy, detailed documents focused on analysis of the many existing PBPK models for trichloroethylene in animals and humans, and on the models’ evolution to the final, updated model utilized in the current risk assessment. It might be worthwhile to point out the large number of PBPK models and the inordinate time and effort expended by many scientists to develop the present version.

The current text should be expanded to describe the basic model structure and key input parameters, including physical/chemical properties and physiological and biochemical indices. A table listing the parameters and referencing the sources of the values is desirable, considering the importance of accurate and up-to-date parameters. Describe the utility of PBPK models in route-to-route, species-to-species, high-to-low dose, duration-to-duration, and human-to-human extrapolations.

It should be emphasized that validated animal and human PBPK models allow one to make scientifically based predictions of target tissue doses of the toxicologically active form of trichloroethylene to monitor (i.e., the dose metric). A clear explanation should be given of how the PBPK model is used to predict/simulate the exposure conditions required to produce the same blood or target tissue dose in animals and humans. The basic steps: (1) Determine the inhaled or ingested dose of chemical required to produce organ damage of a particular magnitude in a test animal; (2) Measure the level of chemical in the damaged animal’s tissue; and (3) Run the model to ascertain what chemical dose to which the human must be exposed to yield the same tissue level of chemical.

The Evaluation assumes that the same tissue chemical level/concentration will cause the same degree of injury in each species. It was not clear to all Committee members that this assumption is valid for all metabolites. The starting point in this exercise can be the point of departure (POD) for toxicity that has been selected. The rodent PBPK model for trichloroethylene is typically run

for a series of exposures to obtain the rodent target organ dose. The human PBPK model for trichloroethylene is then typically run for a series of exposures to establish the relationship between human inhaled concentrations and target tissue doses. This relationship is used to derive human equivalent concentrations (HECs) and doses (HEDs).

Sensitivity analyses are frequently conducted with PBPK models to determine how much impact variance in each input parameter has on model output/simulations. Sensitivity analysis of models facilitates identification of factors, including personal characteristics, that have the largest impact on systemic deposition and adverse effects in organs of interest. This method of analysis allows researchers to learn how characteristics of different individuals or subpopulations may influence internal dosimetry, and in turn their susceptibility to particular chemical health effects.

Use of a PBPK model is reasonable when conducting route-to-route extrapolation, but it does introduce uncertainty.

Recommendation 87: Discuss trichloroethylene metabolites in more detail including available evidence on links from metabolites to fetal heart malformations.

The Evaluation notes that trichloroethylene metabolites, not the parent compound, are suspected as being responsible as the causative agent for fetal heart malformations. The PBPK model used in the EPA risk evaluation can be used to model the effects of trichloroethylene metabolites such as chloral hydrate, trichloroethanol, trichloroacetic acid, dichloroacetic acid, and others. The experiments by Dawson et al. (1990, 1993) and Johnson et al. (2003), were not specific or definitive as to the responsible metabolite(s). The Evaluation should provide additional information on all metabolites modeled and discuss the available evidence on the link from metabolites to fetal heart malformations.

Q 5.7	Have the most scientifically robust critical health effects and corresponding PODs been identified for TCE? Are there additional data regarding other health effects for TCE that EPA needs to consider? If data gaps exist in the TCE database, how could the uncertainty about sensitive health effects and critical windows of exposure be better accounted for in the risk characterization (Sections 3.2 and 4.3.2)?
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Response to Q5.7: Support for critical health effects, data gaps and uncertainties.

Recommendation 88: Modify overstatements in Section 3.2.3.1.1 and 3.2.4.1.3.

The text in Section 3.2.3.1.1 Liver Toxicity makes a couple of statement that the Committee felt are too broad or overstate the case for liver toxicity. One was the statement on page 210, line 713

that “Animals and humans exposed to trichloroethylene consistently experience liver toxicity.” Another on page 210, lines 729-730 states that “Several human studies...reported an association between trichloroethylene exposure and significant changes in serum liver function tests... .”

Klaassen and Plaa (1969) compared the acute hepatotoxicity of trichloroethylene to other halocarbons. The intraperitoneally (ip) injected dose required to cause an increase in serum enzyme activity in mice was almost an LD₅₀ dose. The lowest ip dose (i.e., 500 mg/kg) in rats to cause oxidative damage in the liver of rats produced stage II anesthesia (Toraason et al., 1999). Buben and O’Flaherty (1985) saw a modest increase in serum enzyme activity in mice dosed daily for six weeks at oral dosage levels of >500 mg/kg.

Trichloroethylene-induced hepatotoxicity is not a common finding in humans and was rarely reported in patients for whom it was used as an anesthetic (Pembleton, 1974; Lock and Reed, 2006). Bruning et al. (1998) found renal injury but no evidence of hepatotoxicity in a man rendered unconscious for five days after drinking 70 ml of trichloroethylene in a suicide attempt. A study of 289 British workers, who experienced symptoms of CNS depression from trichloroethylene inhalation and dermal exposure, revealed no clear evidence of hepatotoxicity (McCarthy and Jones, 1983).

The text in Section 3.2.4.1.3, page 220, line 1180 contains the overstatement that “Both animal and human studies consistently observe induction of kidney toxicity...and progression of existing kidney disease.” Nephrotoxicity has not been consistently observed in occupational exposure studies. Evidence of renal proximal tubular damage is usually mild and limited to increases in certain cytoplasmic enzymes in urine. Such effects typically require chronic trichloroethylene exposures.

Recommendation 89: Clarify what information from Kjellstrand et al (1983) is used to calculate the POD for liver toxicity.

In the discussion of liver toxicity in Section 3.2.5.3.2, it is not clear what inhaled concentration examined in the study by Kjellstrand et al. (1983) was used in the Evaluation to calculate the POD. It is difficult to tell from the publication what the NOAEL and/or LOAEL are for increased liver weight. It appears that 75 ppm was the LOAEL for liver weight, but 150 ppm was required to cause cytoplasmic vacuolization. It is not clear whether the vacuolization was due to lipid, glycogen or water accumulation. Any of these could contribute to increased liver weight, which was said on page 240, line 2115 to be “merely adaptive,” as opposed to cytotoxic. The fine vacuolization was shown to be reversible by the researchers. The quality of the Kjellstrand data needs to be better assessed and more discussion provided as to whether the observed effect was adverse or merely adaptive.

Recommendation 90: Address the utility/limitation of using the rat data of Maltoni et al. (1986) to extrapolate to human kidney risk, in view of the substantially greater metabolic activation of trichloroethylene via the GSH pathway in rats than in humans.

As mentioned previously, the Committee expressed concern with the use of the rat data of Maltoni et al. (1986) to establish the POD for nephrotoxicity, considering the relatively high metabolic activation of trichloroethylene in rats. It is important to recognize that trichloroethylene metabolic activation to DCVC and subsequent cytotoxic/mutagenic metabolites is qualitatively, though not quantitatively similar in rodents and humans. Conjugation of trichloroethylene with glutathione (GSH) to form S-(1,2-dichlorovinyl) glutathione (DCVG) occurs primarily in the liver at a rate about ten times more rapidly in rats than humans (Green et al., 1997a). Much of the DCVG is excreted via the bile into the intestines, where it is converted to S-(1,2-dichlorovinyl)-L-cysteine (DCVC). DCVC is reabsorbed and taken up by the liver, where a portion is detoxified by N-acetylation. Bernauer et al. (1996) exposed rats and humans to 160 ppm trichloroethylene vapor for six hours. The rats excreted eight times more N-acetyl-DCVC than did the human volunteers. Some DCVC is taken up from blood by the kidneys and further metabolized by the enzyme beta-lyase to S-(1,2-dichlorovinyl) thiol (DCVSH). Lash et al. (1990) and Cooper (1994) have reported ten times higher cysteine conjugate beta-lyase activity in the rat than in human kidney. DCVSH is converted to unstable, highly reactive products, including chlorothioketene and thionoacylchloride (Lash et al., 2014). Metabolic activation of DCVC to chlorothioketene was shown to occur eleven times more rapidly in rats than humans (Green et al., 1997b). Lash (2001) also demonstrated that cultured rat renal cells were more sensitive to DCVC than human renal cells.

Recommendation 91: Justify why developmental toxicity was not given more consideration in the risk characterization.

There is evidence from both epidemiological and animal studies that developmental toxicity may be an especially sensitive endpoint for trichloroethylene. Exposure to trichloroethylene has been reported to cause congenital heart defects, neurotoxicity, decreased fetal weight, skeletal anomalies and immunotoxicity. The Evaluation discounted investigations describing these effects, because some did not demonstrate dose-dependency, some were mouse strain-specific, or some were not of adequate quality. The Evaluation (page 215) describes numerous papers, including studies from Camp Lejeune that associated developmental trichloroethylene exposure with various developmental outcomes in humans such as spontaneous abortion, developmental neurotoxicity and childhood cancers. It would thus appear that adverse developmental effects may occur in response to trichloroethylene exposures lower than those required to cause toxicity in adults. This makes assessment of developmental toxicity especially important.

The Evaluation states “The only identified study that examined developmental immunotoxicity (Peden-Adams et al., 2006) scored a Low in data evaluation, and a POD could not be sufficiently derived.” They noted that PBPK modeling is difficult when exposure occurs *in utero*, during weaning and early life. As noted, this study exhibited one of the lowest PODs among developmental toxicity studies but was scored a Low for reasons mentioned. This was stated as unacceptable by at least one Committee member, especially when compared to other immunotoxicity studies of inferior quality that were nevertheless deemed of Medium quality and considered to be key studies. The reviewers are asked to accept that the criteria used in the Evaluation for assessing study quality are appropriate. However, when faced with such seemingly

inappropriate manuscript quality ratings, the ability of the quality review system to winnow down large numbers of studies to a chosen few that form the basis for the risk evaluation is called into question.

One Committee member indicated that the Evaluation (and the TSCA program in general) need to define the term “developmental toxicity.” It is not clear whether this refers to toxicity that is induced by developmental exposure, but which may manifest at any time during life, or refer only to pathologies that occur during infancy and childhood.

Recommendation 92: Describe and discuss the findings of recent investigations of adverse effects of trichloroethylene on the developing nervous system.

The developing nervous system is more vulnerable to trichloroethylene and other chemicals than the adult nervous system. Thus, it is important to assess potential adverse effects of trichloroethylene and to search the literature for additional information. The EPA adequately addresses acute neurotoxic effects such as CNS depression, but should consider recent investigations of developmental neurotoxicity. Salama et al (2018) demonstrate that trichloroethylene, in a very low concentration (0.25 μ M), decreases proliferation and differentiation of neuroprogenitor cells, as well as causing apoptosis and reducing cell viability. They also showed that prenatal exposure to 0, 10, and 100 μ g/mL trichloroethylene in drinking water causes neuroinflammation, glutathione (GSH) depletion, and oxidative stress in the cerebellum together with altered locomotor behavior in the offspring of the exposed mice. Another group demonstrated that prenatal ingestion of low levels of trichloroethylene in drinking water causes altered locomotor activity, as well as neuroinflammation, GSH depletion, and oxidative stress in the cerebrum of offspring in mice (Blossom et al., 2017).

Q 5.8	Please comment on any other aspects of the human health hazard assessment that have not been discussed, including the data quality evaluation and the characterization of all assumptions and uncertainties (Section 3.2).
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Response to Q5.8: Comments on other aspects of human health hazard assessment.

Recommendation 93: Make corrections in statements or provide additional justification about trichloroethylene absorption.

Section 3.2, line 537: It was assumed that systemic absorption of inhaled trichloroethylene is 100%. Dallas et al. (1991) reported systemic uptake of about 60% of inhaled trichloroethylene by rats, with the proportion dependent upon vapor concentration and duration of exposure. Absorption of ingested trichloroethylene, in contrast, was relatively complete. More than 90% of trichloroethylene given in water by gavage was absorbed by fasted rats (D’Souza et al., 1985). It

should be recognized that the majority of low oral doses of trichloroethylene are removed from the portal blood by first-pass hepatic and pulmonary elimination, such that very little trichloroethylene reaches the arterial circulation (Liu et al., 2009; Mortuza et al., 2018).

Section 3.2, line 549: The assumed percutaneous absorption of 100% is too high. Twenty to thirty percent would be a high estimate. Some Committee members considered the assumption of keeping trichloroethylene in contact with the skin under occluded conditions for an extended period as not a realistic exposure scenario. One Committee member pointed out that this might happen if a consumer were using a trichloroethylene-containing product without gloves and a product-soaked rag.

Recommendation 94: The document should cite recent reviews of trichloroethylene metabolism that have appeared after release of the EPA trichloroethylene IRIS assessment in 2011.

Section 3.2.1, lines 560-617: Recent reviews of the metabolism of trichloroethylene and the apparent role(s) of CYP and GSH metabolites in mechanisms of cytotoxicity, genotoxicity, and carcinogenicity in different organs of rodents and humans should be cited and abstracted. There has been considerable scientific progress in this field since the EPA trichloroethylene IRIS assessment was published in 2011 (U.S. EPA. 2011b, e). See Lash et al. (2014), Cichocki et al. (2016) and Luo et al. (2018) for comprehensive reviews of trichloroethylene toxicokinetics and mechanisms of toxicity and carcinogenicity.

Recommendation 95: Make sure that broad terminology that may be unclear to some readers is defined.

Section 3.2, lines 487-488, page 202: What exactly does “acute overt toxicity” mean? This is an odd term that needs to be explained.

Recommendation 96: The document needs to provide more accurate and complete discussion regarding some key aspects of trichloroethylene metabolism and the role of key metabolites in adverse effects caused by trichloroethylene.

Section 3.2, lines 595-602, page 205: Regarding species differences in γ -glutamyltransferase (GGT) activity, the text is incorrect; mice are higher than humans. See Hinchman and Ballatori (1990) for information on species differences. Total rat and mouse kidney GGT levels are similar.

Section 3.2.3, page 210-Hazard Identification: Gender- and species-dependent differences, which can be quite prominent, should be mentioned here.

Section 3.2.3.1.2, page 211-Kidney Toxicity, lines 779-780: The text states: “this toxicity is likely caused by DCVC formation, with possible roles for TCOH and TCA...” There are no data supporting a role for trichloroethanol (TCOH) or TCA in kidney toxicity.

Dr. James Bus from Exponent provided written and oral comments at the public meeting that focused primarily on the relevance of the glutathione-dependent metabolism pathway for trichloroethylene and its role in trichloroethylene induced kidney toxicity and kidney cancer. One Committee member provided the following comments and explanation to put these comments into proper perspective:

This pathway has been directly associated with the adverse kidney effects of trichloroethylene. Dr. Bus makes the argument that a previously reported HPLC method (Lash and Anders, 1989; Lash et al., 1995, 1998, 1999a, 1999b, 2000, 2006) used to detect formation of the GSH conjugate of trichloroethylene, abbreviated DCVG, overestimated product formation by several orders of magnitude due to interference from an overlapping peak representing L-glutamate. From this, Dr. Bus repeats the conclusion promulgated and disproven more than two decades ago that metabolic flux through the GSH conjugation pathway for trichloroethylene metabolism is insignificant and that formation of DCVG, followed by its further metabolism to DCVC and formation of reactive metabolites, is responsible for trichloroethylene-induced nephrotoxicity and nephron-carcinogenicity.

Key points regarding these comments are as follows:

- 1) The issues raised by Dr. Bus were not even brought up in the EPA TSCA document.
- 2) The reason why these supposed issues about GSH-dependent trichloroethylene bioactivation and the role of this pathway in trichloroethylene-induced adverse kidney effects are not even mentioned in this document is because they were resolved more than a decade ago. The issues are discussed in Lash et al. (2000), in the 2011 EPA IRIS document, and in the 2014 IARC trichloroethylene monograph.
- 3) Dr. Bus cites a recent publication that directly addressed the supposed assay issues (Zhang et al., 2018), in which the authors (Dr. Bus was a co-author) claim that measured concentrations of DCVG by an LC-MS assay were approximately 4-orders of magnitude lower than those determined by HPLC. However, previous use of an LC-MS assay by Rusyn and colleagues (Kim et al., 2009a,b) reported rates of DCVG formation or DCVG concentrations that were reasonably similar (within an order of magnitude or less) to those previously reported by the HPLC assay.
- 4) The point of the comments made by Dr. Bus is completely unclear in that even dismissing the kidney as a target organ for trichloroethylene would have no impact on the TSCA hazard assessment for trichloroethylene.

Recommendation 97: Clarifications and corrections are needed in the document in Sections 3.2.3 and 3.2.4 about the immune, nervous, and reproductive systems as target organs for trichloroethylene.

Section 3.2.3.1.4, page 212: In discussing trichloroethylene-induced neurotoxicity in humans, the document needs to make it clear that trichloroethylene exposures for neurological effects are generally at quite high doses.

Section 3.2.3.1.4, pages 212-214; lines 837-895: In the overview of immunotoxicity and sensitization, there appears to be confusion regarding immuno-suppression vs. immuno-stimulation. The statements in lines 839-40 appear contradictory to the statement in line 868.

Section 3.2.3.1.5 – Reproductive toxicity, page 214: Six studies published in 2016, 2018, 2019, and 2020 by R. Loch-Caruso and colleagues that provide evidence of female reproductive toxicity of trichloroethylene *in vivo* and DCVC *in vitro* are not identified or discussed. See Hassan et al. (2016); Elkin et al. (2018); Elkin et al. (2019); Hassan et al. (2019); and Elkin et al. (2020).

Section 3.2.3.1.6-Human Data, pages 215-216: The Evaluation states (lines 950-2) that aside from congenital heart defects, it does not identify any repeat-dose experimental studies in animals or human epidemiological studies that would contribute significant additional information for this hazard. Then the Evaluation goes on to describe numerous papers (including studies from Camp Lejeune exposure) that associate developmental trichloroethylene exposure to various developmental outcomes in humans such as spontaneous abortion, developmental neurotoxicity and childhood cancers. This is very confusing and needs to be clarified.

Section 3.2.4.1.5-Reproductive Toxicity: The Evaluation concludes on page 220, lines 1212-1214:

“Both human and animal data provide strong evidence for male reproductive effects from trichloroethylene. Effects observed include effects on sperm, male reproductive organs, hormone levels, and sexual behavior. There is insufficient evidence for determining whether trichloroethylene contributes to female reproductive toxicity.”

At least one Committee member considers this statement as inaccurate. The declaration that there is **strong evidence** from human and animal data of male reproductive effects is, in their opinion, overstated. The statement about insufficient evidence for trichloroethylene-induced female reproductive toxicity is incorrect (see previous comment on reproductive toxicity).

Recommendation 98: Corrections and clarifications are needed in Sections 3.2.3, 3.2.4, and 3.2.5 regarding cancer hazard from trichloroethylene.

Section 3.2.3.2-Genotoxicity and Cancer Hazard, page 218: Improve the discussion to clarify the sex-dependent differences in cancer incidence, especially for kidney and liver.

Section 3.2.4-Weight of Scientific Evidence, page 220, lines 1170-1174: This small section talks about the MOA for liver cancer and discusses the role of peroxisome proliferation. The consensus is that while peroxisome proliferation in rodents is well-established, it is not relevant to humans. This point is never noted.

Section 3.2.4.2.2-Mode of Action: Kidney Cancer, page 227: The document states the following: “the predominant mode of action (MOA) for kidney carcinogenicity involves a genotoxic mechanism.” Although the next paragraph also discusses alternative MOAs, which include cytotoxicity and dysregulated injury and repair cycles, the relative importance of each mechanism and the evidence supporting each mechanism are not appropriately described. For example, while there is clear evidence that DCVC is mutagenic, it is not a particularly potent mutagen (e.g., compared to chemicals like vinyl chloride), and the relative role of mutagenicity vs. cytotoxicity in causing kidney cancer is not known.

Section 3.2.5.2, page 233, lines 1822-1862: NRC (2009) reviewed factors influencing susceptibility of human populations to trichloroethylene toxicity and carcinogenicity. This comprehensive review might be cited here.

Question 6: Risk Characterization:

EPA calculated environmental risk using exposure data (e.g., modeling tools and monitored datasets) and environmental toxicity information, accounting for variability within the environment. EPA concludes that TCE poses a hazard to environmental aquatic receptors, with invertebrates and fish being the most sensitive taxa identified for aquatic exposures. Risk Quotients (RQs) and the number of days a concentration of concern (COC) was exceeded were used to assess environmental risks. The risk characterization section provides a discussion of the risk and uncertainties around the risk calculations.

EPA calculated human health risks for acute (occupational and consumer scenarios) and chronic (occupational scenarios) exposures. For non-cancer effects EPA used an MOE, which is the ratio of the hazard value to the exposure. EPA evaluated potential risks for workers and ONUs, consumer users, and bystanders/non-users. For the most sensitive endpoint of congenital heart defects, a benchmark MOE of 10 was used for both acute and chronic risks. An IUR and OSF that account for the combined extra risk kidney cancer, liver cancer, and NHL was used to evaluate potential chronic risks to cancer endpoints for the worker exposure scenarios. The risk characterization also provides a discussion of the uncertainties surrounding the risk calculations.

After consideration of all identified information, EPA concluded that TCE presents an unreasonable risk of injury to workers and consumer users by inhalation and dermal exposure, and ONUs and bystanders by inhalation exposure, based on the potential for adverse human health effects (See Section 4.2). EPA also concludes that TCE does not present an unreasonable risk to environmental receptors exposed via surface water (see Section 4.1). EPA makes this determination considering risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use without considering costs or other non-risk factors.

<i>Q 6.1</i>	<i>Please comment on whether the information presented to the committee supports the conclusions outlined in the draft risk characterization section concerning TCE. If not, please suggest alternative approaches or information that could be used to further develop risk estimates within the context of the requirements stated in EPA's Final Rule, <i>Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act</i> (82 FR 33726) (Section 4).</i>
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Response to Q6.1a: Support for environmental risk characterization conclusions.

Much of the Committee discussion on the environmental risk characterization (Q 6.1) repeats the discussion provided in support of previous recommendations. See the discussions for the

following recommendations:

Recommendation 5: Include additional discussion on uncertainties for exposure based on the potential for persistent exposure.

Recommendation 8: Add confidence intervals and conduct a model sensitivity analysis to determine if variability associated with the physical-chemical properties would change the EPA's fate assessment.

Recommendation 27: Perform a sensitivity assessment for environmental exposures.

Several Committee members were concerned that overall environmental risks are not determined, but only risks from trichloroethylene released to surface water, and only the risk posed to aquatic organisms is assessed. The terminology related to conditions of use and regulatory nexus disguises the fact that the only media assessed in any meaningful way is water and that the only organisms considered are aquatic organisms. This limitation of the environmental risk assessment needs to be clearly restated in the risk characterization section of the document.

Recommendation 99: Ensure environmental risk characterization statements are consistent with the limitations imposed on the environmental risk assessment.

Conclusions on the environmental risk are inconsistent to represent releases from >6000 facilities. Because the data are insufficient, the Evaluation cannot conclude there is no unreasonable risk to aquatic organisms in surface water. As mentioned previously, the Evaluation underestimates trichloroethylene releases by a factor of 1.5 to 130, with the multiplier dependent on multiple assumptions. Some facilities and species have estimated risks with $RQ > 1$, but this is not translated in the risk determination nor linked to mode of trichloroethylene use.

Recommendation 100: Report the fraction of estimated trichloroethylene releases that are captured by monitoring data and improve the discussion of how total release time is determined.

The Committee understands the modeling process that is used to determine days of exceedance from various commercial uses (Appendix C) but was unable to follow the data analysis that produced the days of exceedance. For example, Sullivan wastewater treatment plant (WWTP) (MO0104736) has a 7Q10 surface water concentration (SWC) of 10.97 µg/L, but the number of exceedances of the algae COC, 3 µg/L, is 7 of 20 (Appendix C, Table Apx C-1, page 513). Solvay-Houston (TX0007072) has a 7Q10 SWC of 75.93 µg/L but days of exceedance are listed as 5 of 20 (Table Apx C-1: 510). There are many other examples of this type of 7Q10 SWC comparison to COC. If the mean SWC exceeds the COC, a description is required to demonstrate how fewer than 50% of the release days exceed the benchmark. If the explanation hinges on a log-normal distribution skewed toward higher concentrations, a quantitative

verification is needed that NONE of the modeled concentrations exceed the ACUTE toxicity COC.

Recommendation 101: Improve the justification for not assessing ambient air emission levels and impacts from commercial and stationary sources.

It is concerning that the emission pathways to ambient air from commercial and industrial stationary sources were excluded on a statutory basis, even though it is expected that most of the trichloroethylene will be removed in wastewater treatment by volatilization during aeration. It is not appropriate to assume that ambient exposure risks are effectively managed by the Clean Air Act (CAA), especially when coming from an aeration basin.

The EPA did not quantitatively assess exposure to sediment organisms, because trichloroethylene is not expected to partition to sediment, based on physical-chemical properties. Section 4.1.4 (page 275, lines 332-333) concludes that “physical-chemical properties do not support an exposure pathway through water and soil pathways to terrestrial organisms.”. The Committee concluded from this that EPA is assuming that volatilization rates do not contribute to exposure to terrestrial organisms. Section 4.1.4 does not consider that soil invertebrates and burrowing mammals in functionally confined spaces may be exposed to trichloroethylene through vapor intrusion from contaminated underground water. This follows from the Agency’s assertion that trichloroethylene volatilizes from soil directly to the atmosphere and is not assumed to migrate to groundwater. This assertion is also made in human health risk evaluation under other EPA regulations (e.g., CERCLA).

Response to Q6.1b: Support for human health risk characterization conclusions.

Consistent with the requirements of TSCA, Section 4.2 of the Evaluation outlines potential human health effects for each use that involves trichloroethylene exposure. The section comprises an extensive array of clear and well-organized tables that list the benchmark MOE and worker MOEs with and without PPE, for each occupational exposure scenario, each health endpoint, and route of exposure. Standard criteria are used to calculate MOE values. Determination of these values and their comparison with the benchmark MOE values, which is used to reach the conclusions about whether unreasonable risks exist for each use, are clearly described, and logically presented.

Comments on the decision to not use fetal heart malformation data to set the non-cancer POD.

The Evaluation identifies and addresses cancer and non-cancer endpoints of heart toxicity, liver toxicity, kidney toxicity, immunotoxicity, neurotoxicity and reproductive and developmental toxicity.

Recommendation 102: Revise and expand the justification for not using fetal cardiac malformation as the unreasonable risk driver.

Overall, the Committee was divided about reliance on fetal heart malformations-for risk characterization. The Committee discussed this issue at length in response to Charge Question 5.1, but it came up again for Charge Question 6.1. Exposure to trichloroethylene during pregnancy linked to cardiac defects is controversial and the Evaluation discussion of the topic does not resolve the matter as far as the Committee is concerned. The Committee agreed that the heart malformations could be used for hazard identification, although the Committee remained divided about the use of these data for risk characterization. The Evaluation needs to better discuss the rationale for excluding fetal heart malformations in light of the decision in the 2011 IRIS (U.S. EPA, 2011e) evaluation to compute a POD for fetal heart malformations.

The Committee noted a disconnect in the Evaluation between the extensive discussion of the heart malformation data, and the controversy surrounding the findings. The Evaluation presents a dose-response analysis for the heart malformation data but ultimately dismisses it in favor of the immunosuppression POD as the unreasonable risk driver. Some Committee members felt that the Evaluation should do a better job of explaining why fetal cardiac malformation are not used as the unreasonable risk driver given (as detailed in Appendix G) that both the Johnson and DeSesso studies identified significant cardiac deficiencies from trichloroethylene developmental exposures (Johnson et al., 2003; DeSesso et al., 2019). To base unreasonable risks on immunosuppression and not on fetal heart malformations appears to some Committee members (and to some public commenters) to accept less protective concentration levels.

See also the discussion for the following recommendations (under charge question 5.1):

Recommendation 71: Reconsider the scores assigned to the epidemiological evidence for trichloroethylene-induced cardiac anomalies.

Recommendation 72: Improve the discussion on the MOA for trichloroethylene-induced fetal cardiac defects and identify gaps in the AOP that need to be filled.

The Committee discussed the Agency's decision not to do an aggregate risk characterization. The Committee has made this recommendation in its review of other TSCA chemical risk evaluations and continues to believe this approach to be worth undertaking. See the discussion related to this issue in the response to Charge Question 4.1:

Recommendation 49: Improve the discussion on aggregate exposure and justification for it not being performed.

Recommendation 103: Identify COUs having very low expectation of appropriate PPE use and incorporate this information in the risk characterization and final risk determination statements.

The Committee continues to be concerned over the Agency's inclusion of calculations based on the use of PPE in occupational scenarios when EPA itself recognizes that it has no confidence that PPE is appropriately used by workers in these scenarios. For example, the likelihood of PPE

adherence in commercial use OES (particularly respiratory protection) is so low the EPA should consider not presenting risk estimates with PPE. Alternatively, these risk estimates could be presented in a separate section or table that describes clearly why EPA is presenting risks with PPE for these scenarios despite the Agency's declared belief that use of exposure controls is unlikely. EPA needs to explain why PPE and "hierarchy of hazard control" are not better considered as mitigation alternatives to be considered by EPA in response to a determination of "unreasonable risk."

See also the discussion for Recommendation 46: Improve the discussion of the exposure control hierarchy.

Recommendation 104: Add discussion of chronic non-cancer risks to consumers.

The Committee argued for added discussion of non-cancer risks to consumers from chronic exposure to trichloroethylene. This need is justified by:

- (1) The Westat survey (U.S. EPA, 1987) being unlikely to capture the full range of high frequency users. High frequency users may be a small fraction of the population for some consumer products and it would require oversampling this fraction of the population to capture them in a population survey.
- (2) Trichloroethylene concentrations can remain elevated for some time after use.
- (3) Products stored in homes after use may emit low levels of chemical into the indoor atmosphere resulting in additional chronic exposure.

Q 6.2	EPA presented overall human health risk conclusions (Section 4.5.2) based on risk estimates for the endpoints that it believes are best representative of acute and/or chronic scenarios (see Question 5.3 - immunosuppression for acute exposure, autoimmunity for chronic exposure). Please comment on EPA's approach including any alternative considerations for determining and presenting risk conclusions including the risk summary tables (Table 4-54 and 4-55).
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Response to Q6.2: Approach for determining and presenting risk conclusions.

Human health risk conclusions are summarized for inhalation and dermal exposures for different occupational exposure scenarios at high-end and central tendency exposure levels. MOE values for acute and chronic noncancer effects and cancer estimates are given. Additionally, each table divides risk calculations between workers with and without PPE. Risk estimates that indicate increased risk vs. the benchmark values are shaded gray. These tables provide a clear summary of the risk conclusions for each occupational COU. This section then presents a similar summary table of human health risks for consumer exposures.

Recommendation 105: Improve the justification for using immunosuppression over congenital heart defects as the unreasonable risk driver for characterizing acute non-cancer risks.

The Committee was aware of and briefly discussed the public questions regarding alleged changes to an early version of this draft risk evaluation. Outside parties claimed that the draft provided for interagency review identified fetal cardiac malformations as the most sensitive endpoint and as the unreasonable risk driver, a finding consistent with prior reviews of trichloroethylene, but that non-scientific pressure caused the Agency to shift to immune findings instead.

The Committee finds that the Evaluation does discuss both endpoints in the hazards section and provides some justification for selection of immunosuppression as the unreasonable risk driver. The rationale for selecting immunosuppression over fetal heart malformations as the endpoint for setting the unreasonable risk driver (given on page 377, lines 132-145) needs improvement. The choice of risk driver for this Evaluation is different than that used in the 2011 IRIS evaluation. This difference should be acknowledged and further discussed.

The Committee suggested that greater transparency is warranted in the rationale for selecting the “best” representative sensitive responses. Because risks are characterized for all potential responses the need for the “best” ones selected should be explicit but at present is not always clear. Some members of the Committee would like more transparency and explanation for why these data were not used as the most sensitive endpoint and wanted to know if this decision was based on uncertainty considerations. A detailed explanation should be provided. There is a disconnect between the decision to exclude the congenital heart defect data and amount of text given to support the decision to use these data in earlier sections. This lack of balance should be clarified.

The Evaluation spells out the human health risk conclusions based on the key studies the Agency used in Tables 4-55 and 4-56 using benchmark values. These tables include derivations based on the Johnson data over which the Committee had divided views. Some Committee members suggested not including the heart defect risk values in Tables 4-55 and 4-56 to allow focus on the immunosuppression risk.

One member of the Committee suggested that the EPA should reevaluate the relevance and the quality of the toxicity data based upon the pathway of exposure. It is not clear that pathways used to expose animals in some of the key studies are appropriate for human extrapolation. Is greater weight being given to data from inhalation studies as opposed to data from oral studies? Is the ADME for inhalation exposures quite different from that of oral exposures? Could this explain the differences between the fetal heart malformation findings and the immunosuppression findings? PBPK models may help, but they are still models, and depend on modeling the pathway effects correctly and not necessarily treating each pathway equally. There is much data on trichloroethylene to allow proper assessment of health endpoints via the inhalation pathway.

Some Committee members called for this Evaluation to consider and discuss the differences between the health effect values derived in this Evaluation and those derived and/or used by other EPA regulatory programs, other federal regulatory agencies, and non-federal entities. This discussion could provide better support for these new TSCA health effect levels, or alternatively, support for more protective health effect levels currently established under other programs. EPA should consider adding a couple of paragraphs summarizing the key drivers in the setting of other exposure guidelines (e.g., based on different health endpoints, includes factors other than health, derived from assessments that are not risk based) to provide context and improve understanding about the various occupational/consumer/public exposure mandates and guidelines.

One Committee members suggested that approaching the setting of health effects levels more in the manner of a meta-analysis might provide a more robust approach than basing this value on a single study and a most sensitive endpoint. This approach might provide a firmer foundation on which to base future risk management decisions.

The Evaluation identifies many conditions of use as posing unreasonable risk. These conclusions follow estimated risks exceeding the MOE for particularly sensitive endpoints that some Committee members consider outliers, and which are the focus of controversy. Consequently, the derived occupational exposure levels are orders of magnitude below those that are currently used to protect worker health by industrial hygienists (e.g., ACGIH Threshold Limit Values, Time Weighted Averages; NIOSH Recommended Exposure Limits (RELs); OSHA Permissible Exposure Limits (PELs)). This presents a risk communication issue for the Agency to consider further.

Recommendation 106: Clarify why Pepper Spray, given that its MOE is below the benchmark MOE, does not present an unreasonable risk.

One Committee member noted that the results for Pepper Spray, presented in Table 4-51, show its MOEs for consumer users are below the benchmark MOE but also below the MOE for the congenital heart defects endpoint. This is an important point to include in the discussion because it is the only consumer COU that is found to not present an unreasonable risk to this higher (but controversial) benchmark.

Recommendation 107: Risks from oral exposures should be discussed and its exclusion justified in the Evaluation.

Worker (Table 4-54) and Consumer (Table 4-55) Risk Summary Tables present details for the benchmark values for dermal and inhalation exposure but oral exposure may occur under some circumstances. The only reference to oral exposures in the Evaluation occurs in ‘footnote b’ to Figure 1-3 - TCE Conceptual Model for Consumer Activities and Uses (Page 58, line 1854-55). Even though oral exposure is expected to be small, the Evaluation should discuss why it is entirely excluded.

Recommendation 108: Explain why risk characterizations for ONUs are appropriately identified as high-end exposures despite being based on central tendency exposure levels of workers.

Tables 4-54 and 4-55 present good summaries of risk characterizations for workers and consumers respectively, although there are some formatting problems that need correction. The links to the summary tables presenting occupational risk estimates for each OES are useful. In Table 4-54, ONU exposures are estimated based on workers' central tendency exposure estimates, which are assumed to represent the high end of potential exposures to ONUs. The notation under the Population column for these ONUs is labeled as "upper limit." This notation is consistent with the expectation that ONU's exposures would be lower than the workers' exposures. Thus, it would be expected that these ONUs exposure estimates correspond to the expected high end, not the central tendency (i.e., they are derived from the central tendency estimate for the worker, but they represent the high-end exposure for the ONU).

Relates to Recommendation 46: While risks are provided with and without PPE, the Committee expressed the opinion that it is inappropriate to consider these as the universe of all possibilities in occupational exposure control. Protective equipment is easily described and quantified with simple (but usually unsupportable) assumptions, however, the hierarchy of control stipulates that PPE should only be invoked after engineering and administrative controls have been implemented. Use of PPE should not be invoked unless structural and administrative controls have been implemented first.

Q 6.3	Please comment on the calculation of risk derived from different exposure data sources (e.g. modeling tools and monitored datasets) and how they account for variability in environmental and human exposure. Please provide specific recommendations as needed for improving the risk characterization and references to support any recommendations (Section 4).
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Response to Q6.3a: Calculation and characterization of environmental risk from different exposure data sources.

The Committee indicated the risk characterization section is clear. The tables present the risk estimates with colored highlighting indicating the responses of concern.

Recommendation 109: Add worst-case scenarios from wastewater contaminated streams and add data on environmental vertebrate receptors for reproductive and developmental effects.

Because hazard is identified but risk characterization is not conducted for aquatic receptors,

additional discussion regarding uncertainty is needed. “Worst-case scenarios” are missing from the Risk Characterization section. From the exposure side of the risk quotient evaluation, monitoring data from National Pollutant Discharge Elimination System (NPDES) should be used for chemical analyses to represent a “worst-case” exposure, particularly in wastewater dominated streams. These data should be available from regional EPA offices. From the effects/hazard side of the risk equation for ecological risk, data is absent for vertebrate reproduction and development in aquatic vertebrates.

Response to Q6.3b: Calculation and characterization of human health risk from different exposure data sources.

Recommendation 110: Include discussion of air emissions, contaminated groundwater and drinking water in the human risk characterization discussion.

The Committee noted that the Evaluation does not consider or discuss the human health and environmental implications of some trichloroethylene releases to the environment that may result in air emissions, contaminated groundwater and drinking water that could add to the exposure of TSCA-related populations. Some Committee members continue to state that not including estimates of these other exposures is unacceptable in the larger framework of risk assessment. They feel that exclusion of these releases in the discussion of trichloroethylene risks implicitly assumes that these potential exposures either result in low and acceptable risks, or are appropriately managed, neither of which may be correct. In addition, exclusion makes it impossible to assess cumulative and aggregate risk to worker, ONU and consumer subpopulations exposed simultaneously via multiple pathways of which occupationally linked pathways is just one.

Relates to Recommendation 46: The Evaluation refers to protection factors when discussing PPE use and its impact on worker risks. In OSHA’s hierarchy of risk control, PPE (and protection factors) are the last resort in the order of priority, preceded by elimination, substitution, engineering controls, and administrative controls. The adequate use of PPE cannot be assumed for many reasons. Many on the Committee support removing the use of PPE in the risk characterization discussions and conclusions. If this is not possible, expectations or evidence of use of PPE under all COUs, and PPE use impacts on risk characterization should be a separate discussion and tied to tables separate from the non-PPE values.

Recommendation 111: The uncertainty in consumer risks from high-end periodic exposures combined with background air and water concentrations should be better characterized and if possible, sensitivity to assumptions and data uncertainties assessed.

The Evaluation on page 322, lines 1044-1047 indicates that risks cannot be ruled out for consumers exposed from high-end frequency of product use that is periodic and not continuous. Associated risks could not be estimated due to the uncertainty in the extrapolation to periodic exposures from continuous exposure studies in animals. The Evaluation expects these high-end

exposures to be unlikely. The Committee expressed concerns that periodic exposures combined with background water and ambient air concentrations may leave consumers with higher risks than calculated in this evaluation.

Recommendation 112: Explore statistical and computational approaches to better utilize available monitoring data and produce more representative exposure estimates.

Monitoring data are unlikely to account for the full range of variability in occupational exposures because the available trichloroethylene monitoring data are not specifically representative of the Occupational Exposure Scenarios (OES). The monitoring data available typically come from what might be labeled as convenience samples that were not intended to accurately reflect the range of exposures for workers across an industry or COU. Few workers are monitored and the monitoring that is performed is typically insufficient to capture within and between worker variability in exposure. Often too few samples are collected to effectively characterize the full range of expected exposures for a given OES. Sampling is often done over short periods of time, being insufficient to capture day-to-day variability. Samples may be collected at only one or a few sites, being insufficient to capture variability across sites for the same OES. Samples may be collected for purposes other than for representative exposure monitoring, meaning that the data and associated statistics are likely biased. The number of samples available varies widely from OES to OES, resulting in differential reliability between sets of samples. Risk estimates based on these samples are unlikely to capture the variability in exposures or the true estimates of central tendency.

Statistical and computational approaches (such as censored estimation, Bayesian methods, and Monte Carlo simulation (see for example Helsel, 2005; Gelman et al. 2004; and Robert and Casella, 2004)) can be used to derive better estimates of exposure statistics (means, medians, variances, interquartile ranges, min and max) from unknown distributions. EPA should explore and use these techniques in TSCA evaluations to overcome some of the limitations in available monitoring data. The alternative is to use TSCA statutory authority to mandate and/or implement adequate monitoring programs to fill this data need. Relates to Recommendation 53.

Monitoring data reports frequently have area samples (also called static samples) collected away from the worker's location. These data could be explored as potential indicators of ONU's exposures. Similarly, modeling estimates of far-field concentrations could be considered as indicators of ONU's exposures.

Q 6.4	Please comment on whether the risk evaluation document has adequately described the uncertainties and data limitations associated with the methodologies used to assess the environmental and human health risks. Please comment on whether this information is presented in a clear and transparent manner (Section 4.3).
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Response to Q6.4: Adequacy of descriptions of uncertainties and data limitations.

The uncertainties of the environmental risk characterization are summarized in section 4.3.1. The section discussing uncertainties in environmental hazard identification (3.1.7) has a more detailed discussion of uncertainties and limitations than that provided in section 4.3.1. One Committee member suggested either expanding section 4.3.1 or cross-referencing much of section 4.3.1 back to section 3.1.7.

Related to Recommendation 112: Occupational exposure limitations are clearly explained. However, it is concerning that EPA did not find enough reasonably available data to determine statistical distributions for air concentrations for workers exposed to trichloroethylene. A similar uncertainty is found for ONUs and consumers. It is recommended that EPA use its statutory authority to request studies to consider in the assessment, particularly given the draft determination of unreasonable risk.

Recommendation 113: Perform a sensitivity analysis on inputs to the consumer exposure model to address uncertainties in representativeness of model outputs.

Page 349, line 1442 the Evaluation states that:

“Certain inputs to which the (*consumer exposure*) model outputs are sensitive, such as zone volumes and airflow rates, were not varied across product-use scenarios. As a result, model outcomes for extreme circumstances such as a relatively large chemical mass in a relatively low-volume environment likely are not represented among the model outcomes. Such extreme outcomes are believed to lie near the upper end (e.g., at or above the 90th percentile) of the exposure distribution.”

The Committee identified that this conclusion represents a source of uncertainty that should be addressed through some form of sensitivity analysis. As it stands, the limited discussion provided here is inadequate.

Recommendation 114: Better organize the discussion on assumptions and uncertainties in Section 4.3 and summarize (tabulate) more of the exposure and hazard uncertainties in this section than simply referring to previous sections.

The uncertainty and data limitation sections lack balance are incomplete and should be expanded. More than two pages are devoted to the exposure assessments and only one short paragraph to human health hazard (Evaluation, page 350, lines 1490-1495). There are numerous

uncertainties/data limitations in the health hazard and referring to section 3.2.6 without highlighting the issues of greatest uncertainty/limitation is not adequate. What is the point of having a full section on uncertainties/data limitations if the reader is simply referred to earlier text?

The summary of uncertainties is too limited; the text directs the reader to section 2.3.1.3 for details. One would expect to see a complete summary of uncertainties in this section. A table format would help (e.g., two columns, one listing the variable/parameter and the other the uncertainties; Table 2-26 on page 183 of the Evaluation could be an applicable template).

Although the concerns and issues with congenital heart defects as a non-cancer endpoint are described elsewhere, this issue is ignored in this section. The issues and related uncertainties should be summarized here, and a reference provided to where this issue is discussed in greater detail.

There are uncertainties in exposure and hazard estimates that translate into uncertainties in the risk characterization. A recurrent issue in this Evaluation and prior evaluations is lack of transparency about how the uncertainties and sensitivity analyses feed forward and get integrated into a balanced evaluation of uncertainty in risk characterization. The Committee believes that an integrated, overall evaluation of uncertainty in the risk characterization would be valuable. This involves risk propagation of uncertainties across the characterization of risk done at least semi-quantitatively, perhaps characterized as high, medium, or low with accompanying statements of why each is rated as it is. The summary table should provide annotation and provide an integrated, semi-quantitative characterization of uncertainty in the risk characterization.

One Committee member recommended using confidence summaries like Slide #48 in the EPA OPPT technical presentation to SACC at the beginning of the meeting. Other Committee members suggested that several other slides (#13, #24, #27) in the presentation are also helpful summaries and should be included in the Evaluation report. (Slide set is available at the docket at: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0500-0055>)

Recommendation 115: Include more discussion on uncertainties in the PBPK model and with route-to-route extrapolation from oral to inhalation.

The cited section (3.2.6) inadequately addresses the uncertainties/data limitations of PBPK modeling approaches (see response to question 5.6). Also, toxicity data from oral exposures are treated as equivalent with data collected from inhalation exposures, ignoring the uncertainties inherent when conducting route-to-route extrapolation, even when using a PBPK model. Discussion on these issues are lacking. See also Recommendation 87.

Q 6.5	Please comment on the clarity and validity of specific confidence summaries presented in Section 4.3.
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Response to Q6.5: Clarity and validity of confidence summaries.

Some Committee members considered Section 4.3 to be a concise summary of the confidence in the data for each endpoint and exposure scenario. However, although the confidence summaries are presented clearly, the Committee noted that it is less clear how the assumptions and uncertainties are weighted to arrive at the overall confidence summaries. Text is sometimes difficult for the reader to follow given that the details are cross-referenced to other sections.

The validity of the confidence statements is difficult to assess without a numerical measure of uncertainty and/or finding from a sensitivity assessment. Despite this, the confidence assessments provided are consistent with the assumptions presented.

Recommendation 116: Integrate sensitivity analysis findings with the discussion of uncertainties.

The Committee recommended that the Evaluation consider uncertainty and sensitivity analysis findings concurrently. For instance, a finding with high uncertainty but low sensitivity suggests the lack of confidence in the estimate for a parameter that has little impact on the ultimate risk estimate. The large variance associated with the insensitive parameter does not significantly change the risk finding, thus there would be little need to decrease the uncertainty in this parameter with further data. On the other hand, a result with medium uncertainty but high sensitivity, suggests that the large associated variability for an impactful parameter implies large uncertainty in the final risk. As a result, there is greater need to get better information on this parameter in order to decrease the uncertainty in the final risk. This recommendation is valid for the entire risk evaluation, given the degree of uncertainty and data gaps encountered, or in any assessment for which we know there will be uncertainties as a matter of process (e.g., life cycle assessments).

The Frank R. Lautenberg Chemical Safety for the 21st Century Act (2016) (amended TSCA) states that “potentially exposed or susceptible subpopulations” (PESS) be considered in the risk evaluation process. PESS is defined in the Lautenberg Act to include populations with greater exposure or greater response, including due to lifestyle, dietary, and biological susceptibility factors, than the general population.

Q 6.6	Has a thorough and transparent review of the available information been conducted that has led to the identification and characterization of all PESS (Sections 2.3.3, 3.2.5.2, and 4.4.1)? Do you know of additional information about PESS that EPA needs to consider? Additionally, has the uncertainty around PESS been adequately characterized?
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Response to Q6.6: Thoroughness and transparency of review regarding PESS.

Recommendation 117: Provide more information for risk assessment of susceptible populations with non-alcoholic fatty liver disease as the prevalence of obesity and overweight has increased to over 30% of the population who have higher levels of fat in their body.

It is always difficult to address the potentially exposed and susceptible subpopulations (PESS) in risk characterization due to the lack of adequate data to support identification of PESS. There are numerous factors, including race/ethnicity, life stage, (biological) sex differences, life style, nutrition, genetic polymorphisms (i.e., CYP, GST), and pre-existing health conditions (i.e., obesity, kidney and liver diseases etc.), which could significantly affect the susceptibility of persons exposed to trichloroethylene but no substantive discussion is found on susceptible populations in section 2.3.3.

Recommendation 118: Provide a more detailed risk assessment focused on the susceptible populations, particularly pregnant women, their developing fetuses, and people with specific health conditions.

In Section 3.2.5.2, the Evaluation provides few details on identified susceptible populations, including pregnant women and their developing fetuses, and people with kidney and liver illness. The Evaluation also addresses TSCA-relevant potentially exposed sub-populations within workers, ONUs, consumers, product users and bystanders associated with consumer use. These are essentially traditional PESS but with more exposure to trichloroethylene in products or during manufacturing and processing. It is not clear to all Committee members that risks to PESS are adequately covered by the uncertainty factors applied. When are expected PESS responses great enough to require explicit risk calculations or additional uncertainty factor adjustments?

Recommendation 119: Provide more of the details to support the conclusion that the HEC99/HED99 is sufficient to account for the susceptible subpopulations.

Recommendation 120: Run the PBPK model to understand effects on individuals with abnormal values from preexisting health conditions such as obesity and hepatitis.

The Agency includes approximate differences between some groups and what is accounted for in the PBPK model in Section 4.4.1. They assume that the use of “the 99th percentile output of the PBPK model, these values are expected to be protective of particularly susceptible subpopulations,” but no further discussion is provided. The Evaluation should mention that the PBPK model does not account for pregnancy or lactation. Further, the Fisher PBPK models for fetal component should be included in the report. It is very essential to run PBPK model for understanding effect on individuals with abnormal values from preexisting health conditions.

While the Evaluation discusses uncertainties with respect to susceptible populations, the Committee was unable to find where the Evaluation quantitatively assesses the impacts of sensitivity to assumption and related uncertainty on risk estimates for susceptible populations.

The EPA characterization of human health risk from inhalation exposure to workers includes estimates of risk both with and without respirator use. These estimates are calculated by multiplying the high end and central tendency MOE or extra cancer risk estimates without respirator use by the respirator assigned protection factors (APFs) of 10 or 50 and the glove protection factors of 5, 10, or 20. EPA also characterized exposure scenarios in which respirator use was unlikely. EPA did not assume occupational nonusers (ONUs) or consumers used personal protective equipment (PPE) in the risk estimation process.

Q 6.7	Please comment on whether EPA has adequately, clearly, and appropriately presented the reasoning, approach, assumptions, and uncertainties for characterizing risk to workers and ONUs using PPE (exposure - Sections 2.3.1.2.6 and 2.3.1.3, Table 2-20; risk - Sections 4.2.2 and 4.3.2.1).
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Response to Q6.7: Characterizing risks to workers and ONUs using PPE.

Overall, the Committee agreed that the Agency clearly and adequately describes assumptions and uncertainties about use of PPE for risk characterization for workers and occupational non-users but not with enough emphasis.

The Committee concluded that while risks are provided with and without PPE, it is inappropriate to provide these two possibilities as the only risk mitigation actions available in COU scenarios. The conversation at this point revisited the same topics summarized for Recommendation 46: Improve the discussion of the exposure control hierarchy.

The primary assumption that exposure control recommendations are followed (or expected to be followed) considering evidence to the contrary should be addressed directly in the Evaluation. At some point, EPA should make a decision as to whether the lack of specific data on PPE use and having essentially no confidence that it is used as recommended by exposure control guidelines results in a decision not to characterize risks with PPE. Alternatively, EPA should transparently and clearly explain why EPA provides exposure and risk estimates with use of PPE in all cases, despite evidence of poor adherence to such use and EPA's recognition of uncertainty about the proper use of PPE in many scenarios. Is PPE use being considered a condition of use or, as many of the Committee consider it, a risk modifier?

Q 6.8	Please comment on any other aspect of the environmental or human health risk characterization that has not been mentioned above (Section 4).
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Response to Q6.8: Other aspects of risk characterization not mentioned previously.

Recommendation 121: Clearly and explicitly state in Section 4 the fundamental objective of the environmental or human health risk characterization.

Overall, the fundamental objectives for the environmental or human health risk characterization need to be more clearly and explicitly stated in Section 4.

Issues or questions such as the following need more emphasis:

1. What is the most sensitive endpoint for each exposure route and use, for both acute and chronic non-cancer effects and cancer?
 - a. As a corollary to #1, explicitly define what is meant by "most sensitive."
2. Limitations and data gaps need to be presented in a more highlighted and obvious manner.
3. Areas of controversy should be highlighted.

The Committee noted that exposure from drinking water is not adequately covered in risk assessment. For example, individuals who consume higher than normal levels of alcohol have been discussed as a potentially exposed susceptible population that could be exposed to trichloroethylene not only through occupational or consumer COUs, but also through contaminated drinking water. See Recommendation 42: Consider breathing rates, alcohol consumption and other models for vapor generation in the inhalation assessment.

Question 7: Overall Content and Organization:

EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

As part of this draft risk evaluation for TCE, EPA evaluated potential environmental, occupational and consumer exposures. The evaluation considered reasonably available information, including manufacture, use, and release information, and physical-chemical characteristics. It is important that the information presented in the risk evaluation and accompanying documents is clear and concise and describes the process in a scientifically credible manner.

To increase the quality and credibility of scientific information disseminated by EPA, EPA uses the peer review process specifically as a tool for determining fitness of scientific information for the intended purpose. The questions below are intended to guide the peer reviewers toward determining if EPA collected, used and disseminated information that is 'fit for purpose' based on utility (the data's utility for its intended users and for its intended purpose), integrity (the data's security), and objectivity (whether the disseminated information is accurate, reliable, and unbiased as a matter of presentation and substance). The peer reviewers' critical focus should pertain to recommendations of the technical information's usefulness for intended users and the public.

<i>Q 7.1</i>	<i>Please comment on the overall content, organization, and presentation of the TCE draft risk evaluation. Please provide suggestions for improving the clarity of the information presented.</i>
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Response to Q7.1: Overall content, organization and presentation.

Committee members commented that some areas were easier to read than others and offered suggestions to improve the clarity. Some of the previous recommendations in previous reviews by the Committee also apply to this Evaluation.

The Evaluation follows the document organization established for all previous TSCA chemical risk evaluations. As mentioned in the Committee review of previous TSCA chemical evaluations, not all Committee members agree that this report structure is the easiest format to follow. The Committee continues to comment on how much information should be included in the main body of the Evaluation, in the appendices, in supplemental documents, and simply citations to other references.

Recommendation 122: Add very concise summary tables that highlight previous hazard assessments and risk assessments (e.g., EPA IRIS document, ATSDR, NTP, IARC, etc.) with their main conclusions.

For example, Section 1.3 on regulation and assessment history does not have enough detail in the main report and instead refers to other documents and Appendix A.

Recommendation 123: Add GHS classification.

One Committee member recommended adding the Global Harmonization System (GHS) classification to Section 1.1 on physical-chemical properties. Including the GHS classification for the substance here as reference makes sense because this is the first description of the characteristics of the chemical. GHS classification provides a standardized way to look at the hazards across chemicals and is the most common way to communicate on hazards of chemicals to industrial users.

Recommendation 124: Enhance Table 1-1 to include additional properties and property variability.

The Committee had several comments on the physical-chemical properties in Table 1-1. Other properties should be added to the table, including properties related to dermal absorption (see Table 6 for dermal parameters recommended by the SACC for inclusion in the current and future TSCA risk evaluations). Include all properties that are used either explicitly or implicitly in modeling. Concern was expressed with the over-reliance on EPI Suite™, a tool that is no longer being supported (e.g., the databases are not being updated). The variability associated with each property estimates should be included. Adding variability estimates allows for quantitative assessment of how this uncertainty impacts Evaluation findings. See also **Recommendation 2** and **Recommendation 8**.

Recommendation 125: Consider including a table or figure that shows mass balance information.

The SACC recommended in previous assessments of TSCA chemical evaluations to include more information on the chemical manufacture, uses, and releases, which the Committee has referred to as the “mass balance” approach. This is a consolidation and expansion of several tables in the Problem Formulation, main report, and appendices. Committee members had differing opinions on the reasonableness of this approach and what it might entail. No consensus was reached on whether such a table would be useful or even able to be created.

The mass-balance issue is related to the discussion on Question 1.6 and aimed at providing readers of the Evaluation with a better understanding of where in the (U.S.) environment trichloroethylene can be found (sources, fluxes and sinks; see Recommendation 21). A secondary goal is putting the COUs evaluated in this Evaluation in context of all manufacturing, uses, and releases. Some of the information is readily available. For example, the Trichloroethylene Market and Use Report (U.S. EPA 2017h) indicates on page 1-1: “In 2014, the U.S. accounted for 24 percent of global demand, second only to China which accounted for 52 percent of global demand (IHS 2014). Currently, U.S. EPA (2017h) reports that 83.6 percent of trichloroethylene is used as an intermediate in the production of the refrigerant HFC-134a, an

alternative to the banned refrigerant CFC-12. Another 14.7 percent of trichloroethylene is used as a degreaser for metal parts (U.S. EPA 2014). The remaining 1.7 percent is attributable to other uses, including as a spot-removal solvent in dry cleaning, as a modifier in PVC polymerization, and in consumer household aerosol products (U.S. EPA, 2014).” One Committee member pointed out that the Evaluation has a purported 2 million pounds of trichloroethylene lost. This is 2% of the total product volume and a mass balance approach would show where this loss is coming from. It would be a higher percentage if the loss came from the approximately 15% used to make trichloroethylene-containing products.

The estimates should also be updated for both the newer reports to EPA, as EPA has stated it will do, and for the market study. The IHS 2017 (U.S. EPA, 2017h) values are noticeably different—“In 2017, China was the largest consumer of trichloroethylene, accounting for 58% of total world demand, followed by the United States at 19%, Japan at 6% and Western Europe at 5%.”

A mass balance would point out amounts missing from TRI, as many of the releases are from the TRI, and allow comparison to environmental levels monitored. Some Committee members commented that the TRI estimated releases are under reported, while another Committee member commented that they are over reported. The Committee agrees that TRI estimated releases are not accurate, although reporters try to report all their releases.

Problems with fulfilling the needs of a mass balance table include CBI, delays between manufacturing and use, and changing uses/formulations. The Committee recommended that EPA investigate possible solutions, such as using a multi-year average and aggregating information to avoid disclosure of CBI.

EPA included what it referred to as a Life Cycle Analysis (LCA) in the Problem Formulation (U.S. EPA, 2018), but this does not contain the parts of a standard LCA (U.S. EPA 2006b, ISO 14040⁹) and does not present the information the Committee has requested. It is good that the Problem Formulation included a summary across different phases of the life cycle and the Agency used life cycle thinking to frame the risk evaluation, but this is not the same as doing an LCA. EPA’s publication on LCA principles and practice says that an LCA “evaluates all stages of a product’s life from the perspective that they are interdependent” and “enables the estimation of the cumulative environmental impacts resulting from all stages in the product life cycle, often including impacts not considered in more traditional analyses.”

Committee members provided Table 7 as one example of what a mass-balance table might look like.

⁹ <https://www.iso.org/obp/ui/#iso:std:iso:14040:en>

Table 6: Dermal parameters recommended for inclusion in the current and future TSCA risk evaluations. (Source: SACC Carbon Tetrachloride Evaluation)

Parameter	Symbol	Typical Units	Description	Rationale	Reference
Aqueous permeability coefficient	$k_{p,sc/w}$	cm/h	Predictor of permeability of stratum corneum from aqueous vehicle	Method previously accepted by USEPA	USEPA RAGS Part E, 2004
Aqueous permeability coefficient	$k_{p,sc/w}$	cm/h	Predictor of permeability of stratum corneum from aqueous vehicle	Alternative to RAGS Part E method	NIOSH CIB 61, 2009
Relative permeability of the stratum corneum to that of the viable epidermis	B	[-]		Indicator of potential error if resistance in viable epidermis is ignored	Cleek & Bunge, 1993
Theoretical maximum steady-state flux	$J_{ss,max}$	$\mu\text{g}/\text{cm}^2\cdot\text{h}$	Product of aqueous permeability coefficient and aqueous solubility	Maximal sustainable absorption rate	
Ratio of evaporation flux to absorption flux	c	[-]		Evaporation competes with absorption for volatile compounds	Kasting & Miller, 2006
Octanol/air partition coefficient	$K_{o/a}$	[-]	2-phase partition coefficient at thermodynamic equilibrium	Analog to octanol/water partition coefficient used to estimate $K_{sc/g}$	
Stratum corneum/gas partition coefficient	$K_{sc/g}$	[L/kg]	2-phase partition coefficient at thermodynamic equilibrium	Key determinant of vapor to skin pathway	Weschler & Nazaroff, 2014
Dermal vapor to inhalation dose ratio, modeled	$D/I_{modeled}$	[-]		Indicator of potential error if dermal uptake from vapor is ignored	Weschler & Nazaroff, 2014
Dermal vapor to inhalation dose ratio, measured	$D/I_{measured}$	[-]		Check on $D/I_{modeled}$	Weschler & Nazaroff, 2014
Observed absorption flux	J	$\mu\text{g}/\text{cm}^2\cdot\text{h}$	In vitro or in vivo human, or in vivo rodent data if available	Check on $J_{max,ss}$; especially important if exposure is to pure compound rather than dilute aqueous solution	

Table 7: Example of data needed to demonstrate balance among inputs and depositions.

	Volume in pounds (kg) x 10 ⁶			
	2012	2013	2014	2015
Total Aggregate US Production Volume	220.5 (100.0)	199.0 (90.3)	192.0 (87.1)	171.9 (78.0)
Domestic Manufactured				
Imported				
Total Used in Processing in the US				
<i>Functional Fluids (Closed System)</i>			160.5 (72.8)	
<i>Solvents for Cleaning and Degreasing</i>			28.2 (12.8)	
Subtotal			188.7 (85.6)	
<i>Adhesives and Sealants</i>				
<i>Lubricant and Greases</i>				
<i>Paints and Coatings</i>				
<i>Cleaning and Furniture Care Products</i>				
<i>Laundry and Dishwashing Products</i>				
<i>Arts, Crafts and Hobby Materials</i>				
<i>Apparel and Footwear Care Products</i>				
<i>Other Commercial Uses</i>				
Recycled				
Disposal and Releases				
<i>Industrial Pre-Treatment</i>				
<i>Industrial Wastewater Treatment</i>				
<i>Publicly Owned Treatment Works (POTW)</i>				
<i>Biosolids</i>				
<i>Landfills</i>				
<i>Surface water</i>				
<i>Air</i>				

Recommendation 126: Use figures instead of tables to display production volume and uses.

Apart from the idea of a mass balance approach, the Committee suggested using figures instead of tables for production volume (Table 1-2) and uses (pages 42-43, lines 1659-1665). Sample figures are below.

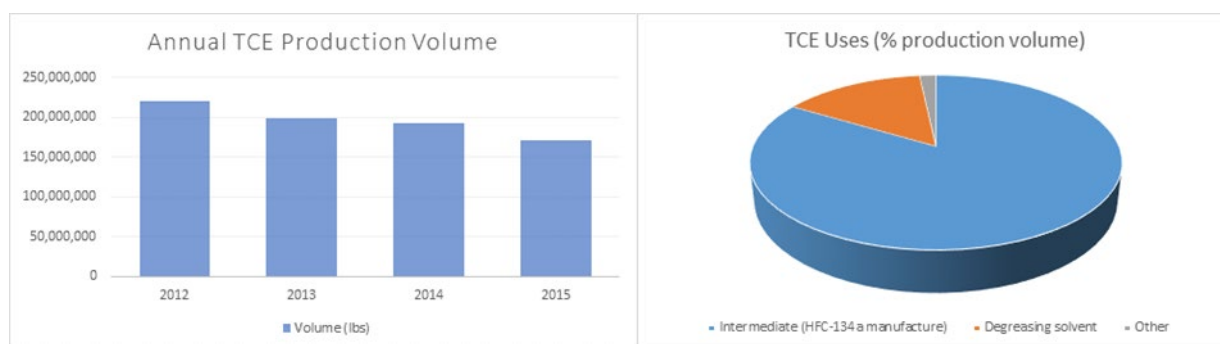


Figure 1: Examples of graphics needed to depict production trends and utilization.

Recommendation 127: Consider using table structures in the TSCA risk evaluation that are similar to those used in the associated IRIS assessment.

When there is an existing IRIS review available for a TSCA chemical under review, it is preferable to use summary table formats in the TSCA risk assessment that have the same structure as the corresponding table in the IRIS report. In the Evaluation, Tables 3-7 to 3-14 report dose-response analysis results for selected studies and present PODs, HECs, HEDs and Uncertainty Factor values used. In the 2011 trichloroethylene IRIS report (U.S. EPA, 2011b), Table 5-13 provides the same information but in a different format. In this case, the IRIS table is clearer. One Committee member strongly recommend the use of the IRIS report format for these tables, if for no other reason than for consistency.

Recommendation 128: Move exposure estimates based on workers central tendency exposures from Section 4 Risk Characterization to Section 2 Exposures.

Unlike in previous evaluations, EPA chose to discuss ONUs' exposure estimates based on modeling or measurements in Section 2- Exposures, but to discuss the central tendency exposure estimates based on workers in Section 4 – Risk Characterization. This is problematic because the estimates for ONUs based on workers are also exposure estimates, although with different levels of assumptions, uncertainty, and confidence. They should be included in Section 2 with the appropriate justification, description of uncertainties, caveats, etc.

Recommendation 129: Provide more consistent and detailed discussion of PPE usage in the main Evaluation document.

The Evaluation should provide more detailed discussion of PPE usage in the main document instead of just referring the reader to the NIOSH Memorandum, as was done for the carbon tetrachloride draft risk evaluation, based on the same reference. The issue of the balance between how much detailed information to present in the main document and how much in appendices remains. PPE use, as handled in this Evaluation, is a critical issue that should have more information in the main document.

Presentation of PPE issues in Section 2 is organized awkwardly. PPE for dermal exposures appears as part of subsection 2.3.1.3.5 – Modeled Dermal Exposures, while for inhalation exposures it is presented in the next subsection, 2.3.1.3.5 – Consideration of Engineering Controls and Personal Protective Equipment, which discusses respirators, but inhalation exposures are described in sections 2.3.1.2.1 through 2.3.1.2.4, well before dermal exposures. Either the presentations of dermal and inhalation protection are made separately for each route of exposure in both cases, or there should be a separate subsection that discusses exposure controls and presents both types of PPE.

Recommendation 130: Present uncertainty and confidence as in Table 2-26 throughout the Evaluation.

One Committee member commented they liked the presentation of uncertainty and overall confidence in a table format such as Table 2-26: Summary of overall confidence in inhalation exposure estimates by OES. If the descriptions are systematized better, it would be a good model to follow for summarizing uncertainties and confidence throughout the Evaluation, including summarizing PESS.

Recommendation 131: Implement the following revisions to improve clarity of the Evaluation.

As stated earlier throughout the Report, the Committee emphasizes the following issues that need attention:

- 1) Cite original sources instead of referring to documents in the docket or to the EPA Web Application Access database where the public may not have easy access.
- 2) On Table 2-3 where estimates for the number of facilities for each OES are provided, the estimation of the number of facilities could be enhanced by adding a sense of uncertainty +/- X percent or X facilities.
- 3) The choice of a tornado graph in Figure 2-1 does not seem to be the best one to promote clarity. It is suggested that a set of pie charts or sectioned bar graph may better illustrate the point.
- 4) Section 2.2.5 mentions surface water concentration maps that are not provided. The color coding is provided but the maps themselves not provided nor is there a link or reference to their source.
- 5) Section 5.1.3 is simply not clear on the final environmental risk determination. From section 4.1 one can deduce that no unreasonable risk to aquatic organisms in surface water was concluded. There are some risks with $RQ > 1$ associated with specific facilities and species, but there is no summary of either in the final risk determination. It is recommended that the Evaluation summarizes the approach and determination for each condition of use.
- 6) Expand use of links in tables to other tables and include links to items in the docket.

Q 7.2	Please comment on the objectivity of the information used to support the risk characterization and the sensitivity of the Agency's conclusions to analytic decisions made.
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Response to Q7.2: Objectivity of information used in risk characterization and sensitivity of conclusions to analytic decisions.

Committee members commented that the Species Sensitivity Distribution (SSD) diagram (a scatterplot) is a good visualization tool to display the potential relative impact of chemical exposure on different species but its utility depends on understanding the ecology of the aquatic environment.

The Committee strongly supports the use of a sensitivity assessment of the consumer exposure model.

The Committee commented in general, the Evaluation does a good job of explaining how the TSCA assessment differs in scope and focus from the IRIS assessment. Moreover, it is mentioned in multiple places that the hazard and risk assessments done previously are used as a starting point and then updated for the present assessment. However, a more informative summary could be provided, for example, that lists the critical endpoints for acute and chronic non-cancer and cancer effects, the critical studies identified for each endpoint and/or those that were used to determine POD values.

Related to Recommendation 71, Recommendation 72: Reconsider the scores assigned to the epidemiological evidence for trichloroethylene-induced cardiac anomalies.

Recommendation 74, Recommendation 82, and Recommendation 106: Some Committee members commented there is the impression of bias in the descriptions of the fetal cardiac malformations in relation to the literature, especially the Johnson et al. (2003) and the Charles River study (2019). The Committee recommended the Agency consider a full and complete description of the issue (i.e., why is this endpoint so controversial?) and provide a more complete discussion of other relevant studies to help explain the results relevant to data coherence between studies conducted by the same route of administration (e.g., Is there coherence in the available literature? Is it consistent with oral, inhalation exposures or both?).

Committee members brought up a concern related to the questions raised publicly regarding alleged changes to the Evaluation. The claim stated that the draft provided for interagency review identified fetal cardiac malformations as the most sensitive endpoint, and used this value to derive the points of departure for making determinations of risk, a decision that was consistent with prior reviews of trichloroethylene (e.g. EPA's 2011 IRIS review - U.S. EPA 2011 b.e). This public

allegation in part justified the Committee engaging in an extensive discussion of the DRE's rationale for excluding fetal heart malformations as the endpoint for setting the point of departure,

Related to Recommendation 74: Several Committee members commented that overall, it seems the EPA judges study quality, but it is difficult to understand how study relevance factors into any conclusion in choosing a particular study from which to develop a POD and resulting value to carry through the risk assessment.

Recommendation 132: Provide more clarity on how cancer risks were estimated by showing computation details.

A Committee member noted the development of cancer risk is difficult to ascertain. In this section (page 250, lines 2463-2476) the Evaluation states that the IUR is “adjusted by a factor of 4 to account for estimating risk from all three cancer types,” yet later suggests lifetime cancer risks are first calculated and then summed across all three types. Which is it?

Recommendation 133: Provide support for the statement on kidney cancer MOA or modify the statement to reflect the lack of consensus.

Recommendation 134: Provide more discussion in the body of the Evaluation to support the statement in the Executive Summary on the kidney cancer MOA.

The Executive Summary, page 30, lines 1237-1240 states: “A linear non-threshold assumption was applied to the trichloroethylene cancer dose-response analysis because there is sufficient evidence that trichloroethylene-induced kidney cancer operates primarily through a mutagenic mode of action while it cannot be ruled out for the other two cancer types.”

One Committee member was uncertain that this is a correct statement, being unaware that there is consensus on the kidney cancer MOA. This may have arisen from the fact that the discussion in Section 3.2.4.2.2 – Kidney Cancer MOA only references the trichloroethylene 2011 IRIS assessment but provides no details in support of the statement above.

Recommendation 135: Use the DHHS definition of adults consistently.

Throughout the document, there is a need to be consistent and correct about the age cut-off for “adults.” The Evaluation should follow the DHHS guideline of adults being age ≥ 18 years. In some places, the Evaluation uses either age 16 or 21 years as a cut-off; it is unclear why there is a lack of consistency. Page 186, lines 3128-3129: has a particularly odd definition of adults as age ≥ 11 years.

EDITORIAL COMMENTS

General:

- All references to document should also include a link to the appropriate record in the EPA HERO database.
- Be mindful to use the proper number of significant figures.
- There are problems with formats in several tables.
- Add a footnote to Tables listing HE and CT indicating what they mean.
- Acronyms and labels used in the Evaluation should be sufficiently long and distinct enough to perform searches: acronyms such as “E1” and “E3” are insufficient.
- Use the word “sex” instead of “gender,” since sex refers to biological difference whereas gender is a social construct.

Specific:

- Pages 115-116, lines 1250-1256: provide citations to OSHA and NIOSH hierarchy of exposure controls.
- Page 119: protect workers from exposure; line 1354 add citations.
- Page 119, lines 1359-1361: something is missing in the sentence, suggest alternative with commas: “Respirator selection provisions are provided in § 1910.134(d) and require that appropriate respirators are (be) selected based on the respiratory hazard(s) to which the worker will be exposed, and (including) workplace and user factors that affect respirator performance and reliability.”
- Page 120, line 1371: provide the reference to the ACGIH TLVs, not to ATDSR, which is a secondary source. Unclear why primary sources of information or data are sometimes not used.
- Page 240, line 2110: “kidney” needs to be changed to “liver.”
- Page 259, lines 25-26 states: “For acute exposures to invertebrates, toxicity values ranged from 7.8 to 33.85 mg/L (integrated into a geometric mean of 16 mg/L). For chronic exposures, toxicity values for fish and aquatic invertebrates were as low as 7.88 mg/L and 9.2 mg/L, respectively.” The Committee was uncertain as to what these values are. Are they median lethality values? EC₅₀s? NOAELs? LOAELs? What is the justification for using a geometric mean? The second sentence discusses chronic values for fish and invertebrates; what do these values represent?
- Figures in Appendix F are captioned as “tables.”

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