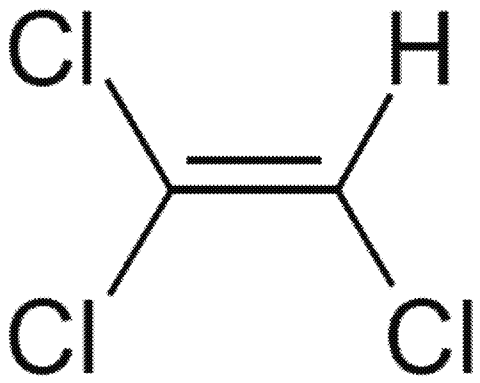
United States
Environmental Protection Agency

EPA Document# 740-R1-4002
June 2014
Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical Risk Assessment

Trichloroethylene:
Degreasing, Spot Cleaning and Arts & Crafts Uses

CASRN: 79-01-6



June 2014

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AUTHORS/CONTRIBUTORS/ACKNOWLEDGEMENTS/REVIEWERS

This report was developed by the United States Environmental Protection Agency (U.S. EPA), Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT). The work plan risk assessment for trichloroethylene (TCE) was prepared based on existing data and any additional information received during the public comment period and peer review process. Mention of trade names does not constitute endorsement by the US EPA.

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Acknowledgements

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Also, portions of this document were prepared for the U.S. EPA by the Syracuse Research Corporation and Versar.

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External Peer Review

EPA/OPPT contracted with The Scientific Consulting Group, Inc. (SCG) to convene a panel of *ad hoc* reviewers to conduct an independent external peer review for the EPA's draft work plan risk assessment for TCE. As an influential scientific product, the draft risk assessment was peer reviewed in accordance with US EPA's peer review guidance. The peer review panel performed its functions by web conference and teleconference on July 9, July 17 and August 21, 2013. The panel consisted of the following individuals:

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Please visit the EPA/OPPT's Work Plan Chemicals web page for additional information on the TCE's peer review process, including the peer review report: http://www.scgcorp.com/tcl2013/

GLOSSARY OF TERMS AND ABBREVIATIONS

ε_0	Vacuum permittivity
$\mu g/m^3$	Microgram(s) per cubic meter
AC	Acute concentration
ADC	Average daily concentration
ADR	Acute dose rate
ADR_{pot}	Potential acute dose rate
AEGL	Acute exposure guideline level
AER	Air exchange rate
AT	Averaging time
Atm	Atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BMD	Benchmark dose
BMDL	Benchmark dose, lower confidence limit(s)
BLS	Bureau of Labor Statistics
BOD	Biochemical oxygen demand
BW	Body weight
C	Contaminant concentration
C_{air}	Air concentration
°C	Degree Celsius
C_{FF}	Average far field concentration
$C_{FF,TWA}$	Time weighted average far field concentration
C_{NF}	Average near field concentration
$C_{NF,TWA}$	Time weighted average near field concentration
Cp_{pot}	Modeled peak concentration
CASRN	Chemical abstracts service registry number
CBI	Confidential business information
CCD	Chemical Control Division
CCRIS	Chemical Carcinogenesis Research Information System
CDR	Chemical data report
CEM	Consumer exposure module
CEPA	Canadian Environmental Protection Act
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFC-12	Dichlorodifluoromethane, also called Freon-12
CH	Chloral hydrate
CI	Confidence interval
cm	Centimeter(s)
cm^3	Cubic meter(s)
CNS	Central nervous system
CO_2	Carbon dioxide

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cRfC	Candidate reference concentration
CYP	Cytochrome P450
DCA	Dichloroacetic acid
DCAC	Dichloroacetyl chloride
DCVC	S-Dichlorovinyl-L-cysteine (collectively, the 1,2- and 2,2- isomers)
DCVG	S-Dichlorovinyl-glutathione (collectively, the 1,2- and 2,2- isomers)
DCVT	Dichlorovinyl thiol
DEv	Duration of an event
DIY	Do-it-yourself
DNA	Deoxyribonucleic acid
DART/ETIC	Developmental and Reproductive Toxicology/Environmental Teratology Information Center
DOS	Disk operating system
ECA	Enforceable consent agreement
ED	Exposure duration
EETD	Economics, Exposure and Technology Division
EF	Exposure frequency
E-FAST2	Exposure and Fate Assessment Screening Tool version 2
EFH	Exposure factors handbook
EMIC	Environmental Mutagens Information Center
EMICBACK	Environmental Mutagen Information Center Backfile databases
EPA	Environmental Protection Agency
ESRD	End-stage renal disease
EU	European Union
EvapTime	Evaporation time
FF	Far field
FMO3	Flavin-containing monooxygenase
FQ	Frequency of product use
FSA	Free surface area
ft	Foot/feet
ft^2	Square foot/feet
ft^3	Cubic foot/feet
g	Gram(s)
g/cm^3	Grams per cubic centimeters
g/L	Grams per liter
G	Average generation rate
GD	Gestational day
GENE-TOX	Genetic Toxicology Data Bank
GGT	Gamma glutamyl transpeptidase
GSH	Glutathione (reduced)
H_{NF}	Near field height
HAPs	Hazardous air pollutants
HCV	Human cancer value
HEC	Human equivalent concentration

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HEC_{50}	Human equivalent concentration at the 50th percentile
HEC_{95}	Human equivalent concentration at the 95th percentile
HEC_{99}	Human equivalent concentration at the 99th percentile
hr(s)	Hour(s)
HSDB	Hazardous Substances Data Bank
HSIA	Halogenated Solvents Industry Alliance, Inc.
HVICL	High Volume Industrial Chemicals List
IA	Indoor air
IARC	International Agency for Research on Cancer
id POD	Internal dose point of departure
InhR	Inhalation rate
IgA	Immunoglobulin A
IL-2	Interleukin-2
IEMB	Indoor Environmental Management Branch
IRIS	Integrated Risk Information System
IUR	Inhalation unit risk
k	Emission rate
K_{ow}	Octanol:water partition coefficient
kg	Kilogram(s)
Koc	Soil organic carbon partition coefficient
L	Liter(s)
lb (s)	Pound(s)
L_{NF}	Near field length
LADC	Lifetime average daily concentration
LADD	Lifetime average daily dose
LEV	Local exhaust ventilation
LT	Lifetime
LOAEL	Lowest-observed-adverse-effect level
m	Meter(s)
m^2	Square meter(s)
m^3	Cubic meter(s)
m^3/hr	Cubic meter(s) per hour
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goal
mg	Milligram(s)
mg/kg-bw/day	Milligram(s) per kilogram body weight per day
mg/L	Milligram(s) per liter
mg/m^3	Milligram(s) per cubic meter
mg/mL	Milligram(s) per milliliter
min	Minute(s)
MITI	Ministry of International Trade and Industry
Mlbs	Million of pounds
mm Hg	Millimeters of mercury
MOE	Margin of exposure

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MOE_{acute}	Margin of exposure for acute exposures
$MOE_{chronic}$	Margin of exposure for chronic exposures
MOU	Memorandum of understanding
MSDS(s)	Material safety data sheet(s)
MW	Molecular weight
NAcDCVC	N-Acetyl-S-(1,2-dichlorovinyl)-L-cysteine or N-acetyl-S (2,2 dichlorovinyl)-L-cysteine
NAICS	North American Industry Classification System
NAPL	Nonaqueous phase liquid
NAS	National Academies
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NEI	National Emissions Inventory
NESHAP	National Emissions Standards for Hazardous Air Pollutants
NF	Near field
NF/FF	Near field/far field
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkins lymphoma
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
nm	Nanometer(s)
NOAEL	No-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHSC	National Occupational Health and Safety Commission
NPI	National Pollutant Inventory
NPL	National Priority List
NPS	Nonpoint source
NTP	National Toxicology Program
OAR	Office of Air and Radiation
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
oz	Ounce(s)
PA	Personal air
PBPK	Physiologically-based pharmacokinetic
p-cRFCs	PBPK model-based candidate RfCs
PEC	Priority Existing Chemical
PFC	Plaque-forming cell

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PND	Postnatal day
POD	Point of departure
POTW	Publicly owned treatment works
ppb	Parts per billion
ppm	Parts per million
PS	Point Source
PSL	Priority Substances List (PSL1)
PVC	Polyvinyl chloride
Q_{FF}	Far field ventilation rate
Q_{NF}	Near field ventilation rate
QA	Quality assurance
QC	Quality control
RAD	Risk Assessment Division
RCRA	Resource Conservation and Recovery Act
RfC	Reference concentration
RfD	Reference dose
RR	Rate ratio
RRm	Summary relative risk
RTECS	Registry of Toxic Effects of Chemical Substances
s	Second(s)
SAB	Science Advisory Board
SARA	Superfund Amendments and Reauthorization Act
SCG	Scientific Consulting Group, Inc.
SD	Standard deviation
t	Time
TCA	Trichloroacetic acid
TCE	Trichloroethylene
TCOG	Trichloroethanol, glucuronide conjugate
TCOH	Trichloroethanol
TOXLINE	Toxicology Literature Online
TRI	Toxics Release Inventory
TTC	Total trichloro compounds
TSCA	Toxic Substances Control Act
TSCATS	Toxic Substance Control Act Test Submission Database
TWA	Time-weighted average
UF	Uncertainty factor
UF_S	Subchronic to chronic uncertainty factor
UF_A	Interspecies uncertainty factor
UF_H	Intraspecies uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	Database uncertainty factor
US or U.S.	United States
U.S. EPA or EPA	United States Environmental Protection Agency
V_{FF}	Far field volume

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v_{NF}	Indoor wind speed
V_{NF}	Near field volume
VCCEP	Voluntary Children's Chemical Evaluation Program
VOC	Volatile organic compound
VP	Vapor pressure
W_{NF}	Near field width
WY	Working years
Yr (s)	Year(s)

EXECUTIVE SUMMARY

The United States Environmental Protection Agency (U.S. EPA), Office of Pollution Prevention and Toxics (OPPT), identified and chose trichloroethylene (TCE) for risk evaluation as part of its Existing Chemicals Management Program under the Toxics Substances Control Act (TSCA).

TCE is a volatile organic compound (VOC) that is classified as a human carcinogen. Its consumption in the U.S. is 255 million pounds (lbs) per year. TCE is widely used in industrial and commercial processes, and also has some limited uses in consumer products.

Main Conclusions of this Risk Assessment

This risk assessment identifies cancer risk concerns and short-term and long-term non-cancer risks for workers and occupational bystanders at small commercial degreasing facilities and dry cleaning facilities that use TCE-based solvents and spotting agents, respectively.

EPA/OPPT also identifies short-term non-cancer risks for consumers and residential bystanders from the use of TCE-containing solvent degreasers and spray-applied protective coatings.

The Focus of this Risk Assessment

This assessment characterizes human health risks from inhalation exposures to TCE for the following uses:

1. Commercial use of TCE as a solvent degreaser
2. Consumer use of TCE as a solvent degreaser
3. Consumer use of TCE as a spray-applied protective coating for arts and crafts
4. Commercial use of TCE as a spotting agent at dry-cleaning facilities

EPA/OPPT selected these uses because they were expected to make frequent use of TCE in high concentrations and/or pose high potential for human exposure. Additional information is provided in the risk assessment regarding the criteria for inclusion of uses and the various assumptions in applying these criteria.

The main route of exposure for TCE is believed to be inhalation for the uses identified in this assessment. EPA/OPPT recognizes that highly volatile compounds such as TCE may also be absorbed through the skin. However, based on the physical-chemical properties of TCE and the scenarios described in this assessment, EPA/OPPT believes that inhalation is the main exposure pathway for this risk assessment. Recent modeled and experimental work supports this assumption that inhalation is the predominant exposure pathway (see Section 1.3.2). This assessment may underestimate total exposures resulting from the uses of TCE due to this assumption.

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This risk assessment does not include an assessment of environmental effects. Based on TCE's moderate persistence, low bioaccumulation, and low hazard for aquatic toxicity, potential environmental impacts are judged to be low for the environmental releases associated to the TSCA uses under the scope of this risk assessment. That judgment should not be misinterpreted as saying that the fate and transport properties of TCE suggest that water and soil contamination is likely low or do not pose an environmental concern. In fact, EPA's Office of Solid Waste and Emergency Response and the EPA Regions are addressing TCE contamination in groundwater and contaminated soils at large number of sites. While the primary concern with this contamination has been human health, there is potential for TCE exposures to ecological receptors in some cases.

Human Populations Targeted in This Assessment

EPA/OPPT assessed acute and chronic risks for workers at small degreasing facilities and dry cleaning facilities that may use TCE as a solvent degreaser or spotting agent, respectively. EPA/OPPT assumes that workers at these small degreasing and dry cleaning facilities would be adults of both sexes (≥16 and older, including pregnant women) based upon occupational work permits, although exposures to younger individuals may be possible in occupational settings. Risks are also estimated for occupational bystanders, who are assumed to be workers in the vicinity of the degreasing and spotting operations, but not actually performing the operation.

EPA/OPPT also examined acute risks for consumer exposures in residential settings. EPA/OPPT assumes that consumers would be individuals that intermittently use TCE in and around their homes, whereas bystanders would be individuals physically close to the use activity but not using the product. EPA/OPPT assumes that consumer users would generally be adults of both sexes (≥16 and older, including pregnant women), although exposures to teenagers and even younger individuals may be possible in residential settings. However, risk estimates are focused on the most susceptible life stage, which are pregnant women and their developing fetus. This focus is supported by the hazard findings in the TCE IRIS assessment, which conclude that developmental toxicity is the most sensitive health effect associated to TCE exposure (EPA, 2011e).

Workplace Exposures at Commercial Degreasing and Dry Cleaning Facilities

In order to estimate TCE emissions in the workplace, EPA/OPPT used readily available information from the National Emissions Inventory (NEI), the Toxics Release Inventory (TRI), and a study on the use of spotting chemicals prepared for the California EPA and EPA Region 9 (CalEPA/EPA, 2007). To estimate workplace exposures, these emission estimates were incorporated into a Near Field/Far Field (NF/FF) mass balance model.

It is important to note that the NF/FF model has been extensively peer-reviewed, is extensively used, and results of the model have been compared with measured data. The comparison indicated that model and measured values agreed to within a factor of about three (Jayjock et al., 2011). In estimating workplace exposures, EPA/OPPT assessed various exposure scenarios.

For example, engineering controls such as local exhaust ventilation (LEV) were taken into account.

Although relevant exposure monitoring data are limited, EPA/OPPT did identify monitoring data from the Occupational Safety and Health Administration (OSHA)(Coble, 2013) and site-specific data from the National Institute for Occupational Safety and Health (NIOSH)(NIOSH, 1997b). The exposure estimates (with and without LEV) were of the same order of magnitude as measured values:

1. For commercial degreasing facilities, EPA's exposure estimate ranged from 0.04 to 197 parts per million (ppm); measured data from OSHA ranged from 0.06 to 380 ppm.
2. For dry cleaning facilities, EPA's site-specific exposure estimate ranged from 0.8 to 2.1 ppm; measured data reported by NIOSH ranged from 2.37 to 3.11 ppm.

Consumer Exposures from Solvent Degreasing and Spray-Applied Coatings

EPA/OPPT used the Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) /Consumer Exposure Module (CEM) (EPA, 2007b) to estimate TCE exposures for the consumer use scenarios. This modeling approach was selected because emissions and monitoring data were not available for the TCE uses under consideration.

The model used a two-zone representation of a house to calculate the TCE exposure levels for consumers and bystanders. The modeling approach integrated assumptions and input parameters about the chemical emission rate over time, the volume of the house and the room of use, the air exchange rate and interzonal airflow rate. The model also considered the exposed individual's locations, body weights and inhalation rates during and after the product use (EPA, 2007b).

The high-end inhalation exposure estimates for the consumer scenarios were as follows:

1. 0.4 ppm for users of TCE-containing clear protective coating sprays
2. 0.1 ppm for bystanders of TCE-containing clear protective coating sprays
3. 2 ppm for users of TCE-containing solvent degreasers
4. 0.8 ppm for bystanders of TCE-containing solvent degreasers

Characterization of Hazards and Risks to Human Health

The assessment uses the hazard and dose-response information published in the final toxicological review that the U.S. EPA's Integrated Risk Information System (IRIS) published in 2011 (EPA, 2011e). The TCE IRIS assessment used a weight-of-evidence approach, the latest scientific information and physiologically-based pharmacokinetic (PBPK) modeling to develop hazard and dose-response assessments for TCE's carcinogenic and non-carcinogenic health effects resulting from lifetime inhalation and oral exposures. In addition to relying on the latest scientific information, the TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by

the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006, external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011, followed by final internal agency review and EPA-led science discussion on the final draft.

TCE's Carcinogenic Hazards and Risks:

TCE is carcinogenic to humans by all routes of exposure as documented in the TCE IRIS assessment. This conclusion is based on strong cancer epidemiological data that reported an association between TCE exposure and the onset of various cancers, primarily in the kidney, liver and the immune system (i.e., non-Hodgkin lymphoma or NHL) (EPA, 2011e). Further support for TCE's carcinogenic characterization comes from (1) positive results in multiple rodent cancer bioassays in rats and mice of both sexes, (2) similar toxicokinetics between rodents and humans, (3) mechanistic data supporting a mutagenic mode of action for kidney tumors, and (4) the lack of mechanistic data supporting the conclusion that any of the mode(s) of action for TCE-induced rodent tumors are irrelevant to humans (EPA, 2011e). Additional support comes from the recent evaluation of TCE's carcinogenic effects by the International Agency for Research on Cancer (IARC). IARC (2014) classifies TCE as carcinogenic to humans (Group 1).

EPA/OPPT used the inhalation unit risk (IUR) of 2×10^{-2} per ppm (4×10^{-6} per $\mu g/m^3$) reported in the TCE IRIS assessment to estimate excess cancer risks for the occupational scenarios. The IUR is the estimated upper bound excess lifetime cancer risk resulting from continuous exposure to an airborne agent at 1 $\mu g/m^3$ (EPA, 2011b). The IUR for TCE is based on human kidney cancer risks and adjusted for potential risks for NHL and liver cancer based on human epidemiological data (EPA, 2011e). There is high confidence in the IUR because it is based on good quality human data and it is similar to unit risk estimates derived from multiple rodent bioassays (EPA, 2011e). Moreover, there is sufficient weight of evidence to conclude that TCE operates through a mutagenic mode of action for kidney tumors, which supports the linear extrapolation approach (EPA, 2011e).

TCE's Non-Carcinogenic Hazards and Risks:

TCE exposure is associated with a range of non-cancer health effects in humans and animals. Non-cancer risks for the various exposure scenarios were evaluated using the dose-response information reported in the TCE IRIS assessment (EPA, 2011e). The TCE IRIS assessment used physiologically-based pharmacokinetic (PBPK) modeling to estimate hazard values (i.e., human equivalent concentrations or HECs) indicative of adverse health effects representing six health effects domains: kidney, liver, immunotoxicity, neurotoxicity, reproductive toxicity, and developmental toxicity.

Different health endpoints were used to evaluate risks based on the expected durations of exposure in the scenarios considered in this assessment. For instance, both acute and chronic health effects endpoints were used for the occupational scenarios (i.e., small commercial degreasers and spot cleaning workers and bystanders). In that case, a variety of health effects

endpoints were used to evaluate repeated (chronic) exposures to TCE (i.e., toxicity to the liver, kidney, nervous system, immune system, the reproductive system, and developmental toxicity). For the consumer use scenarios, developmental toxicity endpoints were used to assess risks for acute exposures.

EPA/OPPT used developmental endpoints for the acute risk assessment based on U.S. EPA's policy that a single exposure of a chemical within a critical window of fetal development may produce adverse developmental effects (EPA, 1991). Particularly, this assessment used the PBPK-derived HECs reported for developmental animal studies reporting fetal cardiac defects. TCE-induced fetal cardiac malformations are biologically plausible based on the weight of evidence analysis presented in the TCE IRIS assessment, which considered human and animal findings as well as mechanistic data.

These hazard values were expressed as HECs at the 50th, 95th or 99th percentile of the combined uncertainty and variability distribution of human internal doses, as estimated by the TCE PBPK model (EPA, 2011e). The HEC_{95} and HEC_{99} were defined as the concentrations of TCE in air for which there is 95% and 99% likelihood, respectively, that a randomly selected individual would have an internal dose less than or equal to the internal dose of the hazard value. On the other hand, the HEC_{50} was defined as the concentration of TCE in air for which there is a 50% likelihood that a randomly selected individual would have an internal dose less than or equal to the internal dose of the hazard value (EPA, 2011e). The TCE IRIS assessment preferred the HEC_{99} for the non-cancer dose-response derivations because the HEC_{99} was interpreted to be protective for a sensitive individual. EPA/OPPT supported the interpretation of the HEC_{99} as expressed in the TCE IRIS assessment. Hence, HEC_{99}-based risk estimates are favored in this assessment over those estimated from the HEC_{50} and HEC_{95} values, but risk estimates for all of the HEC percentiles were presented to provide a sense of the variability in the risk estimates.

EPA/OPPT used margin of exposures (MOEs) to estimate non-cancer risks based on (1) the lowest PBPK-derived HECs within each health effects domain reported in the TCE IRIS assessment; (2) the same endpoint/study-specific uncertainty factors (UFs) that the IRIS program applied to the PBPK-derived HECs; and (3) the exposure estimates calculated for the TCE uses examined in this risk assessment. MOEs allowed us to have a better picture of the non-cancer risk profile of TCE by presenting a range of risk estimates for different non-cancer health effects for different exposure scenarios.

Uncertainties of this Risk Assessment

As with any risk assessment, there are uncertainties that need to be considered when interpreting the results. Assumptions were used in estimating the occupational and consumer exposure scenarios covered in this assessment. In addition, there are uncertainties in the hazard/dose-response and risk characterization assessments. EPA/OPPT discusses these uncertainties qualitatively and recognizes that they may under- or over-estimate actual risks.

The Results of this Risk Assessment

Size of the Exposed Population

- Approximately 30,000 workers and occupational bystanders at small commercial degreasing operations.
- Approximately 300,000 workers and occupational bystanders at dry cleaning operations.
- No data were available to estimate the number of consumers and bystanders exposed to TCE during the use of degreasers and arts/crafts clear protective coating spray.

Cancer Risks:

- There are cancer risk concerns for users and bystanders occupationally exposed to TCE when using TCE-containing vapor degreasers and spot cleaners in small commercial shops and dry cleaning facilities, respectively.
- Many of the commercial vapor degreasing and spot cleaning exposure scenarios exceed the excess lifetime cancer risk probabilities of 1 chance in 10,000, 100,000 or 1 million (i.e., target cancer risks of 10^{-4}, 10^{-5} and 10^{-6}, respectively) of an individual developing cancer.
- The occupational exposures to commercial degreasers show the greatest cancer risk when compared to the spot cleaning exposure scenarios.

Acute Non-Cancer Risks:

- There are acute non-cancer risks for developmental effects (i.e., cardiac defects) for most occupational and residential exposure scenarios (i.e., MOEs were below the benchmark MOE of 10).
- The commercial vapor degreasing and consumer spray degreasing exposure scenarios show greater acute risks for developmental effects than those reported for the spot cleaning exposure scenarios.

Chronic Non-Cancer Risks:

- There are chronic non-cancer risks for a range of human health effects in both the occupational degreaser and spot cleaning exposure scenarios (i.e., MOEs were below the benchmark MOE).
- The greatest concern is for developmental effects (i.e., fetal cardiac defects), followed by kidney effects and then immunotoxicity, with an overall higher chronic risk for the degreaser exposure scenarios. In general, this concern is present for lower and upper-end exposures and in the presence or absence of room ventilation (LEV vs. no LEV).
- There are chronic risks for reproductive effects and neurotoxicity for degreaser worker exposure scenarios and most of the degreaser bystander exposure scenarios. However, the risks concern for these effects are reported for fewer spot cleaning worker and bystander scenarios, and are generally attributed to exposure conditions without room ventilation.
- There are chronic risks for liver effects although the risks were less prominent than those reported for other health effects. These risks were found only in the degreaser worker and

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bystander exposure worst case scenarios, and the spot cleaning worker and bystander worst case scenarios with no LEV.

1 PURPOSE, BACKGROUND, AND SCOPE

1.1 PURPOSE AND AUDIENCE

The purpose of TSCA Work Plan chemical risk assessments, such as this one developed for TCE, is to assess the potential risks of chemicals under the EPA's Existing Chemicals Program. If risks are found in the risk assessments, the information will be used to inform risk management strategies to reduce identified risks.

The target audience for this risk assessment is the risk assessment community, including U.S. EPA's risk assessors and risk managers, as well as U.S. stakeholders that are interested in risk assessment issues related to TCE. The information presented in the risk assessment may be of assistance to other Federal, State and Local agencies as well as to members of the general public who are interested in the chemical risks of TCE. The risk assessment may also help those interested in reducing risk in the identified use areas of commercial and consumer solvent degreasing and arts and crafts products.

1.2 BACKGROUND

1.2.1 Rationale for Selecting TCE for Risk Assessment

TCE is a liquid VOC that ranked high for human health hazards and exposure potential when using OPPT's work plan chemical prioritization criteria (EPA, 2012d)[1]. TCE is classified as a human carcinogen and is widely used in industrial and commercial processes as well as in some consumer products. Moreover, these TCE uses may pose an inhalation hazard as evaporation of TCE readily occurs due to its high vapor pressure. TCE is ubiquitously present in the environment with levels detected in drinking water, indoor environments, surface water, ambient air, groundwater, and soil.

Given these concerns, TCE was identified and chosen for risk evaluation as part of EPA/OPPT's Existing Chemicals Management Program under TSCA[2].

1.2.2 Overview of TCE Uses, Production Volume and EPA's Regulatory History

TCE has historically had a wide range of uses drawn from various markets, including intermediate chemicals (for refrigerant and polyvinyl chloride [PVC] manufacture), industrial and commercial solvents, pharmaceuticals, insecticides, fumigant, textiles (processing and

[1] EPA's TSCA Work Plan Chemicals: Methods Document: http://www.epa.gov/oppt/existingchemicals/pubs/wpmethods.pdf

[2] EPA's TSCA Work Plan Chemicals website: http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html

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flame retardants), adhesives, and paints (as diluent) (Ash and Ash, 2009). However, as of 2011, most U.S. consumption is attributable to two specific uses: 83.6 percent of total TCE production volume is used as an intermediate for manufacturing the refrigerant (closed system) HFC-134a (a major alternative to CFC-12), and 14.7 percent is used as a solvent for metals degreasing solvent; the remaining 1.7 percent is attributed to "other uses." In total, U.S. TCE consumption is 255 million lbs/yr (Glauser and Funda, 2012)[3]. More information on production volumes can be found in Appendix A.

The U.S. EPA regulates TCE through various environmental regulations given TCE's human health hazards and exposure potential. The latter is informed by TCE's high production volume, physical-chemical properties, uses and environmental releases. Appendix B summarizes the U.S. EPA's regulatory history of TCE, including those U.S. EPA offices that manage the implementation of the existing TCE regulations.

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Superfund Amendments and Reauthorization Act (SARA), the U.S. EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) have established a prioritized list of substances most commonly found at facilities on the National Priority List (NPL) (ATSDR, 2011). The listing is based on the frequency of occurrence, toxicity, and potential for human exposure. TCE was ranked 16th out of 847 candidate substances for the 2011 ranking; only the top 275 are considered to be on the list.

1.3 SCOPE OF THE ASSESSMENT

1.3.1 Selection of TCE Uses

This assessment characterizes inhalation exposures to TCE from the following uses:

1. Commercial use of TCE as a solvent degreaser
2. Consumer use of TCE as a solvent degreaser
3. Consumer use of TCE as a spray-applied protective coating for arts and crafts
4. Commercial use of TCE as a spotting agent at dry-cleaning facilities

Table 1-1 lists the primary uses of TCE, indicates whether a use was considered in this assessment, and also presents the rationale for why a use was included or excluded from further consideration. The criteria for inclusion were: high concentration of TCE, frequent use of TCE, and high potential for human exposure.

[3] This source material includes data or information derived from IHS Products provided to the U.S. EPA. IHS products have been provided to the U.S. EPA for its internal use and in the context of a license agreement. By receiving and accessing this material, you agree that IHS is not liable to you or any third party for your use of and/or reliance on the IHS data and information contained in this document, and any such use shall be at your own risk.

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EPA/OPPT made various assumptions in developing the use-related criteria. For instance, when using TCE as an intermediate for refrigerant manufacturing, the frequency of use is likely to be high as is the concentration of TCE. However, the process is expected to take place in a closed system (low potential for human exposure) and thus this use is not considered in this assessment. Also, although the use of TCE as a solvent degreaser at large commercial/industrial operations is expected to be frequent and the concentration of TCE high, human exposures in these settings are expected to be monitored and controlled by Occupational Safety and Health Administration (OSHA); thus, this use is also not considered in this assessment.

Toner aides and mirror edge sealants were dropped from further consideration because these uses reported a low TCE content and we[4] assumed less frequent use when compared to the consumer use of degreasers and arts/crafts products. Although film cleaners had a high TCE content, we did not evaluate this use because the exposure frequency is expected to be low since the U.S. consumer population predominantly uses digital cameras, and even for film use, only people performing home development of camera film would be exposed to these products. We cannot rule out that frequent exposure to TCE could occur in a small population of amateur photographers that use film cleaning products. In addition, professional photographers' use of products containing TCE while developing film would not be assessed as a consumer use.

Table 1-1. Primary Uses of TCE and Determination of Inclusion in this Risk Assessment

Use Category	Typical Percent TCE by Weight	Population Exposed	To Be Considered in this Assessment?
Intermediate in the manufacturing of refrigerant	>99	Workers and bystanders in the refrigerant manufacturing process (all adults[1])	**No** – high content, frequent use, low potential for human exposure (the use of TCE as an intermediate is expected to take place in a closed system)
Solvent degreaser	>90	Workers and bystanders in large commercial/industrial settings (all adults[1])	**No** – high content, frequent use, low potential for human exposure (exposures at large commercial/industrial operations are expected to be monitored and controlled by OSHA)
Solvent degreaser	>90	Workers and bystanders in small commercial settings (all adults[1])	**Yes** – high content, potential for frequent use, high potential for human exposure (*i.e.*, chronic exposures)

[4] For the purpose of this risk assessment, "we" refers to U.S. EPA/OPPT.

Table 1-1. Primary Uses of TCE and Determination of Inclusion in this Risk Assessment			
Use Category	**Typical Percent TCE by Weight**	**Population Exposed**	**To Be Considered in this Assessment?**
Spotting agent	10-100	Workers and bystanders at dry cleaning facilities (all adults[1])	**Yes** – potential for high content, potential for frequent use, high potential for human exposure (i.e., chronic exposures)
Solvent degreaser	>90	Consumer users (adults >16 yrs old [1]) and bystanders [2] (all ages)	**Yes** – high content, low frequency of use, high potential for human exposure (*i.e.*, acute exposures)
Plastic clear protective coating spray (hobbyists; arts/crafts)	20-30		**Yes** – low content, but possibly largest use of consumer products (*i.e.*, acute exposures)
Film cleaner (hobbyists)	>90	Consumer users (adults >16 yrs old [1]) and bystanders [2] (all ages)	**No** – high content, low frequency of use (use of negatives/cameras with film is assumed to be negligible); low potential for human exposure
Toner aide (home office)	15-20		**No** – low content, low frequency of use, low potential for human exposure
Mirror edge sealant (hobbyist/home maintenance)	20-30		**No** – low content, low frequency of use, low potential for human exposure
Notes: [1]= "adults" include individuals of both sexes, including pregnant women (>16 yrs of age) [2]= "bystanders" include individuals of both sexes, including children and pregnant women			

1.3.2 Selection of Exposure Pathway

This risk assessment assumed that TCE is primarily absorbed through the respiratory tract because of TCE's high vapor pressure. EPA/OPPT recognizes that highly volatile compounds such as TCE may also be absorbed through the skin. However, based on the physical-chemical properties of TCE and the scenarios described in this assessment, EPA/OPPT believes that inhalation is the main exposure pathway for this risk assessment. This assessment may underestimate total exposures resulting from the uses of TCE due to this assumption.

Recent modeled and experimental work supports the assumption that inhalation is the predominant exposure pathway. The dermal model described by Tibaldi et al. (2014) estimates that about 1% of TCE on the skin will be absorbed into the epidermis with the other 99% evaporating. Also, an experimental comparison of dermal to vapor exposure found that TCE and hexane had the least dermal absorption amongst a set of volatile solvents. The ratio of dermal to respiratory intake was found to be 0.1 % for TCE (Kezic et al., 2000).

1.3.3 Identification of Human Populations Exposed During TCE Uses

EPA/OPPT assessed risks for workers at small degreasing facilities and dry cleaning facilities that may use TCE as a solvent degreaser or spotting agent, respectively, at some point as a part of their daily activities. We assumed that workers at these small degreasing facilities and dry cleaning facilities would be adults of both sexes (≥16 and older), although exposures to younger individuals may be possible in occupational settings. EPA/OPPT also assumed that pregnant women may be part of the workforce. Risks were also estimated for bystanders (i.e., workers in the vicinity of degreasing and spotting operations, but not actually performing the operation).

This assessment also examined consumer exposures in residential settings. Consumers were individuals that used TCE in and around their homes (Table 1-1), whereas bystanders were individuals that did not use the product but were physically close to the use activity. We assumed that consumer users would be adults of both sexes (≥16 and older, including pregnant women), although exposures to younger individuals may be possible in residential settings.

1.3.4 Risk Evaluation of TCE's Human Health Hazards

Risks for the various exposure scenarios were evaluated using the dose-response information that was reported in the final TCE health assessment prepared by the U.S. EPA's Integrated Risk Information System (IRIS) (EPA, 2011e)[5]. The final TCE IRIS assessment characterizes TCE as carcinogenic to humans and identifies non-cancer hazards associated with TCE exposure. IARC (2014) has also classified TCE as carcinogenic to humans (Group 1).

The TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006 (NRC, 2006)[6], external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011 (EPA, 2011c)[7], followed by final internal agency review and EPA-led science discussion on the final draft.

In light of this, EPA/OPPT decided to use the TCE IRIS assessment as the preferred data source for TCE's human health toxicity information, rather than developing a new hazard and dose-response assessment. See Chapter 2 for more information about the hazard/dose-response approach for cancer and non-cancer health endpoints.

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[5] From now on, the EPA's IRIS Toxicological Review of TCE will be referred as the "*TCE IRIS assessment*".

[6] NAS report, "Assessing the human health risks of trichloroethylene: Key scientific issues (2006)": http://www.nap.edu/catalog.php?record_id=11707

[7] EPA's SAB peer review report for the 2009 EPA's Draft Assessment entitled "Toxicological Review of Trichloroethylene": http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/B73D5D39A8F184BD85257817004A1988/$File/EPA-SAB-11-002-unsigned.pdf

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1.3.5 Why Environmental Risks Were Not Evaluated For Selected TCE Uses

EPA/OPPT did not assess the risks of environmental effects related to the manufacture and use of TCE for the TSCA uses under consideration in this assessment. The decision of not conducting an environmental assessment was based on TCE's moderate persistence, low bioaccumulation, and low hazard for aquatic toxicity. This information supported a low concern for potential environmental impacts related to the TCE releases associated to the TSCA uses under the scope of this risk assessment.

EPA/OPPT also assumed that very low concentrations of TCE would be present in surface water. In making this assumption, EPA/OPPT evaluated the TCE releases to water and wastewater treatment reported to the Toxics Release Inventory (TRI) as well as the fate of TCE in wastewater treatment.

Total releases of TCE to water for all industries reporting to TRI from 1988 to 2012 ranged from a high of 15,849 pounds in 1989 and trended downward to a low of 67 pounds in 2012. Total transfers of TCE to publicly owned treatment works (POTWs) for all industries reporting to TRI from 1988 to 2012 ranged from a high of 78,921 pounds in 1996 and trended downward to a low of 100 pounds in 2012. Also, TCE concentrations are reduced through volatilization when entering surface waters from POTWs. The full environmental fate assessment is located in Appendix C.

Information on the aquatic toxicity of TCE suggested no immediate concern for potential environmental effects for the TSCA uses under consideration. The European Union (EU)'s TCE risk assessment also concluded that there were no concerns for environmental effects on aquatic organisms, including benthic organisms, terrestrial organisms, and the atmosphere (ECB, 2004). The EU conclusions were based on the production and use of TCE, including releases to wastewater treatment plants, to air from all uses, and from dichloroacetic acid (i.e., photodegradation product of TCE).

The absence of an environmental risk assessment of the TCE TSCA uses should not be construed as saying that the fate and transport properties of TCE suggest that water and soil contamination is likely low or do not pose an environmental concern. In fact, EPA's Office of Solid Waste and Emergency Response and the EPA Regions are addressing TCE contamination in groundwater and contaminated soils at large number of sites. While the primary concern with this contamination has been human health, there is potential for TCE exposures to ecological receptors in some cases.

2 HUMAN HEALTH RISK ASSESSMENT

2.1 PHYSICAL-CHEMICAL PROPERTIES

TCE is a colorless liquid with a pleasant, sweet odor resembling that of chloroform. It is considered a VOC because of its moderate boiling point, 87.2 °C, and high vapor pressure, 73.46 mm Hg at 25 °C. TCE is moderately water soluble (1.280 g/L at 25 °C), and has a log octanol:water partition coefficient (K_{ow}) of 2.42. The density of TCE, 1.46 g per cubic meter (cm^3) at 20 °C, is greater than that of water. Table 2-1 lists the chemical/physical properties of TCE.

Table 2-1. Physical-Chemical Properties of TCE

Property	Value
CASRN	79-01-6
Molecular weight	131.39
Molecular formula	C_2HCl_3
Physical state	Colorless liquid
Odor	Sweet, pleasant, resembles chloroform
Density	1.46 g/cm^3 @ 20 °C [a]
Flash point	90 °C (closed cup) [a]
Auto flammability	410 °C [b]
Viscosity	0.53 mPa·s @ 25 °C [c]
Refractive index	1.4775 [d]
Dielectric constant	3.4 ε_0 @ 16 °C [c]
Melting point	-84.7 °C (measured)
Boiling point	87.2 °C (measured)
Vapor pressure	73.46 mm Hg at 25 °C (measured) [e]
Dissociation constant (pK_a)	Not applicable
Henry's law constant	9.85×10^{-3} atm-m^3/mole (measured)
Water solubility	1,280 mg/L at 25 °C (measured) [f]
Octanol/water partition coefficient (K_{ow})	2.61(measured) [g]

Sources:
[a] ECB (2000)
[b] SRC (2012)
[c] Weast and Selby (1966)
[d] O'Neil et al. (2001)
[e] Daubert and Danner (1989)
[f] Horvath et al. (1999)
[g] Hansch et al. (1995)

2.2 OVERVIEW OF ENVIRONMENTAL FATE AND RELEASES OF TCE

Knowledge of the environmental fate (transport and transformation) of a compound is important to understanding its potential impact on specific environmental media (e.g., water, sediment, and soil) and exposures to target organisms of concern.

TCE is a volatile liquid with high vapor pressure, moderate water solubility, and high mobility in soil. TCE is slowly degraded by sunlight and reactants when released to the atmosphere. Volatilization and microbial biodegradation influence the fate of TCE when released to water, sediment or soil. The biodegradation of TCE in the environment is dependent on a variety of factors and so a wide range of degradation rates have been reported (ranging from days to years). TCE is not expected to bioconcentrate in aquatic organisms due to measured bioconcentration factors of less than 1000. More information on TCE's environmental fate is in Appendix C.

The manufacture, processing and use of TCE can result in TCE releases to air, water, sediment, and soil. Most reported environmental releases of TCE are to air with much lower releases to landfills and very little released to surface water. The Toxics Release Inventory database reported some of the highest fugitive and point source air releases reported for TCE when used as a degreaser (*i.e.,* roughly 15 percent of the production/importation volume in the U.S.). Disposal of TCE wastes could be an environmental concern because TCE has moderate persistence under certain environmental conditions, is volatile and water soluble, and has high mobility in soil and groundwater. TCE may enter publicly owned treatment works (POTWs), which will likely result in releases to surface waters and air. More information on TCE's environmental fate is in Appendix C.

2.2.1 Ambient Air Concentrations of TCE

Table 2-2 lists a summary of the ambient air monitoring data for TCE (*i.e.,* measured data) in the U.S. from 1999 to 2006 as reported in EPA (2011e). These data suggest that TCE levels have remained fairly constant in ambient air for the U.S. since 1999, with an approximate mean value of 0.3 $\mu g/m^3$ (*i.e.,* which is equivalent to 5.6×10^{-5} parts per million or ppm).

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Table 2-2. TCE Ambient Air Monitoring Data (µg/m^3) [a]						
Year	**Number of Monitors**	**Number of States**	**Mean**	**Standard Deviation**	**Median**	**Range**
1999	162	20	0.30	0.53	0.16	0.01-4.38
2000	187	28	0.34	0.75	0.16	0.01-7.39
2001	204	31	0.25	0.92	0.13	0.01-12.90
2002	259	41	0.37	1.26	0.13	0.01-18.44
2003	248	41	0.35	0.64	0.16	0.02-6.92
2004	256	37	0.32	0.75	0.13	0.00-5.78
2005	313	38	0.43	1.05	0.14	0.00-6.64
2006	258	37	0.23	0.55	0.13	0.03-7.73

[a] The U.S. EPA's Air Quality System database at the AirData Web site: http://www.epa.gov/airdata/ (as summarized in **EPA (2011e)**. Note that the data were not from a statistically based survey and cannot be assumed to provide nationally representative values.

2.3 ENVIRONMENTAL RELEASES AND OCCUPATIONAL EXPOSURE ESTIMATES FOR SMALL COMMERCIAL DEGREASING OPERATIONS

2.3.1 What is a Small Operation?

There is no standard or universal definition for the term "small shop". The various meanings of this term can depend upon the industry sector (e.g., metal finishing, furniture repair, foam production, chemical manufacturing) or governmental jurisdiction (e.g. OSHA, EPA, other countries). For the purpose of risk assessment of work plan chemicals, EPA generally refers to entities, businesses, operators, plants, sites, facilities, or shops interchangeably and considers a number of factors to categorize these as small. The factors that have been usually considered include revenue; capacity, throughput, or production or use rate of materials, or number of employees.

For this risk assessment, EPA/OPPT has determined that more research will be required to determine which factors will best define small shops for the industries that do vapor degreasing. However, EPA/OPPT's interest in small shops for this assessment is due to the possibility that these shops may have fewer resources or less expertise and awareness of hazards, exposures, or controls as compared to large shops.

2.3.2 A Brief Summary of Solvent Cleaning

Solvent cleaning (degreasing) is widely used to remove grease, oils, waxes, carbon deposits, fluxes, and tars from metal, glass, or plastic surfaces (EPA, 2006d, 2007a).

There are two general types of degreasing machines: batch and in-line. Batch cleaning machines are the most common type, while in-line cleaners are typically used in large-scale

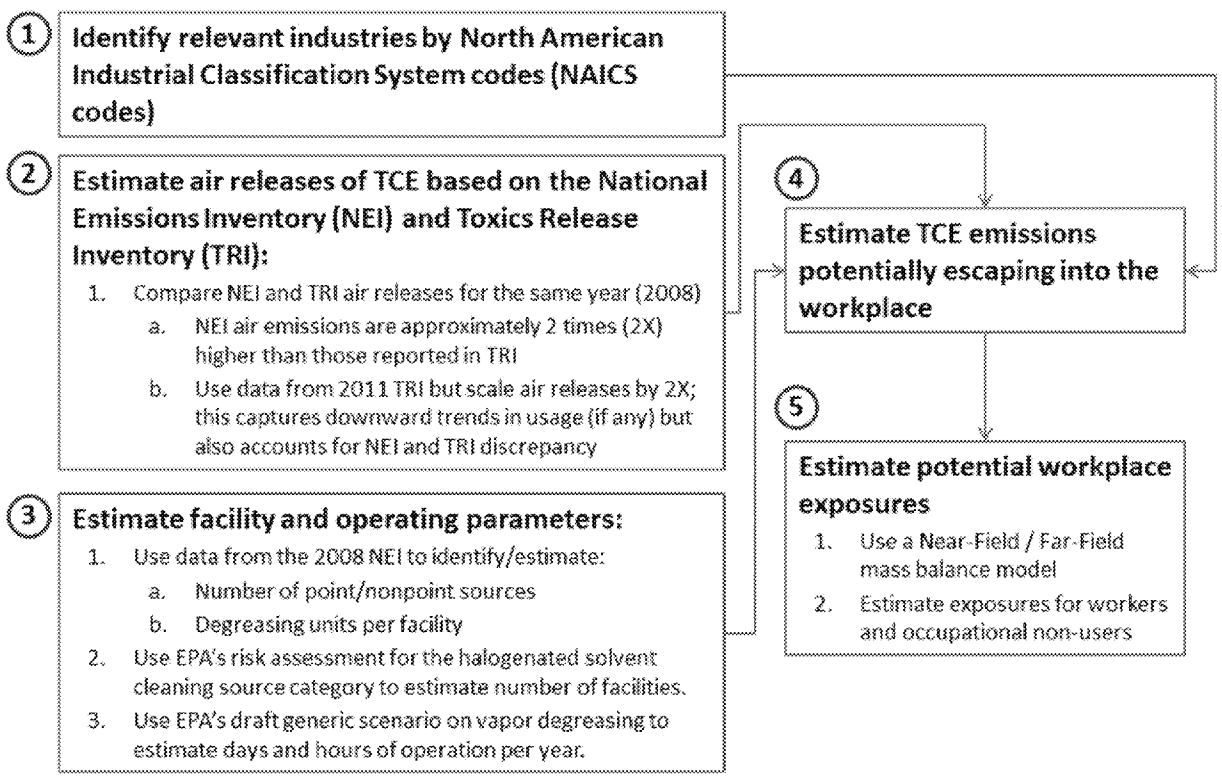
industrial operations (EPA, 2006d). The size of a degreasing machine is defined by the area of its solvent-to-air interface.

Emissions from degreasing machines typically result from (EPA, 2006d):
1. evaporation of the solvent from the solvent-to-air interface
2. "carry out" of excess solvent on cleaned parts
3. evaporative losses of the solvent during filling and draining of the degreasing machine

2.3.3 EPA/OPPT's Release and Exposure Assessment for Degreasing Operations

EPA/OPPT used readily available information from the National Emissions Inventory (NEI) and the Toxics Release Inventory (TRI) to estimate releases of and exposures to TCE from degreasing operations. EPA/OPPT used several steps in order to produce these estimates. An overview of these steps is shown in Figure 2-1. Further elaboration of these steps has been structured to follow the sequence in this figure.

Figure 2-1. Overview of EPA/OPPT's occupational release and exposure assessment for degreasing operations



5. **Identification of relevant industries by North American Industrial Classification System (NAICS) codes:** The degreasing process is used in many industries, both large and small. Based on a review of EPA's 2008 NEI, 78 different NAICS codes were identified. These NAICS codes are listed in Appendix D.

6. **Estimation of air releases of TCE based on NEI and TRI data:** As background, the NEI is a comprehensive and detailed estimate of air emissions of both criteria and hazardous air pollutants (HAPs) from various air emissions sources. The NEI is prepared every three years by the U.S. EPA (EPA, 2008). The TRI is a database that contains detailed information on environmental releases and transfers of certain listed toxic chemicals from industrial facilities. The TRI is maintained by the U.S. EPA and updated annually (EPA, 2012c).

   In 2008, for the NAICS codes listed in Appendix D, total NEI air emissions of TCE were approximately two times (2X) greater than those reported in TRI. Whereas the NEI is the U.S. EPA's primary emissions inventory for HAPs and criteria pollutants, the TRI is another inventory that may be considered. The TRI provides releases to other environmental media besides air (e.g., land and water). However, the TRI may exclude releases from small-scale operations, which are the intended focus of this risk assessment (EPA, 2004a, 2011d).

   In this assessment, EPA/OPPT estimated TCE air emissions based on the 2011 TRI. EPA/OPPT elected to use more recent data from the 2011 TRI to account for downward trends in usage/release of TCE. In order to account for the discrepancy observed between the 2008 NEI and 2008 TRI, TCE air emissions from the 2011 TRI were scaled up by a factor of 2X.

   In NEI, a point source (PS) is a stationary emission source (i.e., sources that remain in one place). A large facility that houses an industrial process is an example of a point source (EPA, 2004a). A nonpoint source (NPS) refers to a smaller and more diffuse emission source. A variety of sources are categorized as NPS, including small commercial operations (EPA, 2004a).

   Point sources usually include large industrial facilities but they can also include small commercial facilities, which have traditionally been classified as NPS (EPA, 2008). However, the choice of whether small commercial facilities are classified as PS or NPS is determined by the appropriate State, Local, or Tribal air agency (EPA, 2008).

   In this assessment, EPA/OPPT assumed that point sources were representative of large industrial facilities, while nonpoint sources were assumed to be representative of small commercial facilities.

   Data from the 2008 NEI can be used to identify the number of TCE emission sources (Table 2-3) (EPA, 2008). As can be seen from Table 2-3, sixty six percent (66%) of TCE emissions in 2008 were from NPS, while approximately 34 percent were from PS. Thus, nearly two-thirds

of TCE emissions came from NPS (small facilities). See Appendix E for additional details on how these data were obtained.

Table 2-3. Number of TCE Emission Sources and Corresponding Total Annual Air Emissions of TCE as reported in the 2008 NEI (EPA, 2008)		
Type of Emission Source	**Number of Sources**	**Total Annual Air Emissions (lbs/yr)**
Point source (Large facility)	180 (degreasing units)	1,480,000
Nonpoint source (Small facility)	1,779 [a]	2,860,000

Notes:
[a] Nonpoint sources are aggregated and reported at the county level. Thus, the number of nonpoint sources (as reported in NEI) will not necessarily correspond to the number of degreasing units.

Based on the NAICS codes listed in Appendix D, the 2008 and 2011 TRI can be queried to identify stack and fugitive air emissions of TCE (Tables 2-4 and 2-5). Thus, NEI and TRI data from the same year (2008) can be compared. In 2008, total TCE air emissions in NEI were approximately two times (2X) greater than those reported in the 2008 TRI[8].

Table 2-4. Total Annual Air Emissions of TCE as Reported in the 2008 TRI (EPA, 2012c)	
Type of Emission	**Total Annual Air Emissions (lbs/yr)**
Stack air emissions	1,320,000
Fugitive air emissions	1,230,000

Table 2-5. Total Annual Air Emissions of TCE as Reported in the 2011 TRI (EPA, 2012c)	
Type of Emission	**Total Annual Emissions (lbs/yr)**
Stack air emissions	850,000
Fugitive air emissions	840,000

From the information described above and presented in Tables 2-3 through 2-5, releases of TCE can be estimated by facility type (large or small). EPA/OPPT's estimate for TCE air emissions from small commercial degreasing facilities is shown in Table 2-6.

[8] Derived by adding the total 2008 NEI emissions (1,480,000 + 2,860,000 = 4,340,000) and dividing this by the total 2008 TRI emissions (1,320,000 + 1,230,000 = 2,550,000), which results in 4,340,000/2,550,000 = 2.

Table 2-6. EPA/OPPT's Estimated Total Annual Air Emissions of TCE from Small Commercial Degreasing Facilities	
Type of Emission	**Total Annual Emissions (lbs/yr)**
Air emission	2,230,800

1. ***In this assessment, EPA/OPPT estimated annual air emissions of TCE from small commercial degreasing facilities as follows:***

   "Total Annual Emissions"= 66% * 2 * "Total 2011 TRI TCE Air Emissions"=
   = 0.66 * 2 * (840,000 + 850,000) = 2,230,800 lbs

1. ***TRI is expected to under report air emissions by a factor of 2. Thus, TCE air emissions from the 2011 TRI were scaled up by a factor of 2.***

2. ***In 2008, small facilities accounted for sixty six percent (66%) of all TCE air emissions (see Table 2-3).***

3. **Estimation of facility and operating parameters:** For the purposes of this assessment, small commercial degreasing processes were assumed to operate 260 days per year (yr) for 2 hours (hrs) per day (EPA, 2001a).

   Based on NEI data for point source emissions, 154 facilities and 180 degreasing units reported emissions of TCE in 2008. This translated into about 1.2 degreasing units per facility. Since these facilities were point sources, they would be considered large industrial facilities rather than small commercial operations.

   In this assessment, EPA/OPPT assumed one degreasing unit per facility for small commercial operations. This is because smaller facilities were expected to have less degreasing units per facility than larger one, which were estimated to have 1.2 degreasing units per facility.

   Based on EPA's 2006 risk assessment for the halogenated solvent cleaning source category, the total number of degreasing facilities was expected to be approximately 1,900 (EPA, 2006d). Thus, the number of small commercial facilities was approximated to be 1,746 (1,900 total facilities minus 154 large industrial facilities). The value of 1,746 total facilities was used to estimate the number of workers and occupational bystanders potentially exposed to TCE at small degreasing facilities.

   NEI data for point source emissions can also be used to identify the types of degreasing machines that were being used at large industrial facilities in 2008 (see breakdown by machine type in Table 2-7). Based on this breakdown, EPA/OPPT estimated that approximately 90 percent (i.e., 116 out of 129) of batch degreasing machines at large industrial facilities would likely be open top vapor degreasing machines, while 10 percent

would be cold solvent degreasing machines. General degreasing units were not included in this calculation because they could not be categorized; their type was unknown.

Table 2-7. Breakdown of Degreasing Machine Type based on NEI Data for Point Sources

Type of Degreasing Machine	Number of Units	Total Annual Air Emissions (lbs/yr)[a]
Open top vapor degreasing (batch vapor)	116	890,000
Cold solvent cleaning (batch cold)	13	140,000
Conveyorized vapor degreasing (in-line)	11	120,000
General degreasing units (unknown)	40	330,000

Source: EPA (2008)
Notes:
[a] The total is equal to 1,480,000 lbs as reported for point sources in Table 2-3.

In this assessment, EPA/OPPT assumed that small facilities would use open top vapor degreasing machines. This is because small commercial facilities were expected to be comprised entirely of batch cleaning units (EPA, 2006d) and because open top vapor degreasing machines seem to be most prevalent (see Table 2-7).

4. Estimation of TCE emissions potentially escaping into the workplace

EPA/OPPT's calculated estimate: Assuming that TCE emissions occur only during the hours of operation, EPA/OPPT estimated an average emission rate of 19 grams (g) of TCE per minute (min) from an open top vapor degreasing machine. Since a small facility was assumed to have only one degreasing unit, this corresponded to 19 g of TCE per min potentially escaping into the workplace at a small degreasing facility (Table 2-8). This emission rate was estimated as follows:

TCE Emission Rate

$$= \left(\frac{\text{Annual TCE air emissions}}{\text{Number of small facilities}}\right) * \left(\frac{1}{\text{Operating days per yr}}\right)$$

$$* \left(\frac{1}{\text{Operating hrs per day}}\right) * \left(\frac{1\text{ hr}}{60\text{ min}}\right)$$

$$= \left(\frac{2{,}230{,}800\text{ pounds per yr}}{1{,}746\text{ small facilities}}\right) * \left(\frac{454\text{ g}}{\text{pound}}\right) * \left(\frac{1}{260\text{ days per yr}}\right)$$

$$* \left(\frac{1}{2\text{ hrs per day}}\right) * \left(\frac{1\text{ hr}}{60\text{ min}}\right)$$

$$= 19\ \frac{\text{g of TCE}}{\text{min}}\text{ per facility}$$

Estimates reported in the literature: Depending on workplace controls (e.g., local exhaust ventilation; LEV), average TCE emissions escaping into the workplace from open top degreasers (i.e., the kind representative of small commercial degreasing operations) can range from 2.57 to 27.29 g of TCE per min (Wadden et al., 1989).

Based on another source, operating emissions from batch cleaning machines can range from 5 to 10 g of TCE per min (EPA, 2001a). In addition, EPA's overall emission limit for implementing the National Emissions Standards for Hazardous Air Pollutants (NESHAP) is 150 kilograms (kg) per square meter (m^2) per month (EPA, 2004b). This translates into an emission rate ranging from 16 to 50 g of TCE per min (Table 2-8). Please also refer to Appendix E for additional details regarding these emission rates.

In comparing EPA/OPPT's estimated TCE emission rate (based on NEI and TRI data) with values reported in the literature, it is evident that these estimates overlap and are of the same order of magnitude. Please refer to Table 2-8 for a summary of these emission rates.

Table 2-8. TCE Emissions Potentially Escaping into the Workplace at Small Commercial Degreasing Facilities (Calculated and Reported Values)

Type of Facility	EPA/OPPT's Calculated Estimate (g TCE/min)	Estimates Reported in the Literature (g TCE/in)
Small degreasing facility	19	2.57 to 27.29 [a] 5 to 10 [b] 16 to 50 [c]

Sources:
[a] Wadden et al. (1989) [b] EPA (2001a) [c] EPA (2004b)

5. Estimation of potential workplace exposures

Workers and occupational bystanders potentially exposed: The National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, estimated that 401,000 workers employed at 23,225 plant sites were potentially exposed to TCE in the U.S. This translates into about 17 workers per facility (ATSDR, 1997). EPA/OPPT assumed that this estimate represented both workers and occupational bystanders at degreasing facilities. EPA/OPPT estimated the average number of workers directly involved with solvent cleaning operations as five workers per facility (EPA, 2001a). The number of occupational bystanders potentially exposed was estimated as 12 per site (i.e., 17 – 5 = 12). Please refer to Appendix F for more information.

In this assessment, EPA/OPPT estimated the population of workers and occupational bystanders potentially exposed to TCE at small degreasing facilities as follows:

1. ***Number of small facilities = 1,746***
2. ***Number of Workers Potentially Exposed = (5 workers/facility)* 1,779 facilities = 8,730***
3. ***Number of Occupational Bystanders Potentially Exposed***
   = (12 occupational bystanders per facility)*1,746 facilities = 20,952

EPA/OPPT's estimated workplace exposures: To estimate workplace exposures, the TCE emissions from Table 2-8 were incorporated into a Two-Zone Near Field/Far Field (NF/FF) mass balance model. The NF/FF model has been extensively peer-reviewed, it is extensively used, and results of the model have been compared with measured data. The comparison indicated that the model and measured values agreed to within a factor of about three (Jayjock et al., 2011).

Appendix G presents the rationale and calculations for estimating inhalation exposures for workers and occupational bystanders at small degreasing facilities. An overview is also provided in Appendix F. Table 2-9 shows a summary of EPA/OPPT's workplace exposure estimates for workers and occupational bystanders at small commercial degreasing facilities. Exposure estimates were calculated for work conditions with and without local exhaust ventilation (LEV). In this assessment, EPA/OPPT assumed an effectiveness of 90% for LEV (Wadden et al., 1989). Thus, LEV could reduce emissions escaping into the workplace by 90%.

Table 2-9. Summary of Potential Workplace TCE Inhalation Exposures at Small Commercial Degreasing Facilities based on the NF/FF Model				
Population Exposed	**Exposure Type (Duration)**	**Estimated TCE Air Concentration (ppm)** **With LEV[4]**	**Estimated TCE Air Concentration (ppm)** **No LEV**	**Estimated Number of People Exposed**
Workers[1]	Inhalation exposure (8-hr TWA[3])	0.3 (low-end estimate) 20 (upper-end estimate)	3 (low-end estimate) 197 (upper-end estimate)	8,730
Occupational bystanders[2]	Inhalation exposure (8-hr TWA)	0.04 (low-end estimate) 17 (upper-end estimate)	0.4 (low-end estimate) 172 (upper-end estimate)	20,952

Notes:
[1] Workers are directly involved with degreasing operations.
[2] Occupational bystanders have the potential to be exposed to TCE but they are not directly involved with degreasing operations
[3] TWA = Time Weighted Average (NOTE: since degreasing facilities are expected to operate 2 hrs per day, to estimate 8-hr TWA exposures, EPA/OPPT assumed no exposure for 6 hrs per day).
[4] LEV = local exhaust ventilation

Workplace exposures based on monitoring data: Although a nationally representative sample of relevant exposure monitoring data were not available, monitoring data from OSHA were identified (Coble, 2013)[9]. These data from 2003 to 2010 were specific to TCE. Also, the data represented time-weighted average (TWA) personal breathing zone measurements relevant to the NAICS codes listed in Appendix D. In Figure 2-2, EPA/OPPT's workplace exposure estimates (Table 2-9) are compared with OSHA monitoring data.

It is evident that estimated and measured exposures are of the same order of magnitude; EPA/OPPT's estimated exposure range captures approximately 95% of OSHA field measurements. These results substantiate the suitability of using the NF/FF mass balance model for the purposes of estimating potential workplace exposures to TCE at small commercial degreasing facilities.

Acute and chronic workplace exposure estimates: In this assessment, EPA/OPPT assessed acute and chronic risks for workers and occupational bystanders. A summary of acute and

[9] OSHA monitoring data and analysis supporting Figure 2-2 can be found in the supplementary file "OSHA IMIS TCE SAMPLES_062314v1.xlsx"

chronic workplace exposures is provided in Table 2-10. Acute workplace exposures were estimated as follows:

$$AC = \frac{C * ED}{AT}$$

where:

AC = acute concentration (24 hr TWA in ppm)
C = contaminant concentration in air (8 hr TWA in ppm; from Table 2-9)
ED = exposure duration (8 hrs/day)
AT = averaging time (24 hrs/day)

EPA/OPPT used the average daily concentration (ADC) and lifetime average daily concentration (LADC) to estimate workplace exposures for non-cancer and cancer risks, respectively. These exposures were estimated as follows:

$$\text{ADC or LADC} = \frac{C * ED * EF * WY}{AT}$$

where:

ADC = average daily concentration (24-hr TWA in ppm) used for chronic non-cancer risk calculations
LADC = lifetime average daily concentration (24-hr TWA in ppm) used for chronic cancer risk calculations
C = contaminant concentration in air (8-hr TWA in ppm; from Table 2-9)
ED = exposure duration (8 hrs/day)
EF = exposure frequency (260 days/yr)
WY = working yrs per lifetime (40 yrs)
AT = averaging time (LT × 365 days/yr × 24 hrs/day; where LT = lifetime; LT = 40 yrs for non-cancer risks; LT=70 yrs for cancer risks)

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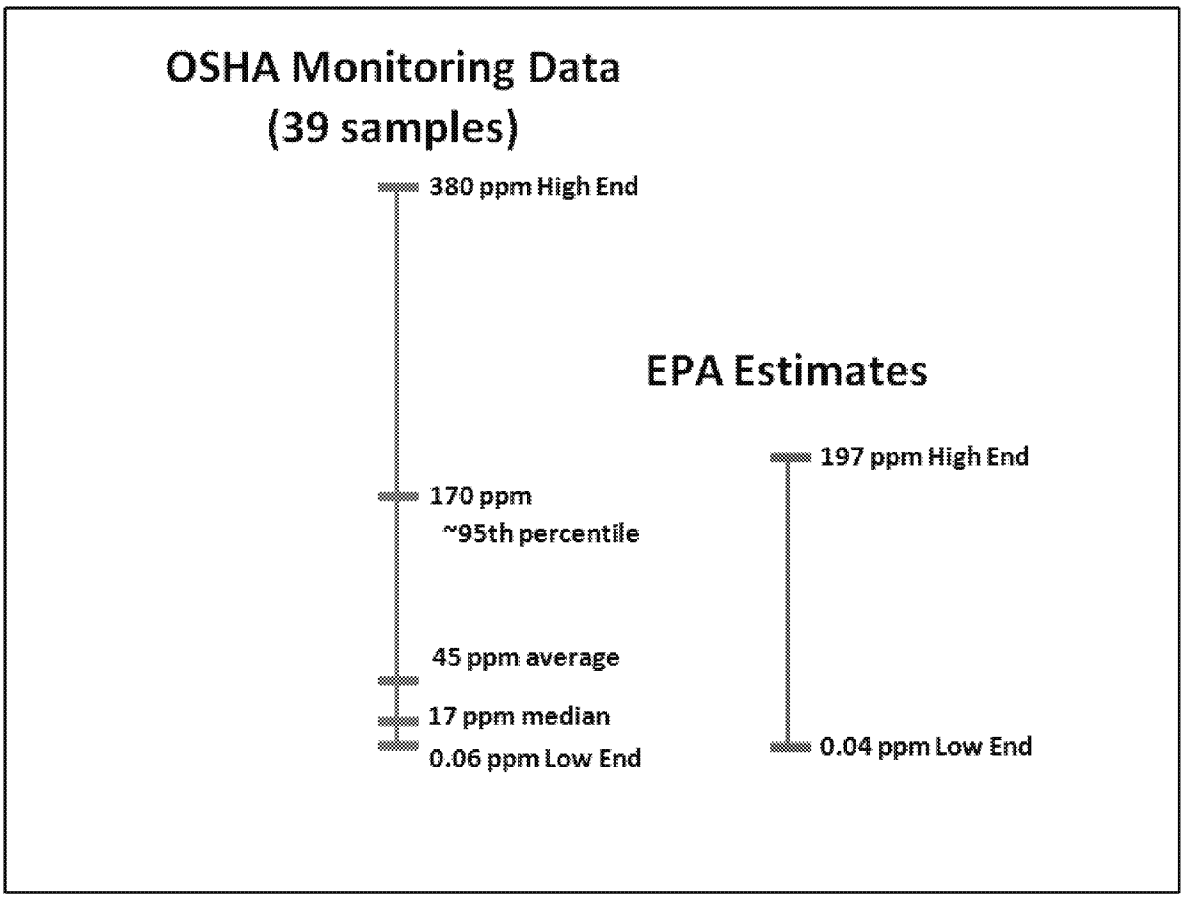
Figure 2-2. Comparison of EPA/OPPT's Workplace TCE Exposure Estimates with 2003-2010 OSHA Monitoring Data for Small Commercial Degreasing Facilities



OSHA sent EPA/OPPT potentially relevant field measurements for TCE. The OSHA monitoring data and EPA/OPPT's assessment of it are included in the supplementary file "OSHA IMIS TCE SAMPLES_062314v1.xlsx". In brief, EPA/OPPT filtered OSHA's data to arrive at 39 relevant field measurements collected between 2003 and 2010. The data were filtered by (1) the NAICS codes listed in Appendix D, (2) Sample Type (personal), and (3) Exposure Type (full shift time weighted average).

Table 2-10. Summary of Acute and Chronic Workplace TCE Inhalation Exposures at Small Commercial Degreasing Facilities						
Population Exposed	Workplace Exposure Concentrations (24-hr TWA[3] in ppm)					
	Acute		Chronic			
			Non-cancer		Cancer	
	With LEV	No LEV	With LEV	No LEV	With LEV	No LEV
Workers[1]	0.1 (low-end estimate) 7 (upper-end estimate)	1 (low-end estimate) 66 (upper-end estimate	0.07 (low-end estimate) 5 (upper-end estimate	0.7 (low-end estimate) 47 (upper-end estimate	0.04 (low-end estimate) 3 (upper-end estimate	0.4 (low-end estimate) 27 (upper-end estimate
Occupational bystanders[2]	0.01 (low-end estimate) 6 (upper-end estimate)	0.1 (low-end estimate) 57 (upper-end estimate)	0.01 (low-end estimate) 4 (upper-end estimate)	0.1 (low-end estimate) 41 (upper-end estimate)	0.005 (low-end estimate) 2 (upper-end estimate)	0.05 (low-end estimate) 23 (upper-end estimate)

Notes:
[1] Workers are directly involved with degreasing operations.
[2] Occupational bystanders have the potential to be exposed to TCE but they are not directly involved with degreasing operations
[3] TWA = Time weighted average
[4] LEV = local exhaust ventilation

The exposure estimates in Table 2-10 are used for deriving MOEs in Tables 2-30 and 2-33, and Figure 2-6

2.4 ENVIRONMENTAL RELEASES AND OCCUPATIONAL EXPOSURE ESTIMATES FOR SPOT CLEANING AT DRY CLEANING OPERATIONS

2.4.1 A Brief Summary of Spot Cleaning at Dry Cleaning Operations

The dry cleaning industry provides garment cleaning services and consists of the following three basic functions: cleaning, drying, and finishing (EPA, 1995a; Luhring and Marks, 2000; NIOSH, 1997a). Releases from dry cleaning operations are primarily to air, water, and solid waste (EPA, 1995a).

1. Prior to being machine washed (cleaning), garments are typically pre-treated for stains (spot cleaning).
2. Next, garments are dried using a combination of aeration, heat and tumbling.
3. If applicable, garments are post-treated for any remaining stains (spot cleaning), and then they are pressed (finishing).

2.4.2 EPA/OPPT's Release and Exposure Assessment for Spot Cleaning Operations

EPA/OPPT used readily available information from a 2007 study on spotting chemicals (CalEPA/EPA, 2007), prepared for the California EPA and U.S. EPA Region 9, to estimate releases of and exposures to TCE from spot cleaning operations at dry cleaning facilities. EPA/OPPT used several steps in order to produce these estimates. An overview of these steps is shown in Figure 2-3; further elaboration of these steps has been structured to follow the sequence in this figure.

1. **Identification of relevant industries:** Based on information provided to EPA/OPPT during the review and comment period for this TSCA Work Plan Chemical risk assessment, the dry cleaning industry was identified as using TCE in spot cleaning processes. In order to assess TCE-based spot cleaning processes, EPA/OPPT used data from a study that were specifically focused on spotting chemicals (CalEPA/EPA, 2007). This study focused on dry cleaning facilities in the state of California.

In this assessment, EPA/OPPT assumed that dry cleaning facilities in the state of California were representative of dry cleaning facilities in the United States.

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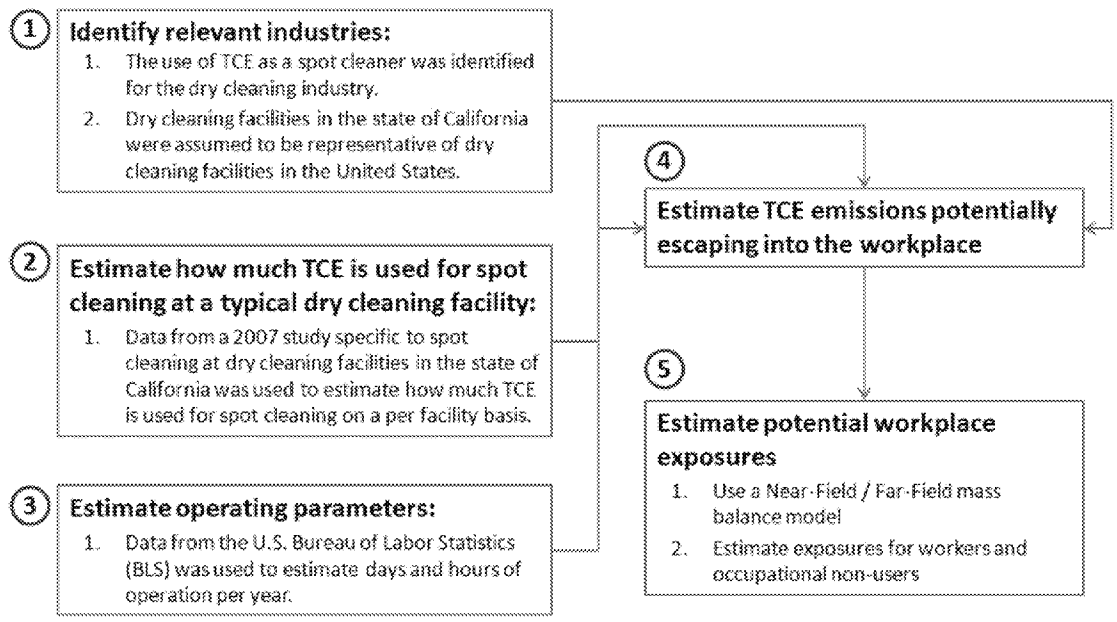
Figure 2-3. Overview of EPA/OPPT's occupational release and exposure assessment for spot cleaning operations



2. **Estimation of how much TCE is used for spot cleaning at a typical dry cleaning facility:** In 2007, the number of textile cleaning facilities in the state of California was estimated to be about 5,000 (CalEPA/EPA, 2007). Further, in consultation with cleaning facilities and their suppliers, it was estimated that about 42,000 gallons per year of TCE-based spotting agents were sold in the state of California (CalEPA/EPA, 2007). Based on an examination of several material safety data sheets (MSDS), the concentration of TCE in spotting agents was observed to vary from 10 percent to 100 percent (CalEPA/EPA, 2007). In this assessment, EPA/OPPT estimated that a typical dry cleaning facility used 0.84 to 8.4 gallons per yr of TCE for spot cleaning operations. This was estimated as follows:

TCE Use Rate

$$= \frac{(\text{Annual Usage of Spotting Agents}) * (\text{TCE Concentration in Spotting Agent})}{\text{Number of Facilities}} =$$

$$\frac{(42{,}000 \text{ gallons per yr}) * (10\% \text{ to } 100\%)}{5{,}000 \text{ facilities}} = 0.84 \text{ to } 8.4 \ \frac{\text{gallons}}{\text{yr}} \text{ per facility}$$

3. **Estimation of operating parameters:** EPA/OPPT estimated that dry cleaning facilities operated 260 days per year; 8 hrs a day for a total of 2,080 hrs per year (BLS, 2012). In addition, EPA/OPPT assumed that spot cleaning operations take place over the course of an 8 hr work day.

4. **Estimation of TCE emissions potentially escaping into the workplace:** Chemical emissions escaping into the workplace can be controlled and thus reduced through the use of engineering controls. For example, tables used to perform spot cleaning (spotting tables) can be equipped with LEV and are commercially available (NIOSH, 1997b). In this assessment, EPA/OPPT assumed an effectiveness of 90% for LEV (Wadden et al., 1989). Thus, LEV could reduce emissions escaping into the workplace by 90%.

In this assessment, EPA/OPPT assumed that the entire amount of spotting agent used at a dry cleaning facility was available for evaporation and thus could be emitted into the workplace. EPA/OPPT assessed scenarios with and without LEV.

A summary of TCE emissions potentially escaping into the workplace from spot cleaning is provided in Table 2-11. These emission rates were estimated as follows:

TCE Emission Rate (with LEV)

$$= (\text{TCE Use Rate}) * \left(\frac{3{,}785\ cm^3}{gallon}\right) * (\text{TCE Density}) * \left(\frac{1\ yr}{2{,}080\ hrs}\right) * \left(\frac{1\ hr}{60\ min}\right) *$$

$$(100\% - \text{LEV Effectiveness}) = \left(\frac{0.84\ to\ 8.4\ gallons}{yr - facility}\right) * \left(\frac{3{,}785\ cm^3}{gallon}\right) * \left(\frac{1.46\ g}{cm^3}\right) *$$

$$\left(\frac{1\ yr}{2{,}080\ hrs}\right) * \left(\frac{1\ hr}{60\ min}\right) * (10\%) = \frac{0.0037\ to\ 0.037\ g\ TCE}{min} \text{ per facility}$$

TCE Emission Rate (no LEV)

$$= (\text{TCE Use Rate}) * \left(\frac{3{,}785\ \text{cm}^3}{\text{gallon}}\right) * (\text{TCE Density}) * \left(\frac{1\ \text{yr}}{2{,}080\ \text{hrs}}\right) * \left(\frac{1\ \text{hr}}{60\ \text{min}}\right) =$$

$$\left(\frac{0.84\ \text{to}\ 8.4\ \text{gallons}}{\text{yr}-\text{facility}}\right) * \left(\frac{3{,}785\ \text{cm}^3}{\text{gallon}}\right) * \left(\frac{1.46\ \text{g}}{\text{cm}^3}\right) * \left(\frac{1\ \text{yr}}{2{,}080\ \text{hrs}}\right) * \left(\frac{1\ \text{hr}}{60\ \text{min}}\right) =$$

$$\frac{0.037\ \text{to}\ 0.37\ \text{g TCE}}{\text{min}} \text{ per facility}$$

Table 2-11. TCE Emissions Potentially Escaping into the Workplace from Spot Cleaning

Type of Facility	TCE Emissions Potentially Escaping into the Workplace (g TCE/min) With LEV [1]	TCE Emissions Potentially Escaping into the Workplace (g TCE/min) No LEV
Dry Cleaning Facility	0.0037 (low-end estimate) 0.037 (upper-end estimate)	0.037 (low-end estimate) 0.37 (upper-end estimate)

[1] LEV = local exhaust ventilation

5. Estimation of potential workplace exposures

Workers and occupational bystander potentially exposed: There are approximately 36,000 dry cleaning facilities (NAICS code 8123000) in the U.S. with a total of about 300,000 workers (USCB, 2011); or about 8 workers per dry cleaning facility. This estimate includes both, workers and occupational bystanders at dry cleaning facilities. Approximately 10% of employees at a dry cleaning facility can be in close proximity to the spot cleaning process (NIOSH, 1997a).

In this assessment, EPA/OPPT assumed one (1) worker per dry cleaning facility was directly involved with spot cleaning operations while the number of occupational bystanders was estimated as seven (7) per dry cleaning facility.

EPA/OPPT's estimated workplace exposures: To estimate workplace exposures, the emissions from Table 2-11 were incorporated into the NF/FF mass balance model. As indicated previously, the NF/FF model has been extensively peer-reviewed, it is extensively used, and results of the model have been compared with measured data. The comparison indicated that the model and measured values agreed to within a factor of about three (Jayjock et al., 2011).

Appendix H presents the rationale and calculations for estimating inhalation exposures for workers and bystanders from spot cleaning at dry cleaning facilities. Table 2-12 shows a summary of EPA/OPPT's workplace exposure estimates for workers and occupational bystanders at dry cleaning facilities. Exposure estimates were calculated for work conditions with and without LEV.

Workplace exposures based on monitoring data: Although relevant exposure monitoring data were limited, EPA/OPPT did identify a study specific to spot cleaning with TCE (NIOSH, 1997a). In this study, TWA exposures to TCE during spot cleaning (with no LEV) ranged from 2.37 to 3.11 ppm, which is within EPA/OPPT's estimated range of 0.08 to 19 ppm (Table 2-12).

The facility in this study had a floor area of approximately 8,500 square feet (ft^2). The room height was not specified. It was assumed to be 10 feet (ft), giving a room volume of 85,000 cubic feet (ft^3) [(or about 2,400 cubic meter (m^3)]. On an average day, workers at this facility used approximately 6 ounces (170 g) of Picrin (NIOSH, 1997a), the contents of which are approximately 100% TCE (CalEPA/EPA, 2007). Assuming an 8-hr work day, this would correspond to a Picrin use rate of about 0.35 g of TCE per min. Based on these site-specific parameters (e.g., room volume, Picrin use rate, no LEV), the NF/FF model estimated that the TWA TCE worker exposures could range from 0.8 to 2.1 ppm, while measured values reported in the study ranged from 2.37 to 3.11 ppm

Table 2-12. Summary of Potential Workplace TCE Inhalation Exposures from Spot Cleaning at Dry Cleaning Facilities				
Population Exposed	**Type of Exposure (Exposure Duration)**	**Estimated TCE Air Concentration (ppm)** **With LEV[4]**	**Estimated TCE Air Concentration (ppm)** **No LEV**	**Estimated Number of People Exposed[5]**
Worker[1]	Inhalation exposure (8-hr TWA[3])	0.008 (low-end estimate) 2 (upper-end estimate)	0.08 (low-end estimate) 19 (upper-end estimate)	36,000
Occupational bystanders[2]	Inhalation exposure (8-hr TWA)	0.0007 (low-end estimate) 2 (upper-end estimate)	0.007 (low-end estimate) 18 (upper-end estimate)	252,000

Notes:
[1] Workers are directly using TCE-based spot cleaners.
[2] Occupational bystanders have the potential to be exposed to TCE but they are not directly involved with spot cleaning.
[3] TWA = Time weighted average
[4] LEV = local exhaust ventilation
[5] The number of people does not sum up to 300,000 due to rounding error.

Since a study specific to spot cleaning with TCE was identified, site-specific parameters from this study were incorporated into the NF/FF model to obtain site-specific model estimates of worker exposure. Model estimates (0.8 to 2.1 ppm) were of the same order of magnitude as measured values (2.37 to 3.11 ppm).

Acute and chronic workplace exposure estimates: In this assessment, EPA/OPPT assessed acute and chronic risks for workers and occupational bystanders from spot cleaning at dry cleaning facilities. A summary of acute and chronic workplace exposures is provided in Table 2-13. Acute workplace exposures were estimated as follows:

$$AC = \frac{C * ED}{AT}$$

where:
AC = acute concentration (24-hr TWA in ppm)
C = contaminant concentration in air (8-hr TWA in ppm; from Table 2-12)
ED = exposure duration (8 hrs/day)
AT = averaging time (24 hrs/day)

EPA/OPPT used the average daily concentration (ADC) and lifetime average daily concentration (LADC) to estimate workplace exposures for non-cancer and cancer chronic risks, respectively. These exposures were estimated as follows:

$$LADC = \frac{C * ED * EF * WY}{AT}$$

where:
LADC = lifetime average daily concentration (24-hr TWA in ppm)
C = contaminant concentration in air (8-hr TWA in ppm; from Table 2-12)
ED = exposure duration (8 hrs/day)
EF = exposure frequency (260 days/yr)
WY = working years per lifetime (40 yrs)
AT = averaging time (LT × 365 days/yrs × 24 hrs/day; where LT = lifetime; LT = 40 yrs for non-cancer risks; LT=70 yrs for cancer risks)

Table 2-13. Summary of Acute and Chronic Workplace TCE Inhalation Exposures from Spot Cleaning at Dry Cleaning Facilities						
Population Exposed	**Workplace Exposure Concentrations (24-hr TWA[3] in ppm)**					
	Acute		**Chronic**			
			Non-cancer		**Cancer**	
	With LEV [4]	**No LEV**	**With LEV**	**No LEV**	**With LEV**	**No LEV**
Workers[1]	0.003 (low-end estimate) 1 (upper-end estimate)	0.03 (low-end estimate) 6 (upper-end estimate)	0.002 (low-end estimate) 0.5 (upper-end estimate)	0.02 (low-end estimate) 5 (upper-end estimate)	0.001 (low-end estimate) 0.3 (upper-end estimate)	0.01 (low-end estimate) 3 (upper-end estimate)
Occupational bystanders[2]	0.0002 (low-end estimate) 1 (upper-end estimate	0.002 (low-end estimate) 6 (upper-end estimate	0.0002 (low-end estimate) 0.5 (upper-end estimate	0.002 (low-end estimate) 4 (upper-end estimate	0.0001 (low-end estimate) 0.3 (upper-end estimate	0.001 (low-end estimate) 2 (upper-end estimate

Notes:
[1] Workers are directly involved with spot cleaning operations.
[2] Occupational bystanders have the potential to be exposed to TCE but they are not directly involved with spot cleaning operations
[3] TWA = Time weighted average
[4] LEV = local exhaust ventilation

The exposure estimates in Table 2-13 are used for deriving MOEs in Tables 2-31 and 2-34, and Figure 2-7

2.5 CONSUMER EXPOSURES – DEGREASER AND ARTS/CRAFTS USES OF TCE

2.5.1 TCE Uses Targeted for Consumer Exposure Assessment

Among the many uses of TCE in consumer products, EPA/OPPT selected those products used as degreasers and arts/crafts products for further risk evaluation. The decision of targeting the assessment to specific consumer products considered (1) consumer product information reported in the National Institutes of Health's (NIH) Household Products Database (DHHS, 2012), (2) information reported in Material Safety Data Sheets (MSDS), and (3) product information on the manufacturer's website.

EPA/OPPT searched the NIH Household Products Database, which links over 13,000 consumer brands to health effects reported in MSDS documents (DHHS, 2012). The database also allows scientists and consumers to research products based on chemical ingredients. Our search found three companies manufacturing 12 consumer products containing TCE (Table 2-14) [10].

EPA/OPPT further researched the products, including a review of the MSDS for each product and inspection of the manufacturer's website. EPA/OPPT confirmed the presence of TCE in six out of the 12 products listed by the NIH Household Products Database (Table 2-14). These six products were degreaser and arts and crafts aerosol spray products that may be used by consumers at home. Three products were absent from the product manufacturer's website and discontinued. The remaining three products in Table 2-14 did not contain TCE and were reformulated by using other chemical alternatives such as tetrachloroethylene, hydrotreated light distillate, dipropylene glycol n-propyl ether, dipropylene glycol methyl ether acetate, aliphatic petroleum solvent, or acetone. There may be other consumer products currently present in the U.S. market that were not reported in the NIH Household Products Database.

After peer review EPA/OPPT became aware of more products that contain TCE that were not included in the Households product database. Another product is sold by Sprayway and is called "No Fray Spray". It can be used to reduce fraying of fabric in sewing and craft projects. It has the same percentage of TCE as the clear protective coating spray (20-30% TCE) listed in the table above and it may result in similar exposures for users.

EPA/OPPT also searched the internet for information about TCE-containing spot cleaners used for consumer uses and identified several spot cleaners for fabrics marketed to U.S. consumers. According to their MSDS, most of these spot cleaners did not contain TCE and the other spot cleaner products did not report the list of ingredients. Thus, we could not preclude consumer exposures if some of these spot cleaners may contain TCE as a main ingredient. Also, OPPT/EPA could not rule out that consumers are using professional-grade spot cleaners.

[10] See supplementary document entitled: "Supplemental Product Information for the TSCA Workplan Chemical Risk Assessment of TCE (External Review Draft)" for further details on the results of the Household Products Database retrieval and for the Material Safety Data Sheets and other information retrieved from company websites.

Table 2-14. TCE Products in NIH's Household Products Database	
Product[a]	**%TCE Content by Weight (as of February 2014)[b]**
EPA/OPPT determined that these products contain TCE	
Sprayway C-60 063 solvent degreaser	>90%
Sprayway C-60 064 solvent degreaser	>90%
Sprayway 201 clear protective coating spray	20-30%
Sprayway 205 film cleaner	>90%
Sprayway 208 toner aide	15-20%
Sprayway 209 mirror edge sealant	20-30%
EPA/OPPT determined that these products did not contain TCE	
Lectra Clean 02018 heavy duty electrical parts degreaser	None
Lectra Clean 02120 Lectra Clean II non-chlorinated heavy duty electrical parts degreaser	None
Sprayway 073 brake parts cleaner	None
EPA/OPPT determined that these products were discontinued	
Sprayway 669 gravel guard	Product not found on manufacturer's product list
Sprayway 732 industrial cleanup dry cleaner	Product not found on manufacturer's product list
TrakAuto Trouble Free Rust Buster	Company no longer in business

Notes:

[a] EPA/OPPT searched the NIH Household Products Database in March 2012 and February 2014. Both searches reported the same list of consumer products containing TCE.However, one product (Sprayway Plastic Spray Clear Fixative No. 201) was categorized for arts/crafts uses in March 2012, but appears to be used as a home office product in February 2014. For the purposes of this assessment, EPA/OPPT relied on the searches obtained in March 2012.

[b] Percent TCE according to Material Safety Data Sheets retrieved from company websites in March, 2012 (See attached document titled "Supplemental Product Information for the TSCA Workplan Chemical Risk Assessment of TCE (External Review Draft).pdf").

2.5.2 Overview of the E-FAST2/CEM Model

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) (EPA, 2007b) was selected for the consumer exposure modeling because it is the appropriate model to use due to the lack of available emissions and monitoring data for the TCE uses under consideration. Moreover, EPA/OPPT did not have the input parameter data required to run more complex indoor air models for the consumer products under the scope of this assessment.

E-FAST2/CEM uses high-end input parameters/assumptions to generate conservative, upper-bound inhalation exposure estimates for aerosol spray products. The advantages of E-FAST2/CEM are the following:

1. CEM model was peer-reviewed in 1999.
2. Accommodates the inputs available for the products containing TCE in the indoor air model.

3. Uses the same calculation engine to compute indoor air concentrations from a source as the Multi-Chamber Concentration and Exposure Model (MCCEM), but it does not require measured emission values (e.g. chamber studies).

The model used a two-zone representation of a house to calculate the potential acute dose rate (mg/kg-bw/day) of TCE for consumers and bystanders. Zone 1 represents the area where the consumer is using the product, whereas Zone 2 represents the remainder of the house. Zone 2 was used for modeling passive exposure to house residents (bystanders), such as children, adults, pregnant women and the elderly.

The general steps of the calculation engine within the CEM model included:
1. introduction of the chemical (i.e., TCE) into the room of use,
2. transfer of the chemical to the rest of the house due to exchange of air between the different rooms,
3. exchange of the house air with outdoor air and,
4. summing of the exposure doses as the modeled occupant moves about the house

The chemical of concern (i.e., TCE) entered the room air through two pathways: (1) overspray of the product and (2) evaporation from a thin film. One percent (1%) of the product was assumed to become instantly aerosolized (i.e. product overspray) and was available in the room air for inhalation.

The CEM model used data from the evaporation of a chemical film to calculate the rate of the mass evaporating from the application surface covered during product use (Chinn, 1981). The model assumed that air exchanged from the room of use (Zone 1) and the rest of the house (zone 2) according to interzonal flow. The model also allowed air exchange from the house (Zone 1 & 2) with the outdoor air.

EPA/OPPT used the default activity pattern in CEM based on the occupant being present in the home for most of the day. As the occupants moved around the house in the model, their exposure to the calculated air concentrations were summed to form a potential 24-hr dose.

The potential inhalation acute dose rates (ADR_{pot}) were computed iteratively by calculating the peak concentrations for each simulated 10-second interval and then summing the doses over 24 hrs. These calculations took into consideration the chemical emission rate over time, the volume of the house and the zone of use, the air exchange rate and interzonal airflow rate, the exposed individual's locations, body weights and inhalation rates during and after the product use (EPA, 2007b). The reader is referred to EPA's E-FAST2 website[11] and Appendix I to obtain additional information about the model, including the model documentation and algorithms used.

[11] EPA's E-FAST2 website: http://www.epa.gov/oppt/exposure/pubs/efast.htm

2.5.3 Consumer Model Scenarios and Input Parameters for Indoor Exposure to Specific TCE Uses

Table 2-15 describes the four acute inhalation indoor scenarios and populations of interest that EPA/OPPT evaluated in the consumer exposure assessment. As indicated in section 1.3.2, EPA/OPPT believes that inhalation is the main exposure pathway. Ingestion exposure of TCE from the use of these consumer products appears to be unlikely given the way they are used (*i.e.*, sprayed onto artwork).

Table 2-15. Consumer Model Scenarios and Populations of Interest

Acute Inhalation Indoor Scenario[1]	Population of Interest[a]
Consumer-degreaser use	Adult consumers >16 yrs old *Most sensitive population of concern:* Pregnant women (fetus)
Bystander to consumer-degreaser use	Individuals of all ages *Most sensitive population of concern:* Pregnant women (fetus) and children
Consumer-clear protecting coating spray use	Adult consumers >16 yrs old *Most sensitive population of concern:* Pregnant women (fetus)
Bystander to consumer-clear protecting coating spray use	Individuals of all ages *Most sensitive population of concern:* Pregnant women (fetus) and children

Notes:
[a] EPA/OPPT believes that the users of these products are generally adults, but young teenagers and even younger children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing. Since there are not survey data for consumer behavior patterns or a way to create varying behavior patterns for different age groups, the indoor air concentrations shown in table 2-17 could be extended to all users.

To estimate exposures to these products, numerous input parameters are required to generate a single exposure estimate. These parameters include the characteristics of the house, the behavior of the consumer and the emission rate of the chemical into the room of use. In the absence of measured values for many of the needed inputs, the E-FAST2/CEM modeling for TCE used a combination of upper percentile and mean or median input parameters and assumptions in the calculation of potential exposure for the user and bystanders. This approach produced high-end acute inhalation estimates instead of central tendency exposures[12] that were hypothetical and intended to be conservative. The input parameters and assumptions are summarized in Table 2-16 and explained more fully in the *Supplemental Information*[13,14] and Appendix I.

[12] High-end exposures represent values above a mean or median and may include the high end of an exposure distribution. A central tendency value represents some measure of the center of a distribution, such as an average or mean or median.
[13] See attached document titled "Supplemental Information on E-FAST2 CEM Outputs (Degreaser Use) TSCA Work Plan Chemical Risk Assessment of TCE (External Review Draft).docx").
[14] See attached document titled "Supplemental Information on E-FAST2 CEM Outputs (Clear Protective Coating Spray) TSCA Work Plan Chemical Risk Assessment of TCE (External Review Draft).docx"

Consumer behavior pattern parameters in CEM include the mass of product used, the duration of use and the frequency of use.The default values in CEM for these consumer behavior parameters are set to high end values.The other parameters (e.g. house volume) in CEM are set to mean or median values from the literature.The default consumer behavior patterns from CEM *were not* used in this risk assessment. This combination of high end and mean or median values is intended to produce a high end acute inhalation exposure estimate.

EPA/OPPT did not locate consumer product survey data for use patterns for the two consumer uses. Instead professional judgment was used for these values and was based on the MSDS and product descriptions.

To determine the appropriateness of the consumer behavior pattern parameters chosen in this risk assessment, EPA/OPPT examined the consumer categories available in the Westat survey (EPA, 1987a). The Westat survey contacted thousands of Americans to gather information on consumer behavior patterns related to product categories that may contain halogenated solvents. The Westat survey data were not completely aligned with the description of the products that we used in this consumer exposure assessment (EPA, 1987a). However the data provided some indication that the values that EPA/OPPT used were below mean or median for the mass, but above the mean for the time spent in the room of use (Appendix I).

The input parameters for household characteristics (e.g., house volume) were all set to mean or median values based on data found in the available literature. Likewise, the user's body weight and inhalation rate were set to either the mean or the median values for the simulations used in this assessment.

The air exchange rate in the room of use is not reflective of open windows or the use of an exhaust fan. While it is possible that some users may employ these exposure reduction techniques inside their homes, the goal of the consumer exposure assessment was to provide an acute exposure estimate for ventilation conditions representing average household air exchange rates. Moreover, residential users would not necessarily have the type of indoor exposure reduction tools/equipment (e.g., gloves, exhaust ventilation) that workers likely have at occupational settings. Consumers would not necessarily be as aware of potential chemical hazards as workers and would not have a standard operating procedure in place to assure that they use exposure reduction techniques each time they use a product.

In this assessment it was assumed that there was no pre-existing concentration of TCE in the home before product use began. The outdoor air was also assumed to be free of TCE, meaning that the air exchange rate described the intake of air with no TCE contamination.

The products were assumed to be sprayed on varying surfaces, e.g. a metallic surface for the degreaser or canvas for the spray fixative. On these surfaces, a thin film of the product was assumed to build up, which then evaporates and contributes to the air concentration of the chemical in the room.

We relied on modeled emission rates because data from chamber studies were not available. To generate emission rates, E-FAST2/CEM used empirical data from studies assessing the emission rates

of pure solvents (Chinn, 1981). E-FAST2/CEM used the Chinn study as surrogate data to calculate the rate of evaporation of TCE from this unknown surface to the air in the home.

These solvent studies supported the use of an exponentially decaying emission rate for TCE from the application surface based on vapor pressure and molecular weight (Chinn, 1981), the equations using the Chinn method are in Appendix I. The solvent degreaser application should be well modeled by the Chinn study since the degreaser product was over 90% TCE. Also, carbon dioxide (CO_2) would be the only other component in the product and it would not be expected to be deposited on the surface or cause significant changes in the TCE emission rate from the surface.

On the other hand, the spray fixative product is a more complicated mixture, and the interaction of these chemicals could alter the evaporation rate of TCE. This introduces uncertainty into the assessment but EPA/OPPT could not find a better data set available to model the emission rates. Within the current exposure assessment, the 24-hr exposure was not strongly dependent on the emission rate due to the amount of time the product user spends in the room of use (see Appendix I for details).

CEM has certain restrictions on the age that is assumed for simulated users, which in turn sets limits for the dose rates generated for different age groups. However, these restrictions should not be interpreted as suggesting that younger users would not be exposed. EPA/OPPT believes that the users of these products are generally adults, but teenagers and even younger children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing. Since there are not survey data for consumer behavior patterns or a way to create varying behavior patterns for different age groups, the indoor air concentrations shown in table 2-17 could be extended to all users.

Lastly, a chronic consumer exposure assessment was not performed because the frequency of product used was considered to be too low to create chronic risk concerns. Although CEM model results given in the supplemental information included chronic exposure estimates, they were not used in this assessment.

Table 2-16. Summary of E-FAST2/CEM's Input Parameters and Assumptions for Estimation of Potential Acute Dose Rates for Specific TCE Uses					
Input Parameters and Assumptions	**Consumer-degreaser use**	**Bystander to consumer-degreaser use**	**Consumer-clear protecting coating spray use**	**Bystander to consumer-clear protecting coating spray use**	**Comments**
TCE mass in product	24 g per use	N/A	11 g per use	N/A	Total mass of product multiplied by weight fraction of TCE
Consumer Product TCE Weight Fraction	0.9 Value from MSDS	N/A	0.3 High end values from MSDS	N/A	Value reported in the MSDS.
Duration of event and occupant behavior pattern (hrs/event)	1 hr using product 2 hrs total spent in room of use 24 hrs in home or outside	0 hr using product 0 hr in room of use 24 hrs in home or outside	0.5 hr using product 2 hrs total spent in room of use 24 hrs in home or outside	0 hr using product 0 hr in room of use 24 hrs in home or outside	The behavior patterns for the user and bystander are based on a day spent mostly at home with 3 hrs outside of the home. Also, model does not allow bystanders to be present in the room of use during use of the product.
Frequency of use (events/day)	1				It was assumed that these exposures represent unique and separate acute exposure events for both users and bystanders. This was based primarily on the short half-life of TCE in humans. Some residual of TCE (or metabolite[s]) would be expected if another exposure occurs the next day. However, EPA/OPPT did not assume that the residual would be substantial or build up based upon pharmacokinetic half-life.
Exposure duration (days)	1				

Table 2-16. Summary of E-FAST2/CEM's Input Parameters and Assumptions for Estimation of Potential Acute Dose Rates for Specific TCE Uses					
Input Parameters and Assumptions	**Consumer-degreaser use**	**Bystander to consumer-degreaser use**	**Consumer-clear protecting coating spray use**	**Bystander to consumer-clear protecting coating spray use**	**Comments**
Age groups (yrs)	Teenager/Young adults: 16-20 yrs Adults: 21-78 yrs	Any age (<1 yr; 1-2 yr; 3-5 yr; 6-10 yr; 11-15 yr; 16-20 yrs; and 21-78 yr)	Teenager/Young adults: 16-20 yrs Adults: 21-78 yrs	Any age (<1 yr; 1-2 yr; 3-5 yr; 6-10 yr; 11-15 yr; 16-20 yrs; and 21-78 yr)	Age groups obtained from EPA's Exposure Factors Handbook (EFH) (EPA, 2011a). Age group-specific simulations showed that the indoor air concentrations of TCE were the same for teenager and adult individuals in each consumer and bystander use categories. Although the age groups for users did not include individuals <16 yrs based on the assumption that adults would be the primary users of these products, EPA/OPPT cannot rule out that these products are used by teenagers (<16 yrs) and even younger children, particularly in the case of the art/crafts clear protecting coating spray. Since there are not survey data for consumer behavior patterns or a way to create varying behavior patterns for different age groups, the indoor air concentrations shown in table 2-17 are extended to all users in this risk assessment.

Table 2-16. Summary of E-FAST2/CEM's Input Parameters and Assumptions for Estimation of Potential Acute Dose Rates for Specific TCE Uses					
Input Parameters and Assumptions	**Consumer-degreaser use**	**Bystander to consumer-degreaser use**	**Consumer-clear protecting coating spray use**	**Bystander to consumer-clear protecting coating spray use**	**Comments**
Air exchange rate (air exchanges per hr)	0.45				Recommended 50th percentile value of residential air exchange rate for all regions within the United States (EPA, 2011a).
Portion of aerosol in air, also called overspray (unitless)	0.01				This value assumed that one percent of the sprayed product is aerosolized and therefore immediately available for uptake by inhalation. Selection based on professional judgment (EPA, 2007b). The model treated aerosolized portion of TCE as a constant emitter over the duration of use.
Whole House Volume (m^3)	369				Value obtained from EPA (1997). Although the updated EFH provides a larger number (492 m^3)(EPA, 2011a), the older value was retained to provide more conservative estimates. The smaller value, 369 m^3, is also close to the median value from the updated EFH (EPA, 2011a), although mean has increased to 492 m^3.

Table 2-16. Summary of E-FAST2/CEM's Input Parameters and Assumptions for Estimation of Potential Acute Dose Rates for Specific TCE Uses					
Input Parameters and Assumptions	**Consumer-degreaser use**	**Bystander to consumer-degreaser use**	**Consumer-clear protecting coating spray use**	**Bystander to consumer-clear protecting coating spray use**	**Comments**
Zone 1 Volume, m^3 (user location)	20	N/A	20	N/A	The volume of 20 m^3 was assigned to a utility room, which was the proxy for a hobby/craft room. The total volume of the house is 369 m^3. The bystanders spend the entire day in either Zone 2 or outside, while the users spend 2 hours in Zone 1 and 22 hours either in Zone 2 or outside.
Zone 2 Volume, m^3 (the rest of the house)	349				
TCE Emission rate constant (hr^{-1})	101.06				Estimated using Chinn's algorithm based on E-FAST model documentation (Chinn, 1981). This algorithm utilizes the molecular weight and vapor pressure to estimate emission rates.
Inhalation rate (m^3/hr)	0.74 – During use 0.61 – After use	Different for each age group as specified in EPA, 2011	0.74 – During use 0.61– After use	Different for each age group as specified in EPA, 2011	During use value is based on short-term exposure during light activity level. After use value is based on data obtained from EFH (EPA, 2011a).

Table 2-16. Summary of E-FAST2/CEM's Input Parameters and Assumptions for Estimation of Potential Acute Dose Rates for Specific TCE Uses					
Input Parameters and Assumptions	**Consumer-degreaser use**	**Bystander to consumer-degreaser use**	**Consumer-clear protecting coating spray use**	**Bystander to consumer-clear protecting coating spray use**	**Comments**
Body weight (kg)	80	Age group-specific value	80	Age group-specific value	Mean value of body weights for all adults (≥21 years) based on the EFH (EPA, 2011a). Body weights for different groupings are in the Supplementary Information and were based on the EFH (EPA, 2011a).

2.5.4 Consumer Model Results

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (zone 1 and zone 2). These concentrations were converted to acute dose rates (ADRs) using the body weight and respiration rate for each age group. The varying weight and respiration rates of the different age groups resulted in different doses; younger age groups had a higher ratio of inhalation rate to body mass creating a larger dose for a given air concentration of a chemical. However, the same air concentrations were used to generate the doses for each age group within the model's calculation engine. The normal output files for CEM did not include the air concentrations for the different parts of the house, only the doses were included.

Table 2-17 presents the results of the conversion from potential acute dose rates (mg/kg-bw/day) to indoor air concentrations (ppm) for the user and bystander for the two product scenarios. As noted in Section 2.5.3, the indoor air concentrations shown in Table 2-17 could be applied to users of different age groups, particularly in the case of the art/crafts clear protecting coating spray. Although adults are generally the users of these products, EPA/OPPT cannot rule out scenarios where teenagers and even younger children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.

Table 2- 17. Estimated TCE Air Concentrations (Time Averaged Over a Day [a]) from the Residential Indoor Use of Solvent Degreasers or Clear Protecting Coating Sprays

Clear Protective Coating Spray User (ppm) [b]	Clear Protective Coating Spray Bystander [c] (ppm)	Solvent Degreaser User (ppm) [b]	Solvent Degreaser Bystander (ppm) [c]
0.4	0.1	2	0.8

Notes:

[a] See Appendix I for details about the model inputs and Appendix J for the method used to convert acute dose rates (ADRs) into air concentration of TCE (ppm).

[b] Air concentrations for the user categories could be extended to different age groups. EPA/OPPT believes that the users of these products are generally adults, but teenagers and even younger children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.

[c] All age categories (<1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20 yrs ; and >21 yrs)

The model output sheet reported the peak concentration of TCE, but this air concentration was not used in the risk assessment. The peak concentration was the highest concentration among all of the 10-second time intervals that CEM simulated within a 24-hr period. The peak concentration may only exist in the room of use for a short duration and was not considered a good indicator of what the concentration of TCE would be for longer time periods. Thus, we did not use the peak concentration in the risk assessment because it was not representative of a 24-hr exposure.

2.5.4.1 Sensitivity of Model Parameters

There is no available data to refine the consumer behavior patterns used in the consumer exposure assessment (i.e., mass of product used, time spent in room of use). Thus, a sensitivity analysis was not conducted because it would not provide a significant improvement to the quality of the exposure assessment.

EPA/OPPT relied on professional judgment from product descriptions as the main source of information for setting the mass of product used and time spent in room of use. Based on our past experience with the CEM model, it is likely that the mass used and time spent in the room of use are particularly sensitive model parameters in the inhalation exposure simulations.

With no refinement of consumer behavior pattern data, a sensitivity analysis may erroneously find certain input parameters to be unimportant based on current assumptions. For example, the relative contribution of the evaporation rate to the model output variability and uncertainty may seem unimportant based on the assumption that the user remains in the room of use for 2 hrs. This assumption may allow a wide range of evaporation rates that would result in all of the TCE entering the room air while the user is in the room.

Measured consumer behavior pattern data could change inputs, like mass of product used and time spent in the room of use, such that a current sensitivity analysis would lead to inappropriate conclusions. The sensitivity of the estimated exposure concentrations over the day of use to the evaporation rate of the chemical is an example of that concern.

2.5.4.2 Indoor Air Monitoring of TCE

TCE can be released to indoor air from the use of consumer products that contain it, as well as from vapor intrusion and volatilization from contaminated ground water (EPA, 2011e). Where indoor air sources are present, it is likely that indoor levels will be higher than outdoor levels (EPA, 2011e).

Testing and monitoring has been used to evaluate potential exposures arising from VOCs entering the indoor environment through contaminated water. Specifically, a study by EPA researchers measured TCE concentrations from the method detection limit (<MDL 0.91 $\mu g/m^3$ or 0.00017 ppm) to 37.4 $\mu g/m^3$ (0.007 ppm) (Lindstrom and Pleil, 1996).

The TCE IRIS assessment included several studies that measured indoor levels of TCE, but none with monitoring data related to the use of consumer products containing TCE (EPA, 2011e). EPA/OPPT also performed a literature search to determine if indoor monitoring data were available for products using TCE, but none were found.

A supplementary document entitled "*Literature Review of Measured TCE Concentrations in Indoor Air*" (November 2013) contains additional information about the indoor monitoring data studies reviewed for this assessment.

2.6 HAZARD/DOSE-RESPONSE ASSESSMENT

2.6.1 Approach and Methodology

2.6.1.1 Selection of TCE IRIS Assessment as the Source Document for the TCE TSCA Assessment

EPA/OPPT's work plan risk assessment for TCE is based on the hazard and dose-response information published in the toxicological review that the U.S. EPA's Integrated Risk Information System (IRIS) published in 2011. EPA/OPPT used the TCE IRIS assessment as the preferred data source for toxicity information, rather than developing a new toxicological assessment. The TCE IRIS assessment used a weight-of-evidence approach, the latest scientific information and physiologically-based pharmacokinetic (PBPK) modeling to develop hazard and dose-response assessments for TCE's carcinogenic and non-carcinogenic health effects resulting from lifetime oral or inhalation exposure.

Development of TCE's hazard and dose-response assessments considered the principles set forth by the various risk assessment guidelines issued by the National Research Council and the U.S. EPA. Primary, peer-reviewed literature identified through December 2010 was included where that literature was determined to be critical to the assessment (EPA, 2011e). Appendix K provides the guidelines that were considered when developing the TCE IRIS assessment. Some of these guidelines discussed the type of considerations that should be made when evaluating the quality of toxicity data and study reliability. Also Appendix K describes the study selection and data quality criteria that the U.S. EPA's IRIS program and OPPT used to evaluate the hazard data.

The TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006 (NRC, 2006)[15], external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011 (EPA, 2011c)[16], followed by final internal agency review and EPA-led science discussion on the final draft.

Furthermore, EPA/OPPT consulted the EPA's Guidelines for Developmental Toxicity Risk Assessment when making the decision to use developmental toxicity studies in the acute risk assessment of commercial and consumer uses of degreasers and arts/crafts spray fixatives containing TCE (EPA, 1991). The basis for this decision relies on the presumption and EPA's

[15] NAS report, "Assessing the human health risks of trichloroethylene: Key scientific issues (2006)": http://www.nap.edu/catalog.php?record_id=11707

[16] EPA's SAB peer review report for the 2009 EPA's Draft Assessment entitled "Toxicological Review of Trichloroethylene": http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/B73D5D39A8F184BD85257817004A1988/$File/EPA-SAB-11-002-unsigned.pdf

policy that a single exposure at a critical window of fetal development may produce adverse developmental effects (EPA, 1991). In other words, a single dose in a developmental toxicity study may be enough to cause developmental effects.

2.6.1.2 Aspects of the TCE IRIS Assessment that Were Adopted in the OPPT Risk Assessment

2.6.1.2.1 Carcinogenic Hazard and Dose-Response Assessment

TCE is carcinogenic to humans by all routes of exposures as documented in the TCE IRIS assessment. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer (EPA, 2011e). The human epidemiological evidence is strong for kidney and more limited for non-Hodgkin lymphoma (NHL) and liver cancer, and less convincing for biliary tract cancer. Less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia (EPA, 2011e). Further support for TCE's carcinogenic characterization comes from positive results in multiple rodent cancer bioassays in rats and mice of both sexes, similar toxicokinetics between rodents and humans, mechanistic data supporting a mutagenic mode of action for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the mode(s) of action for TCE-induced rodent tumors are irrelevant to humans (EPA, 2011e).

The cancer dose-response analysis used linear-dose extrapolation to derive an inhalation unit risk (IUR) of 2×10^{-2} per ppm (4.1×10^{-6} per $\mu g/m^3$) for various cancers[17]. The IUR for TCE was based on human kidney cancer risks that were reported by Charbotel et al. (2006) and adjusted for potential risk for NHL and liver cancer based on human epidemiological data (EPA, 2011e). The IUR is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air (EPA, 2011b). The IUR was used in the EPA/OPPT risk assessment to estimate excess cancer risks for the inhalation occupational exposures scenarios. There is high confidence in the IUR because it was based on good quality human data, and was similar to unit risk estimates derived from multiple rodent bioassays (EPA, 2011e). Moreover, there was sufficient weight of evidence to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

EPA/OPPT decided not to use the IUR to calculate the theoretical cancer risk associated with a single (acute) exposure to solvent degreasers, arts/crafts fixative and spotting agent products containing TCE. NRC (2001) published methodology for extrapolating cancer risks from chronic to short-term exposures to mutagenic carcinogens. These methods were published with the caveat that extrapolation of lifetime theoretical excess cancer risks to single exposures has great uncertainties.

[17] The dose-response analysis for cancer endpoints can be found in Chapter 5 of the TCE IRIS assessment EPA (2011e).

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As NRC (2001) explains, "*There are no adopted state or federal regulatory methodologies for deriving short-term exposure standards for workplace or ambient air based on carcinogenic risk, because nearly all carcinogenicity studies in animals and retrospective epidemiologic studies have entailed high-dose, long-term exposures. As a result, there is uncertainty regarding the extrapolation from continuous lifetime studies in animals to the case of once-in-a-lifetime human exposures. This is particularly problematical, because the specific biologic mechanisms at the molecular, cellular, and tissue levels leading to cancer are often exceedingly diverse, complex, or not known. It is also possible that the mechanisms of injury of brief, high-dose exposures will often differ from those following long-term exposures. To date, U.S. federal regulatory agencies have not established regulatory standards based on, or applicable to, less than lifetime exposures to carcinogenic substances* (NRC, 2001)." Thus, the final EPA/OPPT work plan risk assessment for TCE does not estimate excess cancer risks for acute exposures because the relationship between a single short-term exposure to TCE and the induction of cancer in humans has not been established in the current scientific literature.

2.6.1.2.2 Non-Cancer Hazard and Dose-Response Assessment

EPA/OPPT used margin of exposures (MOEs)[18] to estimate non-cancer risks based on the following:

1. the lowest PBPK-derived human equivalent concentrations (HECs) within each health effects domain reported in the TCE IRIS assessment;
2. the same endpoint/study-specific uncertainty factors (UFs) that the IRIS program applied to the PBPK-derived HECs; and
3. the exposure estimates calculated for the TCE uses examined in this risk assessment (see *Environmental Releases and Exposure Summary*).

MOEs allow for the presentation of a range of risk estimates rather than a single risk estimate based on the inhalation reference concentration (RfC). Given the different exposure scenarios considered (both acute and chronic for small commercial degreasers, and just acute for the two consumer exposure scenarios), different endpoints were used based on the expected exposure durations. For non-cancer effects, risks to developmental effects were evaluated for acute (short-term) exposures, whereas risks to other adverse effects (toxicity to the liver, kidney, nervous system, immune system, and the reproductive system) were evaluated for repeated (chronic) exposures to TCE.

Table 2-18 lists the studies and corresponding HECs and UFs that EPA/OPPT used in the work plan risk assessment for TCE. Key studies in Table 2-18 are briefly described in the *Human Health Hazard Summary* along with other toxicity and epidemiological studies, with detailed descriptions provided in the TCE IRIS assessment (EPA, 2011e). Appendix L contains the complete list of oral and inhalation non-cancer studies within each health effects domain that the TCE IRIS assessment considered suitable for dose-response analysis.

[18] Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure). See equation in Table 2-29. The benchmark MOE is used to interpret the MOEs and consists of the total UF set by the IRIS program for each study in Table 2-18. See section 2.7.1 for an explanation of the benchmark MOE.

The TCE IRIS assessment used a series of steps to generate the PBPK-derived HECs that OPPT used in its risk assessment (Table 2-19). EPA/OPPT did not rely on those steps that were associated with the derivation of candidate RfCs (cRfC) or final RfC value (Table 2-19). Below is a brief discussion of those steps that EPA/OPPT adopted in this risk assessment.

The non-cancer dose-response analysis in the TCE IRIS assessment commenced with the review and selection of high quality epidemiological and toxicity studies that reported both adverse non-cancer health effects and quantitative dose-response data[19] (Table 2-19). Subsequently, *point of departures (PODs)*[20] were identified for those studies that had suitable data for dose-response analysis. PODs can be a NOAEL[21] or LOAEL[22] for an observed incidence, or change in level of response, or the lower confidence limit on the dose at the benchmark dose (BMD)[23].

The dose-response assessment was organized in five health effects domains: (1) neurotoxicity; (2) systemic (body weight) and organ toxicity (liver and kidney effects); (3) immunotoxicity; (4) reproductive; and (5) developmental effects. PBPK modeling was used to estimate internal dose PODs (idPOD) and subsequently HECs based on the oral and inhalation PODs identified in earlier steps. The PBPK modeling integrated internal dose-metrics based on TCE's mode of action and the role of different TCE metabolites in toxicity (EPA, 2011e). Note that the effects within the same health effect domain were generally assumed to have the same relevant internal dose-metrics (EPA, 2011e).

[19] Non-cancer toxicological and epidemiological studies are described in Chapter 4 of the TCE IRIS assessment.

[20] A point of departure (POD) is a dose or concentration that can be considered to be in the range of observed responses, without significant extrapolation. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures EPA (2011b).

[21] NOAEL=No-observed-adverse-effect level

[22] LOAEL= Lowest-observed-adverse-effect level

[23] The benchmark dose (BMD) is a dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background EPA (2011b).

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Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment												
Exposure Duration for Risk Analysis	**Target Organ/ System**	**Species**	**Route of Exposure**	**Range of Doses or Concentrations[1]**	**Duration**	**POD Type[2]**	**Effect**	**HEC_{50} (ppm) [3]**	**HEC_{95} (ppm)**	**HEC_{99} (ppm)**	**Uncertainty Factors (UFs) for Benchmark MOE [4]**	**Reference**
CHRONIC	Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*[5]	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	0.001 to 14 ppm (0.001 to 14 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30* [5]	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hour work shift; mean 5.1 years on job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)

Table 2-18. Lowest PBPK-derived HECs for different effects domains based on analysis in TCE IRIS assessment

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations[1]	Duration	POD Type[2]	Effect	HEC_{50} (ppm) [3]	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) for Benchmark MOE [4]	Reference
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)

Notes:

1 Control concentrations were not included in the table, but discussed in the study summaries in section 2.6.2.

2 POD type can be NOAEL, LOAEL, or BMDL; the IRIS program adjusted all values to continuous exposure.

3 1 ppm = 5.374 mg/m^3

4 UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF. UF values were those used in the TCE IRIS assessment (EPA, 2011e).

5 Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

Table 2-19. Steps of the Non-Cancer TCE IRIS Process that Were Considered in OPPT's Non-Cancer Hazard/Dose-Response Approach [1]		
Step#	**NON-CANCER IRIS APPROACH**	**NON-CANCER OPPT APPROACH** *Considered (+) / Not Considered (—)*
1	Evaluation of all studies (inhalation and oral) that provided (1) non-cancer adverse health effects and (2) quantitative dose-response data	+
2	Identification of the Points of Departure (POD) based on applied dose	+
3	Adjustment of each POD by endpoint/study-specific uncertainty factors (UFs)	—
4	Derivation of candidate reference concentrations (cRfCs) and selection of the lowest values within each health endpoint domain taking into account the confidence of the estimate	—
5	Application of PBPK modeling to estimate internal dose PODs (i.e., HECs) for those candidate critical effects selected from inhalation and oral studies based on applied dose	+
6	Estimation of interspecies and within-human pharmacokinetic variability for the internal dose PODs by PBPK modeling	+
7	Adjustment of each internal dose POD by endpoint/study-specific UFs [2]	—
8	Derivation of PBPK model-based candidate RfCs (p-cRfC) for each candidate critical effect	—
9	Characterization of the uncertainties of the cRfCs derived by applied dose and PBPK modeling (p-cRfC) by using quantitative uncertainty analyses of pharmacokinetic uncertainty and variability from the Bayesian population analysis [3]	—
10	Evaluation of the most sensitive cRfCs and set final RfC value.	—

Notes:
1 Table 2-19 is an adaptation of Figure 5-1 (Chapter 5) in the TCE IRIS assessment (EPA, 2011e).
2 Endpoint/study-specific UFs were used as benchmark MOEs in the OPPT's TCE risk assessment.
3 EPA/OPPT consulted the characterization of the uncertainties in the TCE IRIS assessment and those aspects related to the uncertainties of the individual studies and the generation of PBPK-derived HECs were discussed in the OPPT's TCE risk assessment.

Furthermore, the PBPK model was used to estimate the interspecies and within-human pharmacokinetic variability (or just within-human variability for the human-based PODs) corresponding to each idPOD for each candidate critical effect. The results of this calculation were 50th, 95th and 99th percentile HEC estimates for POD analyzed within each health effects domain. Also, the PBPK model integrated a Bayesian population analysis to characterize pharmacokinetic uncertainties and variability (EPA, 2011e). More information on the PBPK modeling is provided in the next section below, including how the HECs were calculated.

EPA/OPPT used the endpoint/study-specific UFs from the TCE IRIS assessment as the benchmark MOEs for the risk calculations. These UFs were applied to the PBPK-derived PODs to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011b).

2.6.1.3 Absorption, Distribution, Metabolism, and Excretion

TCE is fat soluble (lipophilic) and easily crosses biological membranes. Though there are quantitative differences across species and routes, TCE is readily absorbed into the body following oral, dermal, or inhalation exposure. Because of its lipophilicity, TCE can cross the placenta and also passes into breast milk (EPA, 2011e).

Absorption following inhalation of TCE is rapid and the inhaled absorbed dose is proportional to the exposure concentration, duration of exposure, and lung ventilation rate. Likewise, TCE is rapidly absorbed from the gastrointestinal tract into the systemic circulation (i.e., blood) following oral ingestion. Oral absorption of TCE has been shown to be influenced by dose of the chemical, the dosing vehicle and stomach contents. Absorbed TCE is first transported to the liver where it is metabolized for eventual elimination (i.e., "first-pass effect") (EPA, 2011e).

Rapid absorption through the skin has been shown by both vapor and liquid TCE contact with the skin. EPA (2011e) summarized several volunteer studies in which both TCE liquid and vapors were shown to be absorbed in humans via the dermal route. Following exposures of between 20 and 30 minutes, absorption was rapid, with peak TCE levels in expired air occurring within 15 minutes (liquid) and 30 minutes (vapor).

Regardless of the route of exposure, TCE is widely distributed throughout the body. TCE levels can be found in many different human and rodent tissues including: brain, muscle, heart, kidney, lung, liver, and adipose tissues. It can also be found in human maternal and fetal blood and in the breast milk of lactating women (EPA, 2011e).

Distribution of TCE to the body is determined by how much TCE is absorbed and eliminated by the lungs. The blood-to-air partition coefficient is used to quantify the resulting concentration in blood leaving the lungs at equilibrium with alveolar air. Partition coefficients have been measured *in vitro* and range between 8.1 and 11.7 in humans and between 13.3 and 25.8 in rodents (EPA, 2011e). Once in the alveolar blood, the solubility of TCE in blood is the major determining factor in its distribution to the heart and other parts of the body and is measured by the blood-to-tissue partition coefficient[24]. Other factors influencing its distribution are age-

[24] This represents the ratio of the concentration of TCE in blood to the concentration of TCE in tissue. When the ratio is much less than 1, more TCE would be found in tissue rather than in the circulating blood.

dependencies (i.e., largely based on anatomical and physiological parameters such as metabolic and ventilation rates) and TCE binding to tissues/cellular components.

The metabolism of TCE has been extensively studied in humans and rodents (EPA, 2011e). Animals and humans metabolize TCE to metabolites to varying degrees. These metabolites are known to play a key role in causing TCE-associated toxic effects. TCE metabolites are known to target the liver and kidney. The two major metabolic pathways are (1) oxidative metabolism via the cytochrome P450 (CYP) mixed function oxidase system and (2) glutathione (GSH) conjugation followed by further biotransformations and processing with other enzymes (EPA, 2011e). The liver is the major tissue for the oxidative and GSH conjugation metabolic pathways. Both pathways are saturable, and above the saturable concentration/dose, TCE is excreted unchanged in expired air. Table 2-20 presents the important metabolites formed following both the CYP (oxidation) and GSH (conjugation) pathways in humans and animals. The amount and types of metabolites formed are important for understanding the toxicity of TCE in both animals and humans.

These major TCE metabolites as well as a number of minor metabolites are also observed in the metabolic pathway of TCE-related compounds (Table 2-21). This may be important in determining exposures because people may be co-exposed to many of these solvents at the same time [e.g., dichloroacetic acid (DCA) as disinfection by-products of chlorination of drinking water supplies] (Johnson et al., 1998a). Concomitant exposures to TCE and its related compounds can affect TCE's metabolism and increase toxicity by generating higher internal metabolite concentrations than those resulting from TCE exposure only (EPA, 2011e).

Table 2-20. TCE Metabolites Identified by Pathway

Oxidative Metabolites	GSH Conjugation Metabolites
Chloral ***(metabolized to TCOH[a])***	DCVG[e] (*metabolized to DCVC[f] isomers*)
Trichloroethylene oxide ***(re-arranged to DCAC[b])***	
Trichloroethanol or TCOH ***(metabolized to TCOG[c])***	
Trichloroacetic acid or TCA ***(may lead to DCA[d])***	

Abbreviations: [a] TCOH = trichloroethanol; [b] DCAC= dichloroacetyl chloride; [c] TCOG= trichloroethanol, glucuronide conjugate; [d] DCA=dichloroacetic acid; [e] DCVG= S-dichlorovinyl-glutathione (collectively, the 1,2- and 2,2- isomers); [f] DCVC= S-dichlorovinyl-L-cysteine (collectively, the 1,2- and 2,2- isomers)

A review of *in vitro* metabolism data in the liver suggested that rodents (i.e., especially mice) have greater capacity to metabolize TCE via the oxidation pathway (EPA, 2011e). The *in vitro* data have also reported modest sex- and age-dependent differences in the oxidative TCE metabolism in humans and animals. Significant variability may exist in human susceptibility to TCE toxicity given the existence of CYP isoforms and the variability in CYP-mediated TCE oxidation (EPA, 2011e).

Table 2-21. Common Metabolites of TCE and Related Compounds						
Parent → / Metabolites ↓	Tetrachloro-ethylene	1,1,2,2,-Tetrachloro-ethane	TCE	1,1,1-Trichloro-ethane	1,2,-Dichloro-ethylene	1,1-Dichloro-ethane
Oxalic acid		X	X		X	
Chloral	X		X			
Chloral hydrate (CH)	X		X			
Monochloroacetic acid	X	X	X	X	X	X
Dichloroacetic acid (DCA)	X	X	X			X
Trichloroacetic acid (TCA)	X	X	X	X		
Trichloroethanol (TCOH)	X	X	X	X		
Trichloroethanol-glucuronide	X	X	X	X		
Note: Adapted from Table 2-1 in EPA (2011e)						

Conjugation is a process that generally leads to detoxification. However, this is not the case for TCE and many other halogenated alkanes and alkenes because they are biotransformed into reactive metabolites. The eventual metabolite(s) of concern for TCE are formed several steps from the initial GSH conjugate formed in the liver, which ultimately results in toxicity or carcinogenicity in the kidney (EPA, 2011e). The conjugation of TCE to GSH produces S-(1,2-dichlorovinyl) glutathione or its isomer S-(2,2-dichlorovinyl) glutathione (collectively, S-dichlorovinyl-glutathione or DCVG) (EPA, 2011e). Metabolic enzymes then convert DCVG into two cysteine conjugate isomers: S-(1,2-dichlorovinyl cysteine) [1,2-DCVC] or S-(2,2-dichlorovinyl cysteine) [2,2-DCVC] (collectively, DCVC). N-acetylation then transforms DCVC into N-acetyl-S (1,2 dichlorovinyl)-L-cysteine or N-acetyl-S (2,2 dichlorovinyl)-L-cysteine (collectively, NAcDCVC) (EPA, 2011e).

There are various theories about how DCVC is toxic to the kidney and, to a lesser extent, to the liver. One theory states that a β-lyase enzyme catalyzes the breakdown of 1,2-DCVC to S dichlorovinyl thiol (DCVT), an unstable intermediate that rearranges to other metabolites (enethiols) that form covalent bonds with cellular nucleophiles and results in toxicity (EPA, 2011e). Another theory is that there is a kidney enzyme (L-alpha-hydroxy [L-amino] acid oxidase) that can form intermediates and keto acid analogues that decompose to DCVT. In rat kidney homogenates, this enzyme appeared to be responsible for up to 35 percent of the GSH pathway but is not found in humans (EPA, 2011e). A third theory suggests involvement of sulfoxidation of either the DCVC or NAcDCVC by flavin-containing monooxygenase (FMO3) and CYP3A enzymes, respectively (EPA, 2011e).

In contrast to the CYP oxidation pathway, there appear to be sex and species differences in TCE metabolism via the GSH pathway (EPA, 2011e). Animal data show that rates of TCE GSH conjugation in male rats/mice are higher than females. According to some *in vitro* data, the rates of DCVG production in liver/kidney cytosol are highest in humans, followed by mice, and then rats. *In vitro* data also suggest that γ-glutamyl transpeptidase (i.e., GGT, an enzyme involved in DCVC production) activity in kidneys seems to be highest in rats, then humans, and

then mice (EPA, 2011e). Furthermore, species-dependent enzymatic activities have been reported for the β-lyase and FMO3 enzymes (EPA, 2011e).

Thus, the key in evaluating the TCE metabolism data is to determine the relative roles of CYP and GSH pathways. It appears that, in rodents and humans, the oxidation pathway is clearly more dominant than the GSH pathway. EPA (2011e) suggests that the GSH pathway may play a larger role in humans than it does in rodents, but there is substantial uncertainty based on the available data. In fact, Jollow et al. (2009), using essentially the same data, suggested that rodents have a higher capacity to conjugate TCE with GSH and are thus more susceptible to kidney toxicity/cancer compared with humans.

The majority of TCE absorbed into the body is eliminated by the metabolic pathways discussed above. With the exception of unchanged TCE and CO_2, which are excreted by exhalation, most TCE metabolites (i.e., TCA, TCOH, GSH metabolites) are primarily excreted in urine and feces. Elimination of TCE metabolites can also occur through the sweat and saliva, but these excretion routes are likely to be relatively minor (EPA, 2011e).

Half-lives are useful indicators for the bioaccumulation potential of the chemical. The excretion of unchanged TCE in exhaled air was studied by Sato et al. (1977) who exposed four male volunteers to 100 ppm TCE for 4 hrs. Sato et al. (1977) reported three first-order phases of pulmonary excretion in the first 10 hrs after cessation of exposure, with fitted half-times of pulmonary elimination of 0.04, 0.67, and 5.6 hrs, respectively (EPA, 2011e). Opdam (1989) reported terminal half-lives of 8-44 hrs at rest following exposure of both female and male volunteers to 6-38 ppm TCE for 0.5-1 hr exposures with up to 20-310 hrs of subsequent monitoring of alveolar air.

Another human toxicokinetic study was conducted by Chiu et al. (2007), in which male human volunteers were exposed to 1 ppm TCE for 6 hrs with alveolar air collected during exposure and up to 6 days post-exposure. Chiu et al. (2007) reported pulmonary terminal half-lives of 14-23 hrs (EPA, 2011e). The long terminal half-times suggest that the lungs require considerable time to completely eliminate TCE, primarily due to high partitioning to adipose tissues (EPA, 2011e). As for rodent data, rats and mice exposed to TCE by gavage showed unchanged TCE and CO_2 as exhalation excretion products (EPA, 2011e).

Various laboratories have studied the urinary elimination kinetics of TCE and its major metabolites in humans and rodents. The current practice is to measure urinary oxidative metabolites, including total trichloro compounds (TTC), because urinary levels of unchanged TCE have been at or below detection limits. Ikeda and Imamura (1973) measured various metabolites (i.e., TTC, TCOH, TCA) in human volunteers for three post-exposure days in five exposure groups (no concentrations provided in the study). The elimination half-lives for TTC were 26.1–48.8 hrs in males and 50.7 hrs in females. The elimination half-lives for TCOH were 15.3 hrs and 52.7 hrs for males and females, respectively. The elimination half-lives for TCA were 39.7 hrs and 57.6 hrs for males and females, respectively (EPA, 2011e).

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Ikeda (1977) evaluated the urinary elimination of TCE and its metabolites at the occupational setting. Female and male workers were intermittently exposed to 50 ppm and 200 ppm TCE, respectively at the work place (exposure duration not reported). Urinary elimination half-lives for TTC, TCOH, and TCA were 26.1, 15.3, and 39.7 hrs in males, respectively, and 50.7, 42.7 and 57.6 hrs in females, respectively (EPA, 2011e).

Animal studies have shown that rodents exhibit faster urinary elimination kinetics than humans. For instance, Ikeda and Imamura (1973) evaluated the urinary elimination of TTCs following inhalation exposure to TCE for 8 hrs to 50, 100, or 250 ppm TCE. A second experiment exposed rats to 1.47 g/kg TCE by intraperitoneal injection. The urinary elimination half-lives of TTCs were 14.3–15.6 hrs for female rats and 15.5–16.6 hrs for male rats; the route of administration did not appear to influence half-life value (EPA, 2011e). Oral rodent studies reported urinary elimination of radiolabeled TCE within 1 or 2 days after exposure (Dekant et al., 1984; Green and Prout, 1985; Prout et al., 1985).

2.6.1.4 PBPK Modeling Approach Supporting the TCE IRIS Assessment

Given the complicated metabolic profile of TCE, understanding the relationship between the external dose/concentration (*i.e.*, exposure) and internal dose at the target organ of interest is critical to quantifying potential risk(s) because internal dose is more closely associated with toxicity at the target tissue (EPA, 2006a). Predictions of internal dose in chemical risk assessments are achieved by employing PBPK modeling.

PBPK models use a series of mathematical representations to describe the absorption, distribution, metabolism and excretion of a chemical and its metabolites. Because PBPK modeling assumes that the toxic effects in the target tissue are closely related to the internal dose of the biologically active form of the chemical, knowledge about the chemical's mode of action guides the selection of the appropriate dose metric[25]. Traditional risk estimates based on applied dose carry higher uncertainties than those based on PBPK-derived internal dose metrics. This reduction in uncertainty and the versatility of PBPK approaches have resulted in a growing interest to use these models in risk assessment products (EPA, 2006a).

U.S. EPA developed a comprehensive Bayesian PBPK model-based analysis of TCE and its metabolites in mice, rats and humans (EPA, 2011e)[26]. This model is briefly discussed below to provide clarity on how the PBPK modeling was used to estimate the PBPK-derived HECs.

Physiological, chemical, *in vitro* and *in vivo* data were considered when building the PBPK model, including many studies in animals and humans that quantified TCE levels in various

[25] Dose metric is defined as the target tissue dose that is closely related to ensuing adverse responses. Dose metrics used for risk assessment applications should reflect the biologically active form of chemical, its level and duration on internal exposure, as well as intensity EPA (2006a).

[26] Refer to the TCE IRIS assessment to obtain a summary of the history of the TCE PBPK models that have been built over the years as well as detailed information on the updated model reported in both Evans et al. (2009) and Chiu et al. (2009).

tissues following oral and inhalation exposures. Some of these studies provided key data/parameters for the calibration of the PBPK model used in the IRIS assessment (EPA, 2011e). All of this information was used to build a model that was able to predict different dose-metrics as measures of potential TCE toxicity. Each dose-metric was developed to evaluate a different metabolic pathway/target organ effect based on the dose-response analysis and understanding of metabolism (Tables 2-22 and 2-23).

Table 2-22. List of All of the PBPK-Modeled Dose Metrics Used in the TCE IRIS Assessment

Dose-Metric Identifier	*Explanation of What the Dose-Metric Identifier Represents*
ABioactDCVCBW$^{3/4}$	Amount of DCVC bioactivated in the kidney per unit body weight
ABioactDCVCKid	Amount of DCVC bioactivated in the kidney per unit kidney mass
AMetGSHBBW$^{3/4}$	Amount of TCE conjugated with GSH
AMetLiv1BW$^{3/4}$	Amount of TCE oxidized in liver
AMetLivOtherBW$^{3/4}$	Amount of TCE oxidized to metabolites other than TCA or TCOH per unit body weight
AMetLivOtherLiv	Amount of TCE oxidized to metabolites other than TCA or TCOH per unit liver weight
AMetLngBW$^{3/4}$	Amount of TCE oxidized in respiratory tract (per unit body weight)
AMetLngResp	Amount of TCE oxidized in respiratory tract per unit respiratory tract tissue
AUCCBld	Area under the curve of venous blood concentration of TCE
AUCCTCOH	Area under the curve of blood concentration of TCOH
AUCLivTCA	Area under the curve of the liver concentration of TCA
TotMetabBW$^{3/4}$	Total amount of TCE metabolized per unit body weight
TotOxMetabBW$^{3/4}$	Total amount of TCE oxidized per unit body weight
TotTCAInBW	Total amount of TCA produced

Table 2-23. Dose-Metrics for Cancer and Non-Cancer Endpoints Used in the OPPT Assessment

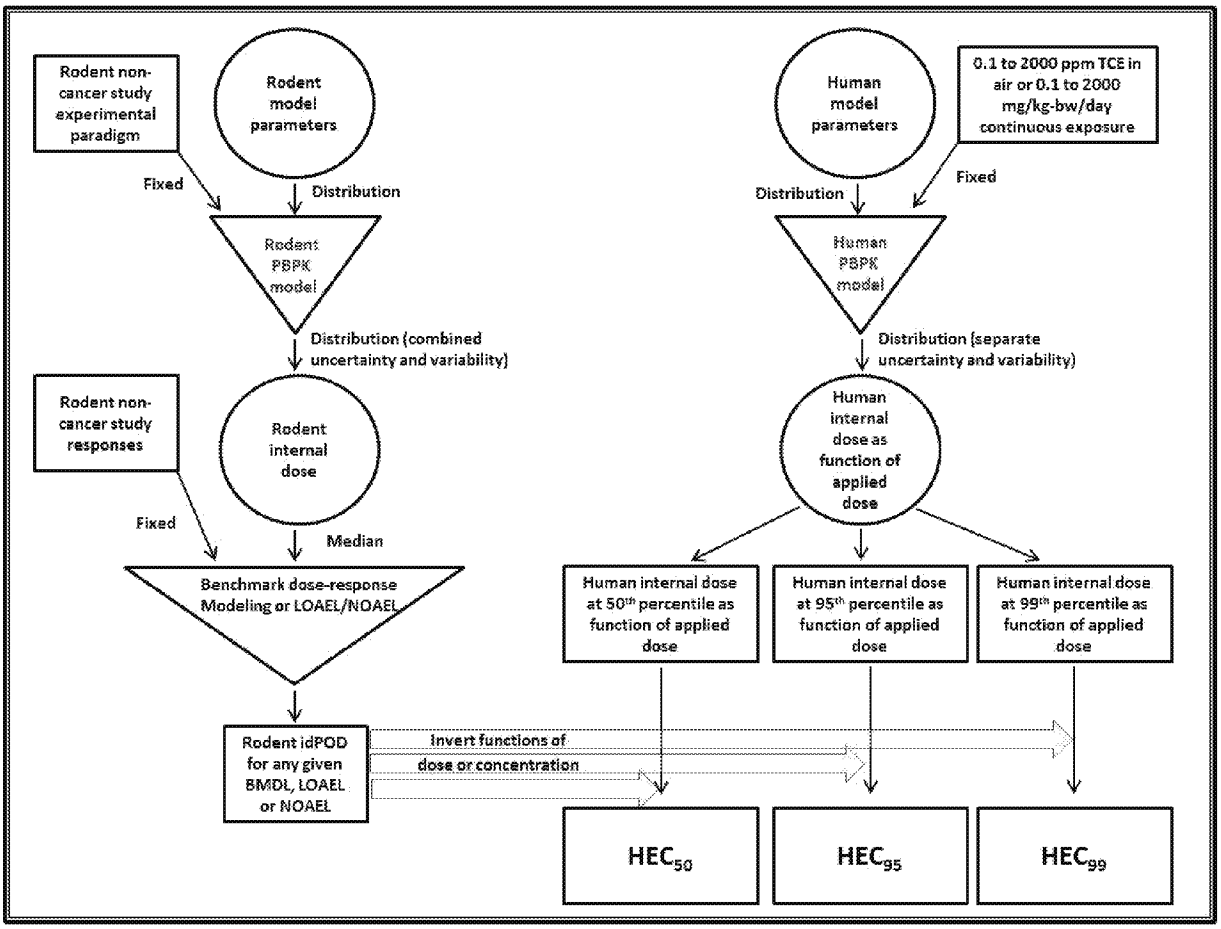
	Target Organ/ System	Reference	Preferred Dose-Metric [1]
Non-Cancer Endpoints	Liver	Kjellstrand et al. (1983)	AMetLiv1BW$^{3/4}$
	Kidney	NTP (1988)	ABioactDCVCBW$^{3/4}$
	Nervous System	Arito et al. (1994)	TotMetabBW$^{3/4}$
	Immune System	Keil et al. (2009)	TotMetabBW$^{3/4}$
	Reproductive System	Chia et al. (1996)	TotMetabBW$^{3/4}$
	Developmental effects [2]	Johnson et al. (2003)	TotOxMetabBW$^{3/4}$
Cancer	Carcinogenic effects in various organs	Charbotel et al. (2006)(kidney cancer) and human epidemiological studies for NHL and liver cancer	ABioactDCVCBW$^{3/4}$ (IUR for kidney cancer) AMetLiv1BW$^{3/4}$ (IUR for liver cancer) TotMetabBW$^{3/4}$ (IUR for NHL)

Notes:
1 The non-cancer dose-metrics correspond to those studies resulting in the lowest PBPK-derived HECs as listed in Table 2-19 based on the analysis presented in the TCE IRIS assessment (EPA, 2011e).
2 The maternal dose metric was used as surrogate for fetal exposure.

For developmental toxicity endpoints, the TCE PBPK model did not incorporate a pregnancy model to estimate the internal dose of TCE in the developing fetus. In this case, the maternal dose-metric was used as the surrogate measure of target tissue dose in the developing fetus. A complete description of the TCE PBPK model, including the rationale for parameter choices in animals and humans, choice of dose metric, and experimental information used to calibrate and optimize the model is found in the TCE IRIS assessment (EPA, 2011e).

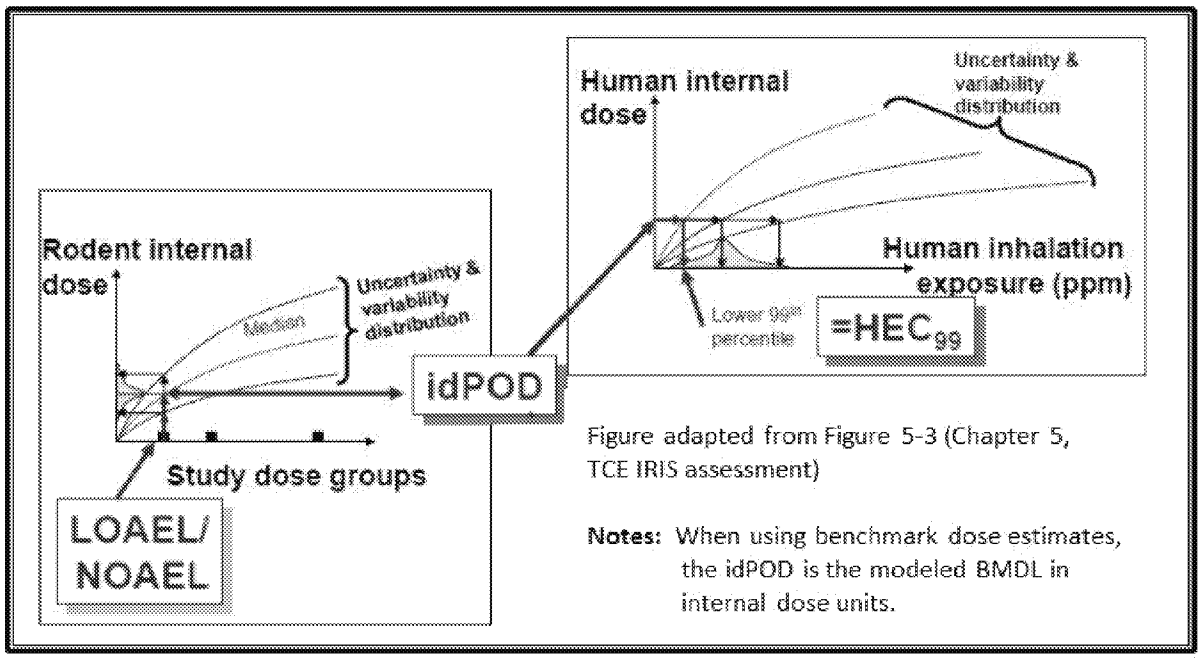
As shown in Figures 2-4 and 2-5, several steps were needed to derive the PBPK-derived HECs used in this assessment. First, the rodent PBPK model was run to estimate rodent idPODs for the applied dose PODs (i.e., LOAEL, NOAEL, or BMDL) that were identified in the TCE IRIS assessment. Separately, the human PBPK model was run for a range of continuous exposures from 0.1 to 2,000 ppm or 0.1 to 2,000 mg/kg-bw/day to establish the relationship between human exposure air levels and internal dose for the same dose-metric evaluated in the rodent PBPK model. This relationship was used to derive HECs corresponding to the idPOD by interpolation (EPA, 2011e).

Figure 2-4. Dose-Response Analyses of Rodent Non-Cancer Effects Using the Rodent and Human PBPK Models



Notes: Figure adapted from Figure 5-2 (Chapter 5, TCE IRIS assessment) (EPA, 2011e). Square nodes indicate point values, circle nodes indicate distributions and the inverted triangle indicates a (deterministic) functional relationship.

Figure 2-5. Example of HEC_{99} Estimation through Interpecies, Intraspecies and Route-to-Route Extrapolation from a Rodent Study LOAEL/NOAEL



The rodent population model was designed to characterize study-to-study variation and used median values of dose-metrics to generate idPODs. The rodent PBPK model did not characterize variation within studies and assumed that the rodent idPODs were for pharmacokinetically identical animals. The basis of that assumption was that animals with the same sex/species/strain combination were considered pharmacokinetically identical and represented by the group average. In practice, the use of median or mean internal doses for rodents did not make much difference except when the uncertainty in the rodent dose-metric was high (EPA, 2011e).

On the other hand, the human population model characterizes toxicokinetic uncertainty and individual-to-individual variation and used median, 95th and 99th percentile values of dose-metrics to general human idPODs. The 50th, 95th or 95th percentile of the combined uncertainty and variability distribution of human internal doses was used to derive the HEC_{50}, HEC_{95} or HEC_{99} estimates, respectively. The HEC_{95} and HEC_{99} were interpreted as being the concentrations of TCE in air for which there is 95% and 99% likelihood, respectively, that a randomly selected individual will have an internal dose less than or equal to the idPOD derived from the rodent study. The HEC_{50} was interpreted as being the concentration of TCE in air for which there is 50% likelihood that a randomly selected individual will have an internal dose less than or equal to the idPOD from the rodent study. The TCE IRIS assessment preferred the HEC_{99} for the non-cancer dose-response analysis because the HEC_{99} was interpreted to be protective for a sensitive individual (EPA, 2011e).

EPA/OPPT supported the interpretation of the HEC_{99} as expressed in the TCE IRIS assessment. Hence, HEC_{99}-based risk estimates are favored in this assessment over those estimated from the HEC_{50} and HEC_{95} values. However, risk estimates based on the HEC_{50} and HEC_{95} values are also included.

Presenting risks for the HEC_{50}, HEC_{95} and HEC_{99} values is intended to provide a sense of the difference between the median, the 95% and 99% confidence bound for the combined uncertainty and variability. Calculations of $HEC_{50}/_{95}$ and $HEC_{50}/_{99}$ ratios generally showed a 2-3 fold difference for the various studies identified in Table 2-18. The exception was the study reporting kidney effects (NTP, 1988) that showed high $HEC_{50}/_{95}$ and $HEC_{50}/_{99}$ ratios (i.e., 5-9-fold) due to uncertainties in the rodent internal dose estimates (EPA, 2011e). In contrast, HEC_{95} values were closely similar to HEC_{99} values with $HEC_{95}/_{99}$ ratios showing a 1.3-1.5 fold difference.

In this assessment, it was assumed there was no substantial buildup of TCE in the body between exposure events due to TCE's short biological half-life in humans (~51 hrs). This assumption was supported by PBPK simulations presented in Tables 2-24 and 2-25. In these simulations, the TCE PBPK model was used to estimate HECs at the 50th and 99th percentile for the cardiac malformation endpoint under continuous or intermittent exposure to TCE for different exposure durations (i.e., 1 day, 3 weeks, or 9 months). The 1-day HEC at the 50th and 99th percentile did not show significant variation when compared to the HECs for the other exposure durations (i.e., 3 weeks and 9 months) for the continuous or intermittent exposures (Tables 2-24 and 2-25). Thus, the results from the PBPK simulations showed that the assumption (i.e., no substantial buildup of TCE in the body between exposure events) is reasonable to use in the EPA/OPPT's risk assessment.

Table 2-24. Comparison of TCE Human Equivalent Concentrations (HECs) Under Constant, Continuous Exposure for Different Exposure Durations

Duration	HEC Equivalent to the Benchmark Dose Lower Confidence Limit for Cardiac Malformations ($\mu g/m^3$) [a]	
	Median estimate	Upper 99th percentile estimate
Chronic (steady-state)	62	20
9 months (40 weeks)	62	20
3 weeks	63	20
1 day	71	21

Notes:

[a] The internal dose metric of μg oxidized per day per [kg body weight]$^{3/4}$ was selected as the basis for interspecies, intraspecies, and route-to-route extrapolation for the cardiac malformations endpoint in the 2011 TCE IRIS assessment (EPA, 2011e). The PBPK model was parameterized for human females. HECs are rounded to two significant figures.

Table 2-25. Comparison of TCE Human Equivalent Concentrations (HECs) Under Intermittent (Occupational) Exposure for Different Exposure Durations		
Duration	**HEC Equivalent to the Benchmark Dose Lower Confidence Limit for Cardiac Malformations (μg/m³)** [a]	
	Median estimate	Upper 99th percentile estimate
Chronic (steady-state)	62	20
9 months (40 weeks)	62	20
3 weeks	63	20
1 day	68	21

Notes:

[a] The internal dose metric of μg oxidized per day per [kg body weight]$^{3/4}$ was selected as the basis for interspecies, intraspecies, and route-to-route extrapolation for the cardiac malformations endpoint in the 2011 TCE IRIS assessment (EPA, 2011e). The PBPK model was parameterized for human females. HECs are rounded to two significant figures. Note that standard duration adjustments have been applied to the chronic HECs calculated from the PBPK model. Specifically, for chronic, nine month, and three week durations, an adjustment for 8/24 hours per day and 5/7 days per week has been applied; for the one day duration, an adjustment of 8/24 hours per day has been applied. For instance, the median HEC for the 1 day duration was calculated as a single, 8 hour exposure at 203 μg/m³, to which a duration adjustment of 8/24 was applied to derive the reported value of 68 μg/m³.

2.6.2 Human Health Hazard Summary

This section summarizes both cancer and non-cancer hazard information for TCE. The information was largely taken from the U.S. EPA's TCE IRIS assessment (EPA, 2011e). Regarding the non-cancer hazard studies, the emphasis is on the repeated-dose oral and inhalation studies that the TCE IRIS assessment identified as the most appropriate to be carried forward for the dose-response assessment.

2.6.2.1 Genetic Toxicity of TCE and its metabolites

The TCE IRIS assessment evaluated data on TCE and its metabolites in a variety of *in vitro and in vivo* test systems. TCE does not appear to be a direct-acting mutagen, but has the potential to bind or induce damage to the structure of DNA or chromosomes. In bacterial test systems, TCE did not induce mutations unless there was metabolic activation (i.e., the presence of metabolizing enzymes) (EPA, 2011e).

It is thought that TCE metabolites may be responsible for TCE genotoxicity. TCA, an oxidative metabolite of TCE, exhibited little, if any, genotoxic activity *in vitro*. Other TCE metabolites (DCA, chloral hydrate, DCVG, and particularly DCVC) induced mutations without metabolic activation (EPA, 2011e). Despite these positive results, uncertainties with regard to the characterization of TCE genotoxicity remain because not all of TCE metabolites have been sufficiently tested in the standard genotoxicity screening battery (EPA, 2011e).

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2.6.2.2 Human Toxicity Following Acute Exposure to TCE

The interim acute exposure guideline levels (AEGLs) document for TCE was consulted and used in this assessment to briefly summarize the acute toxicity data (NAC, 2008). Note that the EPA/OPPT risk assessment used the developmental studies, but not the acute toxicity studies described below, for assessing acute risks for reasons explained in the *Approach and Methodology* section of the *Hazard/Dose-Response* assessment. The next section ("*Toxicity Following Repeated Exposures to TCE (Including Cancer)*") describes the developmental toxicity studies that were used for the acute scenarios evaluated in this assessment.

In humans, TCE odors can be detected at concentrations of ≥50 ppm (HSDB, 1992). It was once commonly used as an anesthetic agent with concentrations ranging from 5,000 to 15,000 ppm for light anesthetic use and from 3,500 to 5,000 ppm for use as an analgesic (Parfitt et al., 1999).

Information on the toxicity of TCE in humans comes from either case reports in the medical/occupational literature or human inhalation studies. Lethality data in humans have been reported following accidental exposure to TCE. However, there is insufficient information about the exposure characterization of these incidents (NAC, 2008).

Human inhalation studies have shown that acute exposure to TCE results in irritation and central nervous system (CNS) effects in humans. Mild subjective symptoms and nose and throat irritation were reported by human volunteers exposed to 200 ppm TCE for 7 hrs/day on the first day of exposure during a 5-day exposure regimen. The study also reported minimal CNS depression following TCE exposure (Stewart et al., 1970).

CNS depression and effects on neurobehavioral functions were seen in human volunteers exposed to 1,000 ppm TCE for a 2-hr period (Ferguson and Vernon, 1970; Vernon and Ferguson, 1969). In the same studies, volunteers were also exposed to 100 or 300 ppm TCE for 2 hrs. Some subjects had similar CNS effects at the middle concentration (300 ppm), with no such effects observed at the 100 ppm concentration (NAC, 2008). Ettema et al. (1975) also observed slight to marginal neurobehavioral effects after exposure to 300 ppm TCE for 2.5 hrs.

Cardiac arrhythmias have been reported in humans exposed to high concentration of TCE (NAC, 2008). Several animal studies have reported neurobehavioral effects and the potential for inducing cardiac sensitization following acute inhalation exposure to TCE. These studies reporting cardiac effects in humans and animals are not discussed in this assessment and the reader is referred to the AEGL document (NAC, 2008) to obtain the study descriptions.

2.6.2.3 Toxicity Following Repeated Exposures to TCE

The studies and corresponding PODs briefly discussed below were those used to evaluate the risks of acute and repeated (chronic) exposures to TCE-containing degreasers and arts/crafts products.

EPA/OPPT relied on the systematic study review that the IRIS program conducted as part of the process of developing the TCE IRIS assessment. Briefly, the IRIS program critically reviewed the

publicly available animal and human studies that reported adverse cancer and non-cancer health effects following TCE exposure. In addition, other relevant data such as mechanistic data, *in vitro* data, or toxicokinetic data, were reviewed. The review process started with the identification of primary, peer reviewed literature through January 2011. Multi-disciplinary teams conducted a systematic review of the study quality of the identified studies using the principles set forth by the various risk assessment guidelines issued by the National Research Council and the U.S. EPA (Appendix K) as well as their professional judgment. Data were then synthesized and integrated to reach hazard conclusions about the biological plausibility of the relationship between TCE exposure and a particular health effect. Those studies that had quantitative dose-response information were carried forward into the cancer and non-cancer dose-response assessments. During the assessment of dose-response data, the IRIS program adjusted all of the POD values to continuous exposure (i.e., 24 hr/7-day exposures). This process has been documented in the TCE IRIS assessment, particularly in Chapters 4 and 5 (EPA, 2011e).

2.6.2.3.1 Liver Toxicity (Including Cancer)

Animals and humans exposed to TCE consistently experience liver toxicity. Specific effects include the following structural changes: increased liver weight, increase in deoxyribonucleic acid (DNA) synthesis (transient), enlarged hepatocytes, enlarged nuclei, and peroxisome proliferation. In addition, U.S. EPA concluded that TCE exposure causes liver tumors in mice but not rats and there is "*...minimal support for association between TCE exposure and liver and gallbladder/biliary cancer*" (EPA, 2011e, page 4-238).

For both cancer and non-cancer effects on the liver, the role of metabolites is important but not well understood. Many investigators have dosed animals with TCE, as well as with many of its metabolites to determine the role and potency of each in terms of target organ toxicity. It appears that the oxidation pathway is important for the development of liver toxicity, but the specific role of each metabolite (i.e., that of TCA, DCA, and chloral hydrate), as well as the parent TCE, is unclear. As for liver cancer, the TCE IRIS assessment concluded that multiple TCE metabolites (i.e., and thus pathways) likely contribute to TCE-induced liver tumors (EPA, 2011e).

Human Data

Several human studies (including those in TCE degreaser operations) reported an association between TCE exposure and significant changes in serum liver function tests used in diagnosing liver disease, or changes in plasma or serum bile acids (see Table 4-57 in EPA, 2011e for a summary of the human studies). There was also human evidence for hepatitis accompanying immune-related generalized skin diseases, jaundice, hepatomegaly, hepatosplenomegaly, and liver failure in TCE-exposed workers (EPA, 2011e). Cohort studies examining cirrhosis mortality and either TCE exposure or solvent exposure are generally null, but these studies cannot rule out an association between TCE and liver disorders/toxicity because of the limitations of the studies (EPA, 2011e). Overall, while some evidence exists of liver toxicity in humans, the data are inadequate for making conclusions regarding causality (EPA, 2011e).

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The TCE IRIS assessment evaluated cohort, case-control, and community (geographic) studies reporting liver and biliary tract cancer, primary liver cancer, and gallbladder and extra-hepatic bile duct cancer (see Table 4-57 in EPA, 2011e for a summary of the human studies). Most of these studies have small numbers of exposed cases and controls due to the rarity of liver and biliary tract cancer. The IRIS program conducted meta-analyses of the studies and reported a small, statistically significant summary relative risk (RRm) for liver and gallbladder/biliary cancer with overall TCE exposure (EPA, 2011e). However, the meta-analyses reported a lower, nonstatistically significant RRm for primary liver cancer when using the highest exposure groups (EPA, 2011e).

Animal Data

The TCE IRIS assessment reviewed many oral and inhalation studies in rats and mice (see Tables 4-58 and 4-59 in EPA, 2011e for a summary of the animal studies). Animals exposed to TCE reported increased liver weight, a small, transient increase in DNA synthesis, enlarged hepatocytes, increased size of nuclei of liver cells, and proliferation of peroxisomes (EPA, 2011e).

The IRIS program determined that the studies of Buben and O'Flaherty (1985); Kjellstrand et al. (1983) and Woolhiser et al. (2006) were suitable for the dose-response assessment of the liver health effects domain (Appendix L). These three studies reported increased liver/body weight ratios.

Kjellstrand et al. (1983) exposed NMRI male mice (10-20/group) with up to nine different TCE concentrations. These concentrations ranged from 37 to 3,600 ppm and included an air control group. Exposures were conducted for various durations (1, 2, 4, 8, 16, or 24 hrs/day) and for different time frames (from 30 to 120 days). The IRIS program calculated a benchmark concentration lower-bound confidence limit of 21.6 ppm based on the 10% benchmark response ($BMDL_{10}$) for increased liver/body weight ratios.

In Woolhiser et al. (2006), Sprague-Dawley female rats (16/group) were exposed to TCE via inhalation at concentrations of 0, 100, 300, or 1,000 ppm for 6 hrs/day, 5 days/week for 4 weeks. A $BMDL_{10}$ of 25 ppm was estimated for increased liver/body weight ratio.

Finally, the Buben and O'Flaherty (1985) exposed Swiss-Cox male mice (12-15 group) to TCE by gavage. Mice were exposed to a range of TCE doses (100 to 3,200 mg/kg-bw/day plus control) for 5 days/week for 6 weeks. A $BMDL_{10}$ of 82 mg/kg-bw/day was identified as the POD for increased liver/body weight ratios.

With respect to liver carcinogenicity, TCE and its oxidative metabolites TCA, DCA, and CH are clearly carcinogenic in mice, with strain and sex differences in potency. Data in other laboratory animal species are limited; thus, except for DCA which is carcinogenic in rats, inadequate evidence exists to evaluate the hepatocarcinogenicity of TCE and its metabolites in rats or hamsters (EPA, 2011e).

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2.6.2.3.2 *Kidney Toxicity (Including Cancer)*

Studies in both humans and animals have shown changes in the proximate tubules of the kidney following exposure to TCE. As for cancer, the TCE IRIS assessment concluded that TCE is "carcinogenic to humans" based on convincing evidence of a causal relationship between TCE exposure in humans and kidney cancer. A recent review of TCE by the International Agency for Research on Cancer (IARC) also supported this conclusion (IARC, 2014).

TCE metabolites appear to be the causative agents that induce renal toxicity, including cancer. DCVC (and to a lesser extent other metabolites) appears to be responsible for kidney damage and kidney cancer following TCE exposure (EPA, 2011e). Toxicokinetic data suggest that the TCE metabolites derived from GSH conjugation (in particular DCVC) can be systemically delivered or formed in the kidney. Moreover, DCVC-treated animals showed the same type of kidney damage as those treated with TCE (EPA, 2011e).

The toxicokinetic data and the genotoxicity of DCVC further suggest that a mutagenic mode of action is involved in TCE-induced kidney tumors, although cytotoxicity followed by compensatory cellular proliferation cannot be ruled out (EPA, 2011e). As for the mutagenic mode of action, both genetic polymorphisms (GST pathway) and mutations to tumor suppressor genes have been hypothesized as possible mechanistic key events in the formation of kidney cancers in humans (EPA, 2011e).

Human Data

Human studies reported increased excretion of urinary proteins among TCE-exposed workers when compared to unexposed controls. While some of these studies included subjects previously diagnosed with kidney cancer, other studies report similar results in subjects who are disease free. Occupational studies showed increased levels of kidney damage (proximal tubules) in workers exposed to "high" levels of TCE (EPA, 2011e).

Some additional support for TCE-induced nephrotoxicity in humans came from two studies of end-stage renal disease (ESRD). Radican et al. (2006) observed a greater incidence of ESRD in TCE-exposed workers as compared to unexposed controls. Jacob et al. (2007) reported a greater risk for progression from IgA nephropathy or membranous nephropathy glomerulonephritis to ESRD following TCE exposure.

As stated previously, the TCE IRIS assessment classified TCE as "carcinogenic to humans" based on convincing evidence of a causal relationship between TCE exposure in humans and kidney cancer. The carcinogenic classification was based on a review of more than 30 human studies, including studies in TCE degreasing operations, and meta-analyses of the cohort and case-control studies. Relative risk estimates for increased kidney cancer were consistent across a large number of epidemiological studies of different designs and populations from different countries and industries (EPA, 2011e). This strong consistency of the epidemiologic data on TCE and kidney cancer argues against chance, bias, and confounding as explanations for the elevated kidney cancer risks (EPA, 2011e).

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There appears to be greater susceptibility to TCE-induced kidney cancer in those individuals that carry an active polymorphism in a gene associated with the GST metabolic pathway. Particularly, the gene is associated with the β-lyase gene region which is responsible for converting DCVC to the unstable intermediate DCVT (EPA, 2011e). Also, there are some human studies suggesting a role for mutations to the tumor suppressor gene, von Hippel Lindau (VHL gene). This tumor suppressor gene appears to be inactivated in certain TCE-induced kidney cancers (EPA, 2011e).

Animal Data

In the animal studies, renal toxicity was evident in both rats and mice following inhalation or gavage exposures. The toxicity included damage to the renal tubules (e.g., both cytomegaly and karyomegaly). Under chronic gavage exposure scenarios, rodents exhibited almost 100 percent kidney toxicity induction. Under inhalation exposure scenarios, male rats were more susceptible than female rats or mice to kidney toxicity. As noted earlier, this toxicity is likely caused by DCVC formation, with possible roles for TCOH and TCA (EPA, 2011e).

The IRIS program selected five animal studies reporting kidney toxicity for further non-cancer dose-response analysis (Appendix L). Maltoni and Cotti (1986), NCI (1976) and NTP (1988) reported histological changes in the kidney, whereas Kjellstrand et al. (1983) and Woolhiser et al. (2006) reported increased kidney/body weight ratios (EPA, 2011e).

Maltoni and Cotti (1986) exposed Sprague-Dawley male rats (116-124/group) to TCE via inhalation (0, 100, 300, or 600 ppm) for 7 hrs/day, 5 days/week for 104 weeks (and allowed all rats to continue unexposed until they died). The investigators also conducted an oral (gavage) study that dosed rats with a range of TCE doses (50 to 250 mg/kg-bw/day) for 4-5 days/week for 52 weeks. $BMDL_{10}$ values of 40.2 ppm and 34 mg/kg-bw/day were calculated for the inhalation and gavage studies, respectively, based on renal tubular pathological changes (EPA, 2011e).

The National Cancer Institute (NCI) conducted a 90-week oral (gavage) study that dosed B6C3F1 female mice (20-50/group) with a range of TCE doses (869 to 1,739 mg/kg-bw/day) for 5 days/week for 78 weeks (NCI, 1976). Mice were then left unexposed for the final 12 weeks of the study. A LOAEL of 620 mg/kg-bw/day was identified as the POD for toxic nephrosis (EPA, 2011e).

In another oral (gavage) study, the National Toxicology Program exposed Marshall female rats (44-50/group) to TCE (i.e., 0, 500, or 1,000 mg/kg-bw/day) for 5 days/week for 104 weeks (NTP, 1988). Rats developed toxic nephropathy following TCE exposure. A $BMDL_{05}$ of 9.45 mg/kg-bw/day was calculated for the observed kidney effects (EPA, 2011e).

Woolhiser et al. (2006) conducted an inhalation study that exposed Sprague-Dawley female rats (16/group) to 0, 100, 300 or 1,000 ppm TCE for 6 hrs/day for 5 days/weeks for 4 weeks. At the end of the study, rats exhibited increased kidney/body weight ratios and a $BMDL_{10}$ of 15.7 ppm was estimated for these effects (EPA, 2011e).

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Increased kidney/body weight ratios were also seen in Kjellstrand et al. (1983). NMRI male mice (10-20/group) were exposed to a range of TCE concentrations (37 to 3,600 ppm) for 30 to 120 days on continuous and intermittent exposure regimens. A $BMDL_{10}$ of 34.7 ppm was identified as the POD for increased kidney/body weight ratios (EPA, 2011e).

Cancer bioassays with TCE in animals (i.e., both gavage and inhalation exposure routes) did not show increased kidney tumors in mice, hamsters, or female rats, but did show a slight increase in male rats. Kidney tumors in rats are relatively rare (EPA, 2011e).

2.6.2.3.3 Neurotoxicity

Neurotoxicity has been demonstrated in animal and human studies under both acute and chronic exposure conditions (EPA, 2011e). Due to the effects on the nervous system, TCE was initially synthesized for use as an anesthetic in humans in the early part of the 20th century. These anesthetic-like effects occurred at high concentrations. A brief summary of these effects is provided below.

Human Data

Evaluation of the human studies has reported the following TCE-induced neurotoxic effects: alterations in trigeminal nerve and vestibular function, auditory effects, changes in vision, alterations in cognitive function, changes in psychomotor effects, and neurodevelopmental outcomes (EPA, 2011e). Section 2.6.2.3.6 (*Developmental Toxicity*) discusses the neurodevelopmental outcomes in more detail.

The strongest neurological evidence of human toxicological hazard is for changes in trigeminal nerve function or morphology and impairment of vestibular function (EPA, 2011e). Fewer and more limited epidemiological studies are suggestive of TCE exposure being associated with delayed motor function, and changes in auditory, visual, and cognitive function or performance, and neurodevelopmental abnormalities (EPA, 2011e).

Multiple epidemiological studies in different populations have reported TCE-induced abnormalities in trigeminal nerve function in humans (EPA, 2011e). However, two epidemiological studies did not report an association between TCE exposure and trigeminal nerve function. These studies generally had study design limitations such as limited statistical power, missing control groups, and missing methodology for measuring trigeminal nerve function (EPA, 2011e).

Among the human studies, Ruijten et al. (1991) was the only epidemiological study that the IRIS program deemed suitable for further evaluation in the TCE's dose-response assessment for neurotoxicity. Ruijten et al. (1991) evaluated the TCE exposures and possible health effects of 31 male printing workers (mean age: 44 yrs) and 28 unexposed control subjects (mean age: 45 yrs). The exposure duration was expressed as "cumulative exposure" (concentration × time). Using historical monitoring data, mean exposures were calculated as 704 ppm × number of years worked, where the mean number of years was 16 (range: 160-2,150 ppm x yr) (EPA, 2011e). The study measured the trigeminal nerve function by using the blink reflex, but no abnormal findings were observed. However, the study found a statistically significant average

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increase in the latency response time in TCE-exposed workers on the masseter reflex test, another test commonly used to measure the integrity of the trigeminal nerve. The POD derived from the dataset was a LOAEL of 14 ppm (EPA, 2011e).

Human studies have consistently reported vestibular system-related symptoms such as headaches, dizziness, and nausea following TCE exposure. Although these symptoms are subjective and self-reported, these effects have been reported extensively in human chamber, occupational, and geographic-based/drinking water studies (EPA, 2011e).

Animal Data

The TCE IRIS assessment reviewed many animal studies reporting a variety of neurotoxic effects under different exposure conditions. Animal studies have reported the following TCE-induced neurotoxic effects: morphological changes in the trigeminal nerve, disruption of the auditory system, visual changes, structural or functional changes in the hippocampus, sleep disturbances, changes in psychomotor effects, and neurodevelopmental effects (EPA, 2011e). Only the following four animal studies were suitable for dose-response analysis for the neurotoxicity endpoint (Appendix L).

Arito et al. (1994) exposed Wistar male rats (5/group) to TCE via inhalation to concentrations of 0, 50, 100, or 300 ppm for 8 hrs/day, 5 days/week for 6 weeks. Exposure to all of the TCE concentrations significantly decreased the amount of time spent in wakefulness during the exposure period. Some carry over was observed in the 22 hr-post exposure period, with significant decreases in wakefulness seen at 100 ppm TCE. Significant changes in wakefulness-sleep elicited by the long-term exposure appeared at lower exposure levels. The LOAEL for sleep changes was 12 ppm (i.e., LOAEL, adjusted for continuous exposure)(EPA, 2011e).

Isaacson et al. (1990) dosed weanling Sprague-Dawley male rats (12/dose group) via the oral route (drinking water) in an experimental protocol for an 8-week period. The control group had unexposed rats for 8 weeks. The experimental group#1 exposed rats to 47 mg/kg-bw/day TCE for 4 weeks and then no TCE exposure for 4 weeks. The experimental group#2 exposed rats to 47 mg/kg-bw/day TCE for 4 weeks, no TCE exposure for the following 2 weeks, and then 24 mg/kg-bw/day TCE for the final 2 weeks. Rats in group#3 reported a decreased latency to find the platform in the Morris water maze test. Also, all of the TCE-treated groups exhibited hippocampal demyelination. The LOAEL for cognitive effects (i.e., demyelination in the hippocampus) was 47 mg/kg-bw/day (EPA, 2011e).

Gash et al. (2008) evaluated the effects of TCE on dopamine-containing neurons. F344 male rats (9/group) were exposed by oral gavage to doses of 0 or 1,000 mg/kg-bw/day TCE for 5 days/week for 6 weeks. Exposed rats showed degeneration of dopamine-containing neurons in the substantia nigra. The LOAEL for loss of dopamine containing neurons was 710 mg/kg-bw/day (EPA, 2011e).

Kjellstrand et al. (1987) studied the effect of TCE on the regeneration of the sciatic nerve. Under heavy anesthesia, the sciatic nerve of NMRI male mice and Sprague-Dawley female rats was artificially crushed to create a lesion. Prior to the lesion, some animals were pre-exposed to TCE for 20 days and then for an additional 4 days after the lesion. Another set of animals was

only exposed to TCE for 4 days following the sciatic nerve lesion. The inhalation exposures to TCE for the 4 or 20-day exposures were as follows: 0, 150, or 300 ppm TCE for 24 hrs/day for mice; and 0 or 300 ppm TCE for 24 hrs/day for rats. Both mice and rats exhibited inhibition of the sciatic nerve regeneration. LOAELs of 150 ppm and 300 ppm were identified as the POD for the decreased regeneration of the sciatic nerve in mice and rats, respectively (EPA, 2011e).

2.6.2.3.4 Immunotoxicity (Including Cancer)

Immune-related effects following TCE exposures have been observed in both animal and human studies. In general, these effects were associated with inducing enhanced immune responses as opposed to immunosuppressive effects. Of concern are the immune-related and inflammatory effects reported in TCE-exposed animals and humans. These effects may influence a variety of other conditions of considerable public health importance, such as cancer and atherosclerosis (EPA, 2011e).

Human Studies

Studies have reported a relationship between systemic autoimmune diseases, such as scleroderma, and occupational exposure to TCE. The TCE IRIS assessment performed a meta-analysis of a number of human studies evaluating a possible connection between scleroderma and TCE exposure. Results indicated a significant odds ratio (OR) in men, whereas women showed a lower but not significant OR. These results may not reflect a true gender difference because the incidence of this disease is very low in men (approximately one per 100,000 per yr) and somewhat higher in women (approximately one per 10,000 per yr). In addition, these results may be affected by gender-related differences in exposure prevalence, the reliability of the exposure assessment, gender-related differences in susceptibility to TCE toxicity or chance (EPA, 2011e).

There have been a large number of case reports in TCE-exposed workers developing a severe hypersensitivity skin disorder, distinct from contact dermatitis, and often accompanied by systemic effects (hepatitis, lymph nodes, and other organs). These effects appeared after inhalation exposures ranging from <9 to >700 ppm TCE. Similar effects have been observed in guinea pigs and mice treated with TCE (EPA, 2011e).

Increased levels of human inflammatory cytokines were measured in an occupational study of degreasers exposed to TCE (Iavicoli et al., 2005). Moreover, similar changes in inflammatory cytokines were seen in infants exposed to TCE via indoor air. These findings were supported by studies in auto-immune prone mice (described below) in which short exposures to TCE resulted in increased levels of inflammatory cytokines (EPA, 2011e).

TCE-related immunosuppression has been reported in one study (Lagakos et al., 1986). This study found an association between TCE exposure and reported history of bacterial or viral infections.

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Animal Data

Numerous studies have shown increased autoimmune responses in autoimmune-prone mice, including changes in cytokine levels similar to those reported in human studies, with more severe effects, including autoimmune hepatitis, inflammatory skin lesions, and alopecia, manifesting at longer exposure periods (EPA, 2011e). B6C3F1 mice, a strain that lacks susceptibility to autoimmune disease have reported immunotoxic effects following TCE exposure (EPA, 2011e). Furthermore, TCE-exposed guinea pigs and mice have developed hypersensitivity responses pre- and postnatally following TCE exposure via drinking water. In addition, evidence of localized immunosuppression has also been reported in mice and rats (EPA, 2011e).

Only the following four animal studies were suitable for the IRIS' non-cancer dose-response analysis for the immunotoxicity endpoint (Appendix L).

Keil, D. E. et al. (2009) exposed B6C3F1 mice (10/group), a standard test strain not genetically prone to develop autoimmune disease, to TCE via drinking water for 27 or 30 weeks at concentrations in water of 0, 1.4, or 14 ppm (0.35 or 3.5 mg/kg-bw/day). The study reported a significant decrease in thymus weight concentrations and thymic cellularity as well as an increase in autoantibodies to ssDNA and dsDNA. A LOAEL of 0.35 mg/kg-bw/day was identified as the POD for the thymic and autoimmune effects (EPA, 2011e).

Kaneko et al. (2000) exposed auto-immune prone mice (5/group) to TCE at concentrations of 0, 500, 1,000, or 2,000 ppm for 4 hrs/day, 6 days/week, for 8 weeks. At concentrations ≥500 ppm, mice exhibited dose-related liver inflammation, splenomegaly and hyperplasia of lymphatic follicles. Immunoblastic cell formation in lymphatic follicles was observed in mice treated with 1,000 ppm TCE. The LOAEL of 70 ppm was identified for these effects (EPA, 2011e).

In Sanders et al. (1982), male and female CD-1 mice (7-25/group) were given TCE in drinking water concentrations of 0, 0.1, 1.0, 2.5, or 5.0 mg/mL (0, 18, 217, 393 or 660 mg/kg-bw/day) for 4 or 6 months. Female mice showed decreased humoral immunity at 2.5 and 5 mg/mL (393 or 660 mg/kg-bw/day), whereas cell-mediated immunity and bone marrow stem cell colonization decreased at all four concentrations. Male mice were relatively unaffected after both 4 and 6 months of exposure. A LOAEL of 18 mg/kg-bw/day was identified as the POD for immunosuppressive effects (EPA, 2011e).

Another study that was previously discussed for liver and kidney effects (Woolhiser et al., 2006) also reported immunosuppressive effects. Sprague-Dawley female rats (16/group) were treated with 0, 100, 300 or 1,000 ppm TCE for 6 hrs/day, 5 days/week for 4 weeks. Four days prior to study termination, the rats were immunized with sheep red blood cells (SRBC), and within 24 hrs following the last exposure to TCE, a plaque-forming cell (PFC) assay was conducted to determine effects on splenic anti-SRBC IgM response. At 1,000 ppm, rats demonstrated a 64% decrease in the PFC assay response. A $BMDL_{1SD}$[27] of 24.9 ppm was identified for this immunosuppressive effect (EPA, 2011e).

[27] $BMDL_{1SD}$=the lower-bound confidence limit of the benchmark dose where the effect is 1 standard deviation (SD) from control value.

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One of the three cancers for which the TCE IRIS assessment based its cancer findings was non-Hodgkin's lymphoma (NHL) (the other two being kidney and liver cancer) (EPA, 2011e). The human epidemiological studies strongly support a causal relationship between TCE exposure and NHL. Further support comes from animal studies reporting rates of lymphomas and/or leukemias following TCE exposure. For a detailed examination of the cancers of the immune system, please refer to Chapter 4 of the TCE IRIS assessment (EPA, 2011e).

2.6.2.3.5 Reproductive Toxicity

The toxicological literature provides support for male and female reproductive toxicity following TCE exposure. Both the epidemiological and animal studies provide suggestive, but limited, evidence of adverse outcomes to female reproductive outcomes. However, much more extensive evidence exists in support of an association between TCE exposures and male reproductive toxicity (EPA, 2011e).

The available human data that associate TCE with adverse effects on male reproductive function are limited in size and provide little quantitative dose data. However, the animal data provide strong and compelling evidence for TCE-related male reproductive toxicity. Strengths of the animal database include the presence of both functional and structural outcomes, similarities in adverse treatment-related effects observed in multiple species, and evidence that metabolism of TCE in male reproductive tract tissues is associated with adverse effects on sperm measures in both humans and animals. Additionally, some aspects of a putative mode of action (e.g., perturbations in testosterone biosynthesis) appear to have some commonalities between humans and animals (EPA, 2011e).

The effects of TCE on cancers of the reproductive system have been evaluated in males and females in both epidemiological and experimental animal studies. However, the association between TCE exposure and these cancers is generally not robust. Please refer to Chapter 4 (section 4.8.2) of the TCE IRIS assessment for more details about the cancer studies in the reproductive system (EPA, 2011e).

Human Studies

Most human studies support an association between TCE exposure and alterations in sperm density and quality, as well as changes in sexual drive or function and serum endocrine levels. Fewer epidemiological studies exist linking decreased incidence of fecundability (time-to-pregnancy) and menstrual cycle disturbances in women with TCE exposures (EPA, 2011e).

Among the human studies, Chia et al. (1996) was the only epidemiological study that the IRIS program deemed suitable for further evaluation in the TCE's dose-response assessment for reproductive toxicity. Chia et al. (1996) examined a cohort of 85 workers in an electronics factory. The workers provided urine, blood, and sperm samples.The mean urine TCA level was 22.4 mg/g creatinine (range: 0.8–136.4 mg/g creatinine). In addition, 12 workers provided personal 8-hr air samples, which resulted in a mean TCE exposure of 29.6 ppm (range: 9–131 ppm). There were no controls in the study. Males experienced decreased percentage of normal

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sperm morphology and hyperzoospermia. A $BMDL_{10}$ of 1.4 ppm was identified as the POD for these effects (EPA, 2011e).

Animal Data

Laboratory animal studies provide evidence for similar effects, particularly for male reproductive toxicity. These animal studies have reported effects on sperm, libido/copulatory behavior, and serum hormone levels, although some studies that assessed sperm measures did not report treatment-related alterations (EPA, 2011e). Additional studies have observed TCE-related histopathological lesions in the testes or epididymides, altered *in vitro* sperm-oocyte binding or *in vivo* fertilization due to TCE or metabolites, and reduced fertility (EPA, 2011e). The reduced fertility effects in male rodents were observed in one study and attributed to systemic toxicity. However, the total database of reproductive studies suggested that TCE does induce reproductive toxicity independent of systemic effects (EPA, 2011e).

Fewer animal studies are available for the female reproductive toxicity endpoint. While *in vitro* oocyte fertilizability has been reported to be reduced as a result of TCE exposure in rats, a number of other laboratory animal studies did not report adverse effects on female reproductive function effects (EPA, 2011e).

Only the following eight reproductive animal toxicity studies were suitable for non-cancer dose-response analysis in the TCE IRIS assessment (Appendix L).

Xu et al. (2004) exposed male CD-1 mice (27/group) to TCE at concentration of 0 or 1,000 ppm for 6 hrs/day, 5 days/week for 6 weeks. Inhalation exposure to TCE did not result in altered body weight, testis and epididymis weights, sperm count, or sperm morphology or motility. Percentages of acrosome-intact sperm populations were similar between treated and control animals. However, decreased *in vitro* sperm-oocyte binding and reduced *in vivo* fertilization were observed TCE-treated male mice. A LOAEL of 180 ppm was identified as the POD for these effects (EPA, 2011e).

Kumar et al. (2000) and Kumar et al. (2001) exposed male Wistar rats by inhalation at concentrations of 0 or 376 ppm TCE. Both study protocols exposed rats for 4 hrs/day, 5 days/week, but had variable duration scenarios. For instance, Kumar et al. (2000) treated rats for the following exposure durations: 2 weeks (to observe the effect on the epididymal sperm maturation phase), 10 weeks (to observe the effect on the entire spermatogenic cycle), 5 weeks with 2 weeks of rest (to observe the effect on primary spermatocytes differentiation to sperm), 8 weeks with 5 weeks of rest (to observe effects on an intermediate stage of spermatogenesis), or 10 weeks with 8 weeks of rest (to observe the effect on spermatogonial differentiation to sperm). Kumar et al. (2001) exposed rats for either 12 or 24 weeks.

Kumar et al. (2000) reported altered testicular histopathology, increased sperm abnormalities, and significantly increased pre- and/or postimplantation loss in litters in the groups with 2 or 10 weeks of exposure, or 5 weeks of exposure with 2 of weeks rest. Multiple sperm effects were observed in Kumar et al. (2001). After 12 weeks of TCE exposure, rats exhibited decreased number of spermatogenic cells in the seminiferous tubules, fewer spermatids as compared to controls, and the presence of necrotic spermatogenic cells. Following 24 weeks of exposure,

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male rates showed reduced testes weights and epididymal sperm count and motility, testicular atrophy, smaller tubules, hyperplastic Leydig cells, and a lack of spermatocytes and spermatids in the tubules. Testicular marker enzymes were altered at both 12 and 24 weeks of exposure. A LOAEL of 45 ppm was identified as the POD for the sperm and male reproductive effects reported in both studies (EPA, 2011e).

Forkert et al. (2002) exposed male CD-1 mice (6/group) by inhalation to 0 or 1,000-ppm TCE for 6 hrs/day, 5 days/week for 19 days over a 4-week period. Mice exhibited sloughing of epididymal epithelial cells following TCE exposure. A LOAEL of 180 ppm was identified as a POD for the effects in the epididymis epithelium in male rats (EPA, 2011e).

Kan et al. (2007) also provided evidence for the damage to the epididymis epithelium and sperm. CD-1 male mice (4/group) were exposure by inhalation to 0 or 1,000-ppm TCE for 6 hrs/day, 5 days/week for 1 to 4 weeks. As early as 1 week after TCE exposure, exposed mice showed degeneration and sloughing of epithelial cells. These effects increased in severity at 4 weeks of exposure. A LOAEL of 180 ppm was identified as a POD for the effects in the epididymis epithelium which is consistent with the results from (EPA, 2011e); Forkert et al. (2002).

DuTeaux et al. (2004) conducted a drinking water study that treated two strains of male rats (Sprague-Dawley or Simonson albino; 3/group) with 0, 0.2%, or 0.4% TCE (v/v) (0, 143, or 270 mg/kg-bw/day) in a solution of 3% ethoxylated castor oil for 14 days. These TCE concentrations were within the range of those reported in formerly contaminated drinking water wells. Cauda epididymal and vas deferens sperm from treated males were incubated in culture medium with oviductal cumulus masses from untreated females to assess *in vitro* fertilization capability. Results showed a dose-dependent decreased fertilization in both rat strains with a LOAEL of 141 mg/kg-bw/day identified as the POD for the observed effects (EPA, 2011e).

Narotsky et al. (1995) administered TCE to F344 timed-pregnant rats (8-12 dams/group) by gavage. Dams were exposed to TCE doses of 0, 10.1, 32, 101, 320, 475, 633, 844 or 1125 mg/kg-bw/day during gestational days (GD) 6 to 15. The study was a prequel to a complicated protocol with other chemicals in a mixture study. Delayed parturition was observed at ≥475 mg/kg-bw/day. The LOAEL for female reproductive effects was 475 mg/kg-bw/day (EPA, 2011e).

Narotsky et al. (1995) exposed F344 male and female rats to TCE via the diet at estimated doses of 0, 72, 186, or 389 mg/kg-bw/day. Male and female animals were treated for one week pre-mating and then for 13 weeks. Pregnant rats were continued on TCE-treated diet throughout gestation. Results showed a decrease in mating in both sexes and the LOAEL of 389 mg/kg-bw/day was used as the POD for consideration in the TCE IRIS' dose-response assessment (EPA, 2011e).

2.6.2.3.6 Developmental Toxicity

An evaluation of the overall weight and strength of the evidence of the human and animal developmental toxicity data suggests an association between pre- and/or postnatal TCE exposures and potential developmental adverse outcomes. TCE-induced heart malformations in animals have been identified as the most sensitive developmental toxicity endpoint in the TCE

IRIS' dose-response analysis. This information is briefly discussed below, including a summary of the weight of evidence for the fetal cardiac malformations observed in animal data (EPA, 2011e).

EPA/OPPT relied on the PBPK-derived HECs reported for the developmental animal studies reporting fetal cardiac defects to estimate acute risks for exposures to TCE-containing degreasers, dry cleaning spotting agents, and arts/crafts products. This approach is consistent with EPA's current policy that a single exposure of a chemical at a critical window of fetal development may produce adverse developmental effects (EPA, 1991).

Human Studies

The TCE IRIS assessment evaluated numerous human studies that examined the possible association of TCE with various developmental outcomes, including prenatal (e.g., spontaneous abortion and perinatal death, decreased birth weight, and congenital malformations) and postnatal (e.g., growth, survival, developmental neurotoxicity, developmental immunotoxicity, and childhood cancers) effects. Most of these studies represent workplace exposures [e.g., Finnish studies of Taskinen et al. (1989) and Taskinen et al. (1994)]. In addition, geographically-based epidemiological studies have been conducted in various parts of the United States, including Arizona (Tucson Valley), Colorado (Rocky Mountain Arsenal), Massachusetts, New York (Endicott), Camp Lejeune, North Carolina and Milwaukee, Wisconsin.

The Endicott, New York, and the Camp Lejeune studies focused on reproductive and developmental outcomes (ATSDR, 1998, 2006, 2008). The Camp Lejeune studies have been the subject of an NAS investigation (NRC, 2009). Some of these studies have reported associations between parental exposure to TCE and spontaneous abortion or perinatal death, and decreased birth weight. However, other occupational and geographically-based studies have failed to detect a positive association between TCE exposure and developmental toxicity in humans (EPA, 2011e). Note that none of these studies were suitable for dose-response analysis in the TCE IRIS assessment due to study limitations (e.g., small sample size, co-exposures with other chemicals, lack of exposure levels) (EPA, 2011e).

There have been some epidemiological studies that have consistently reported an increased incidence of birth defects in TCE-exposed populations. For instance, ATSDR has conducted studies at Camp Lejeune, North Carolina, where individuals were exposed to VOC-contaminated drinking water [e.g., ATSDR (1998), Ruckart et al. (2013)]. TCE was one of the main contaminants found in the drinking water.

Ruckart et al. (2013) recently conducted a case control study to determine if children born from mothers exposed to contaminated drinking water during pregnancy at Camp Lejeune were more likely to develop childhood hematopoietic cancers, neural tube defects, or oral clefts. The study found an association between neural tube defects and TCE exposure above 5 ppb during the first trimester of pregnancy (i.e., OR of 2.4; 95% confidence limit: 0.6-9.6).

Yauck et al. (2004) conducted a small case-control study of 245 cases and 3,780 controls in Milwaukee, Wisconsin. The study used a geographic information system to estimate distances between maternal residences and facilities emitting TCE emissions. The study observed a strong

relative risk estimate of 6.2 (95% CI: 2.6, 14.5) for cardiac defects in infants born to mothers aged 38 years or older after controlling for potential confounding. No association for cardiac defects was observed among infants of mothers aged less than 38 years (RR = 0.9, 95% CI: 0.6, 1.2).

Since the publication of the 2011 TCE IRIS assessment, one recent update for the Endicott, NY community was published by the NY State Health Department that evaluated maternal exposure to TCE and other VOCs and pregnancy outcome (Forand et al., 2012). The study evaluated all births recorded in Endicott, NY from either 1978 to 2002 (to assess low birth weight, pre-term and fetal growth) or from 1983 to 2000 (birth defects). The comparison group was the rest of NY State except for the city of New York. A large chemical spill occurred in the town in 1979, and monitoring of the contaminant plume occurred for years. Residents obtained their drinking water from an uncontaminated water source. However, TCE and other VOCs have been measured in groundwater, soil, and inside buildings, the latter due largely to vapor intrusion. The study authors reported significant adjusted rate ratios (RRs) for the TCE-contaminated area for, among others, the following endpoints: low birth weight (RR of 1.36; 95 percent confidence interval (CI) of 1.07 to 1.73), small for gestational age [RR of 1.23; 95 percent (CI) of 1.03 to 1.48], and cardiac defects (RR of 2.15; 95 percent CI of 1.27 to 3.62).

Other studies have addressed the potential immunological effects in children exposed to TCE. Lehmann et al. (2001) studied the relationship between indoor VOC exposure and the risk of atopy in premature neonates and 36-month-old neonates. The study found no association between TCE exposure and allergic sensitization to egg white and milk, or to cytokine producing peripheral T-cells. However, Lehmann et al. (2002) reported a significant reduction in Th1 IL-2 producing cells in exposed newborns.

As for human developmental neurotoxicity, the available studies collectively suggest that the developing brain is susceptible to TCE toxicity. These studies have reported an association with TCE exposure and CNS birth defects and postnatal effects such as delayed newborn reflexes, impaired learning or memory, aggressive behavior, hearing impairment, speech impairment, encephalopathy, impaired executive and motor function and attention deficit (ATSDR, 2001; Bernad et al., 1987; Bove, 1996; Bove et al., 1995; Burg and Gist, 1997; Lagakos et al., 1986; White et al., 1997). These studies have many limitations; thus the reported associations must be interpreted with caution (EPA, 2011e).

Leukemia and CNS cancers during childhood have been observed in a number of studies in children exposed to TCE. However, other studies have not confirmed the increased risk for childhood leukemia and CNS cancers (EPA, 2011e).

Animal Data

Many of the TCE-related developmental effects reported in humans have been observed in animal studies: pre- or post-implantation losses, increased resorptions, perinatal death, decreased birth weight, and congenital anomalies. Some of these effects appear to be strain-specific. Overall, based on weakly suggestive epidemiologic data and fairly consistent laboratory animal data, it can be concluded that TCE exposure poses a potential hazard for prenatal losses and decreased growth or birth weight of offspring effects (EPA, 2011e).

The TCE IRIS assessment found 5 animal studies that were suitable for non-cancer dose-response analysis for the following developmental outcomes: pre- and postnatal mortality; pre- and postnatal growth; developmental neurotoxicity; and congenital heart malformations (Appendix L).

Although the focus of the discussion below is on these 5 studies and corresponding endpoints, it is important to mention that developmental immunotoxicity has been shown in TCE-treated animals. The most sensitive immune system response was reported by Peden-Adams et al. (2006). In this study, B6C3F1 mice were exposed to TCE via drinking water. Treatment occurred during mating and through gestation to TCE levels of 0, 1.4, or 14 ppm. After delivery, pups were further exposed for either 3 or 8 more weeks at the same concentration levels that the dams received in drinking water. Suppressed PFC response was seen in male pups after 3 and 8 weeks of exposure, whereas female pups showed the suppression of PFC response and delayed hypersensitivity at 1.4 ppm following 8 weeks. At the higher concentration (14 ppm), both of these effects were observed again in both males and females following 3 or 8 weeks of postnatal exposure. A LOAEL of 0.37 mg/kg-bw/day served as a POD for the decreased PFC and increased delayed hypersensitivity responses (EPA, 2011e).

-- Pre- and Postnatal Mortality and Growth

The following two studies were suitable for non-cancer dose-response analysis for pre- and postnatal mortality and growth effects. Healy et al. (1982) exposed female Wistar rats (31-32 dams/group) to TCE via inhalation at concentrations of 0 or 100 ppm for 4 hrs/day during GD 8 to 21. Study reported increased resorptions in dams exposed to 100 ppm. After adjusting to a continuous 24-hr exposure, the LOAEL of 17 ppm was identified and used as the POD in the dose-response analysis. The same study also reported reduced fetal weight at 100 ppm (adjusted LOAEL of 17 ppm) (EPA, 2011e).

Narotsky et al. (1995) was the other study in which a POD was identified for mortality in the developing fetus. This study was mentioned above in the reproductive toxicity section. F344 timed-pregnant rats (8-12 dams/group) were treated with TCE by gavage during GD 6 to 15. The $BMDL_{01}$ for resorptions was 32.2 mg/kg-bw/day (EPA, 2011e).

-- Developmental Neurotoxicity

There is evidence of alterations in animal brain development and in behavioral parameters (e.g., spontaneous motor activity and social behaviors) following TCE exposure during the development of the nervous system. Among all of the available studies, there were two oral studies that reported behavioral changes which were used in the dose-response evaluation for developmental toxicity.

Fredriksson et al. (1993) treated male NMRI mouse pups (12/group, selected from 3–4 litters) with TCE via gavage (0, 50, or 290 mg/kg-bw/day) during postnatal days (PND) 10 to 16. Locomotor behavior was evaluated at PND 17 and 60. TCE-treated mice showed decreased rearing activity at both dose levels on PND 60, but not PND 17, resulting in a LOAEL of 50 mg/kg-bw/day as a POD (EPA, 2011e).

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Taylor et al. (1985) conducted a drinking water study where pregnant Sprague-Dawley rats were given TCE at concentrations of 0, 312, 625, or 1,250 mg/L (0, 45, 80 or 140 mg/kg-bw/day). Exposure occurred 14 days prior to breeding and from GD 0 to PND 21. The number of litters/group was not reported, nor did the study state how many pups per litter were evaluated for behavioral parameters. Exploratory behavior was measured in the pups on PND 28, 60, and 90, whereas wheel-running, feeding, and drinking behavior were monitored on PNDs 55–60. TCE-treated male showed increased exploratory behavior on PND 60 and 90 at all dose levels, with the largest effect observed at the highest dose level. The LOAEL for this effect was 45 mg/kg-bw/day (EPA, 2011e).

Blossom et al. (2012) and Blossom et al. (2013) found effects of developmental exposure to TCE via drinking water (0, 2, or 28 mg/kg/day). MRL mice were maternally exposed from birth through weaning. Subsequently, males only were exposed directly via drinking water from PND 21 (weaning) to PND 42. The study reported alterations in brain neurotrophin expression, glutathione redox homeostasis, DNA hypomethylation and a number of behavioral parameters, such as increased motor activity, and novelty/exploratory behavior at the highest dose tested (28 mg/kg/day). The NOAEL for neurobehavioral impairments was 2 mg/kg/day with a $BMDL_{1SD}$ ranging from 14-20 mg/kg/day depending upon the neurobehavioral endpoint (Appendix M)[28].

-- *Congenital Heart Defects*

In vivo animal studies in rats and chicks have identified an association between TCE exposures and cardiac defects in the developing embryo and/or fetus. Mechanistic studies have also examined various aspects of the induction of cardiac malformations. The critical window for cardiac development is 1-2 weeks for rodents, 1-2 weeks for chickens, and from the 3rd to the 8th week for the human fetus. As discussed above, human studies have also reported increased risk of cardiac defects following TCE exposure. Taken together, after evaluating both positive and negative findings, the TCE IRIS assessment concluded that TCE exposure poses a potential hazard for congenital malformations, including cardiac defects in offspring. This conclusion is based on the weakly suggestive epidemiological data in combination with the findings of the animal and mechanistic studies (EPA, 2011e).

The scientific literature also has examples of well-conducted studies in rats, mice, or rabbits that have failed to provide evidence for TCE-induced cardiac malformations. It is postulated that the differences in response across studies may be partially attributed to experimental design differences (EPA, 2011e).

The fetal cardiac defects reported in Dawson et al. (1990), Dawson et al. (1993), Johnson et al. (2003), Johnson et al. (2005) and Johnson (2014) were identified as the most sensitive endpoint within the developmental toxicity domain and across all of the health effects domains evaluated in the TCE IRIS assessment. Johnson et al. (2003) reported data from different experiments over a several-year period in which pregnant Sprague-Dawley rats (9-13/group; 55 in control group) were exposed to TCE via drinking water at concentrations of 0, 0.00045,

[28] EPA conducted BMD analysis using the dose-response data reported in the Blossom et al. study (2013). For further information on the BMD analysis, please refer to Appendix M and supplemanty files: 1_Blossom_NObject_SD.xlsm and 2_Blossom_NMouse_SD.xlsm).

0.048, 0.218 or 129 mg/kg-bw/day. Treatment of pregnant rats occurred during the entire gestational period (i.e., GD 0 to GD22). The study reported a statistically and biologically significant increase in the formation of heart defects at the 0.048 mg/kg-bw/day dose level at both the individual fetus level and the litter level. There was a statistically significant increase in the percentage of abnormal hearts and the percentage of litters with abnormal hearts at 0.048 mg/kg-bw/day and higher dose levels[29]. A $BMDL_{01}$ of 0.0207 mg/kg-bw/day was identified as the POD for heart malformations (EPA, 2011e).

The fetal cardiac findings in the Johnson et al. studies have been controversial due to limitations in their study design, data reporting issues and inconsistencies with the database. EPA/OPPT received a number of comments from the public and the peer review panel objecting to the use of the Johnson et al. studies based on methodological issues and the fact that the findings have not been replicated in other animal and human studies. A recent erratum (Johnson, 2014) and subsequent evaluation of the developmental toxicity data reaffirmed that the Johnson et al. studies are adequate to use in hazard identification and dose-response assessment (Appendix M). While the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with the remaining body of human, animal and mechanistic evidence (EPA, 2011e). Appendix N discusses the weight-of-evidence analysis supporting the association of TCE exposure and fetal cardiac malformation.

-- Summary of Weight-of-Evidence Analysis for Congenital Heart Defects

TCE exposure has been associated with cardiac malformations in chick embryos studies (Boyer et al., 2000; Bross et al., 1983; Drake, V. et al., 2006; Drake, V. J. et al., 2006; Loeber et al., 1988; Mishima et al., 2006; Rufer et al., 2008) and oral developmental toxicity studies in rats (Dawson et al., 1990, 1993; Johnson et al., 2005; Johnson, 2014; Johnson et al., 2003). In addition to the consistency of the cardiac findings across different species, the incidence of congenital cardiac malformation has been duplicated in several studies from the same laboratory group and has been shown to be TCE-related (EPA, 2011e).

TCE metabolites have also induced cardiac defects in developmental oral toxicity studies (Epstein et al., 1992; Johnson et al., 1998a, 1998b; Smith et al., 1989, 1992). For example, the Johnson et al. and Smith et al. studies reported increased incidences of cardiac malformation following gestational TCA exposures (Johnson et al., 1998a, 1998b; Smith et al., 1989). Similarly, pregnant rats exhibited increased incidence of cardiac defects following DCA exposure during pregnancy (Epstein et al., 1992; Smith et al., 1992).

A number of studies have been conducted to elucidate the mode of action for TCE-related cardiac teratogenicity. During early cardiac morphogenesis, outflow tract and atrioventricular endothelial cells differentiate into mesenchymal cells (EPA, 2011e). These mesenchymal cells have characteristics of smooth muscle-like myofibroblasts and form endocardial cushion tissue, which is the primordia of septa and valves in the adult heart (EPA, 2011e). Many of the cardiac

[29] The EPA Science Advisory Board EPA (2011c) reviewed these data and suggested that the IRIS program use the Johnson et al. (2003) study as one of the principal studies for RfD/RfC derivation with the critical effect of cardiac malformations.

defects observed in humans and laboratory species involved septal and valvular structures (EPA, 2011e). Thus, a major research area has focused on the disruptions in cardiac valve formation in avian *in ovo* and *in vitro* studies following TCE treatment. These mechanistic studies have revealed TCE's ability to alter the endothelial cushion development, which could be a possible mode of action underlying the cardiac defects involving septal and valvular morphogenesis in rodents and chickens (EPA, 2011e). These mechanistic data provide support to the plausibility of TCE-related cardiac effects in humans (EPA, 2011e).

Other modes of actions may also be involved in the induction of cardiac malformation following TCE exposure. For example, studies have reported TCE-related alterations in cellular Ca^{2+} fluxes during cardiac development (Caldwell et al., 2008; Collier et al., 2003; Selmin et al., 2008).

2.6.2.4 Summary of Hazard Studies Used to Evaluate Acute and Chronic Exposures

Table 2-26 summarizes the hazard studies, health endpoints by target organ/system, PBPK-derived HEC_{99} and UFs that are relevant for the risk evaluation of acute and chronic exposure scenarios. Risk estimates were estimated for a range of HECs, but the HEC_{99} was preferred since it is considered protective for a sensitive individual as discussed in the TCE IRIS assessment (EPA, 2011e). Appendix L contains the complete list of oral and inhalation non-cancer studies within each health effects domain that the TCE IRIS assessment considered suitable for dose-response analysis.

2.7 HUMAN HEALTH RISK CHARACTERIZATION

TCE and its metabolites are associated with adverse effects on cardiac development based on a weight-of-evidence analysis of developmental studies from rats, humans and chickens.These adverse cardiac effects are deemed important for acute and chronic risk estimation for the scenarios and populations addressed in this risk assessment. The rationale for using TCE associated fetal cardiovascular lesions for acute scenarios is based on the relatively short critical window of vulnerability in humans, rodent and avian cardiac development.The rationale for using fetal cardiac effects for chronic risks estimation is also based on the fact that relatively low dose short term/acute exposures can result on long-term adverse consequences on cardiac development persisting into adulthood.

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Table 2-26. Summary of Hazard Information Used in the Risk Evaluation of Acute and Chronic Scenarios								
Exposure Duration for Risk Analysis	**Target Organ/ System**	**Species**	**Route of Exposure**	**POD Type**	**Effect**	**HEC_{99} (ppm)**	**Total Uncertainty Factor (UF) for Benchmark MOE**	**Reference**
CHRONIC	Liver	Mouse (male)	Inhalation	$BMDL_{10}$ = 21.6 ppm	Increased liver/body weight ratio	9.1	*Total UF=10*	Kjellstrand et al. (1983)
	Kidney	Rat (female)	Oral (gavage)	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.0056	*Total UF=10*	NTP (1988)
	Nervous System	Rat (male)	Inhalation	LOAEL = 12 ppm	Significant decreases in wakefulness	4.8	*Total UF=300*	Arito et al. (1994)
	Immune System	Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.033	*Total UF=100*	Keil et al. (2009)
		Mouse (female)	Oral (drinking water)	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.033	*Total UF=30*	Keil, D. E. et al. (2009)
	Reproductive System	Human (male)	Inhalation	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	0.5	*Total UF=30*	Chia et al. (1996)
ACUTE OR CHRONIC	Developmental effects	Rat (female)	Oral (drinking water)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.0037	Total UF=10	Johnson et al. (2003)

Notes:

[1] 1 ppm = 5.374 mg/m^3

[2] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UFs for effects repoted by the same study (EPA, 2011e).

Other adverse non-cancer effects are deemed relevant for risk estimations for other populations for the chronic scenarios, but may not occur at the lowest exposures found with cardiac defects and they include kidney toxicity, immunotoxicity, male reproductive toxicity, neurotoxicity, liver toxicity and cancer of kidney, liver and immune system (NHL).

TCE is carcinogenic to humans. The cancer risk assessment uses the IUR derived in the 2011 TCE IRIS assessment based on human kidney cancer. The weight-of-evidence analysis for the cancer endpoint was sufficient to conclude that TCE operates through a mutagenic mode of action for kidney tumors (EPA, 2011e).

2.7.1 Risk Estimation Approach for Acute and Repeated Exposures

Tables 2-27 and 2-28 show the use scenarios, populations of interest and toxicological endpoints used in the acute and chronic risk assessment, respectively.

Table 2-27. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Acute Risks to TCE-containing Degreasers, Spotting Agents and Arts/Crafts Products

Use Scenarios / Populations And Toxicological Approach	(1) Solvent degreasing at small commercial facilities	(2) Spot cleaning at dry cleaning facilities	(3) Residential use of degreaser product	(4) Residential use of arts/crafts clear protective coating spray
Population of Interest and Exposure Scenario: *Users*	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 2-hr exposure during an 8-hr workday [2,3,4].	Adult pregnant[1] worker (>16 years old) exposed to TCE for a single 8-hr exposure [2,3].	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 1-hr exposure when using product 2X per month [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.	Adult pregnant [1] consumers (>16 yrs old) exposed to TCE for a single 0.5-hr exposure when using product once per week [2,3,4]. Residential exposure model provided the 24-hr acute exposure estimate.
Population of Interest and Exposure Scenario: *Bystander*	Adult pregnant women [1] (>16 years old) exposed to TCE indirectly by being in the same building.		Adult pregnant bystander[1] and individuals of several age groups that are exposed to indirect TCE exposures by being in the rest of the house.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Fetal cardiac defects (Johnson et al., 2005; Johnson, 2014; Johnson et al., 2003)[5] 1. *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs)* (EPA, 2011e): 24-hr HEC_{50}: 0.012 ppm 24-hr HEC_{95}: 0.0051 ppm 24-hr HEC_{99}: 0.0037 ppm Cancer Health Effects: Acute cancer risks were not estimated. Relationship is not known between a single short-term exposure to TCE and the induction of cancer in humans.			
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	(UF_S=1) x (UF_A= 3) x (UF_H=3) x (UF_L=1) [6] = 10 (EPA, 2011e). Total UF=Benchmark MOE=10			

Notes:

[1] The acute risk assessment focused on the most sensitive life stage in humans, which is women of childbearing age and fetus (i.e., pregnant worker) due to concerns for developmental effects.

[2] Exposure estimate was adjusted to a 24-hr exposure estimate in order to combine it with the 24-hr HECs.

[3] It is assumed no substantial buildup of TCE in the body between exposure events due to TCE's short biological half-life (~51 hrs).

[4] EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.

[5] The acute risk assessment focused on developmental toxicity effects as the most sensitive health effect when compared to other potential acute effects (i.e., neurotoxicity).

[6] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF

Table 2-28. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Chronic Risks to TCE-containing Degreasers and Spotting Agents		
Use Scenarios → / Populations And Toxicological Approach ↓	**(1) Solvent degreasing at small commercial facilities**	**(2) Spot cleaning at dry cleaning facilities**
Population of Interest and Exposure Scenario: ***Users***	Adult worker (>16 years old) [1] exposed to TCE for 2-hr exposure during an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.	Adult worker (>16 years old) [1] exposed to TCE for an 8-hr workday for 260 days per year for 40 working years. Lifetime average daily concentration was calculated. Note that the 8-hr exposure estimate was adjusted to a 24-hr exposure estimate.
Population of Interest and Exposure Scenario: ***Bystander***	Adult worker (>16 years old) [1] repeatedly exposed to indirect TCE exposures by being in the same building.	
Health Effects of Concern, Concentration and Time Duration	Non-Cancer **2.** *Non-cancer health effects*: A range of possible chronic non-cancer effects in liver, kidney, nervous system, immune system, reproductive system and developmental effects[2] **3.** *PBPK-derived Non-Cancer Hazard values or Point of Departures (PODs):* The lowest POD (i.e., 24-hr HEC_{50}, HEC_{95} or HEC_{99} expressed in ppm) within each health endpoint domain (EPA, 2011e). See Table 2-18. Cancer **1.** *Cancer health effects:* Possible cancer effects in kidney, liver or non-Hodgkins lymphoma from chronic exposure. **2.** *PBPK-derived Cancer Inhalation Unit Risk (IUR)*: 2×10^{-2} per ppm (EPA, 2011e).	
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	Study- and endpoint-specific UFs from the TCE IRIS assessment. See Table 2-18.	

Notes:
[1] Adult workers (>16 years old) include both healthy female and male workers.
[2] The chronic risk assessment for developmental effects focused on the most sensitive life stage in humans, which are women of child-bearing age and fetus (i.e., pregnant worker). For other health effects (e.g., liver, kidney, etc.), healthy female or male workers were assumed to be the population of interest.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) were used in this assessment to estimate non-cancer risks (Table 2-29).

Table 2-29. Equation to Calculate Non-Cancer Acute or Chronic Risks Using Margin of Exposures

$$MOE_{acute\ or\ chronic} = \frac{\text{Non-cancer Hazard value (POD)}}{\text{Human Exposure}}$$

MOE =	Margin of exposure (unitless)
Hazard value (POD) =	HEC_{50}, HEC_{95}, or HEC_{99} (ppm) derived from TCE IRIS assessment (EPA, 2011e)
Human Exposure =	Exposure estimate (in ppm) from occupational or consumer exposure assessment. ADCs were used for non-cancer chronic risks and acute concentrations were used for acute risks (see sections 2.3.3 and 2.4.2).

As discussed previously, each non-hazard PBPK-derived POD was adjusted by endpoint/study-specific UFs as described in the TCE IRIS assessment (EPA, 2011e). These UFs accounted for (1) the variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4)the uncertainty in extrapolating from a LOAEL rather than from a NOAEL (EPA, 2011e).

The total UF for each non-cancer PBPK-derived POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The MOE estimate was interpreted as human health risk if the MOE estimate was less than the benchmark MOE (=total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Cancer risks for repeated exposures to TCE were estimated using the equation in Table 2-30. Estimates of cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or excess individual lifetime cancer risk).

Table 2-30. Equation to Calculate Cancer Risks

$$\text{Risk} = \text{Human Exposure} \times \text{IUR}$$

Risk =	Cancer risk (unitless)
Human exposure =	Exposure estimate (LADC in ppm) from occupational exposure assessment
IUR =	Inhalation unit risk (2×10^{-2} per ppm) (EPA, 2011e)

2.7.2 Acute Non-Cancer Risk Estimates for Inhalation Exposures to TCE

The acute inhalation risk assessment used developmental toxicity data to evaluate the acute risks for the TSCA TCE use scenarios. As indicated previously, EPA's policy supports the use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure of a chemical at a critical window of fetal development, as in the case of cardiac development, may produce adverse developmental effects (EPA, 1991).

After evaluating the developmental toxicity literature of TCE, the TCE IRIS assessment concluded that the fetal heart malformations are the most sensitive developmental toxicity endpoint associated with TCE exposure (EPA, 2011e). Thus, EPA/OPPT based its acute risk assessment on the most health protective endpoint (i.e., fetal cardiac malformations; Johnson et al., 2003) representing the most sensitive human population (i.e., adult women of child-bearing age and fetus > 16 yrs).

The acute risk assessment used the PBPK-derived hazard values (HEC_{50}, HEC_{95}, or HEC_{99}) from Johnson et al. (2003) developmental study for each degreaser and spot cleaner use scenario. Note that the variability among these hazard values is small and no greater than 3-fold (i.e., 2-fold for HEC_{50}/HEC_{95} ratios; 3-fold for HEC_{50}/HEC_{99} ratios; 1.4-fold for HEC_{95}/HEC_{99} ratios).

Acute inhalation risks were reported for most occupational and residential exposure scenarios based on concerns for developmental effects, irrespective of who is using the product (user vs. bystander), the type of exposure (typical vs. worst case scenario) and the room ventilation system (LEV vs no LEV). For instance, most of the degreaser and spot cleaner exposure scenarios and all of the residential use scenarios reported MOE values below the benchmark MOE of 10 irrespective of the percentile HEC value used to estimate the MOEs. Only one use scenario reported MOEs above 10, which was the spot cleaner use scenario representing bystander exposures under typical occupational exposure levels with LEV (i.e., "Bystander + LEV—Typical Exposure") (Tables 2-31, 2-32 and 2-33).

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Table 2-31. Acute Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**0.12**	**0.0018**	**0.012**	**0.00018**	**0.9**	**0.002**	**0.09**	**0.00021**	10
HEC_{95}= 0.0051	**0.051**	**0.0008**	**0.0051**	**0.00008**	**0.38**	**0.0009**	**0.038**	**0.000089**	
HEC_{99}= 0.0037	**0.037**	**0.0006**	**0.0037**	**0.00006**	**0.28**	**0.0007**	**0.028**	**0.000065**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-10.

Table 2-32. Acute Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)

Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	WORKER NON-CANCER MOEs				BYSTANDER NON-CANCER MOEs				Total UF or Benchmark MOE
	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	With LEV—Low-end exposure estimate	With LEV—Upper-end exposure estimate	No LEV—Low-end exposure estimate	No LEV—Upper-end exposure estimate	
HEC_{50}= 0.012	**4.5**	**0.018**	**0.45**	**0.0019**	51.4	**0.018**	**5.1**	**0.002**	10
HEC_{95}= 0.0051	**1.9**	**0.0077**	**0.19**	**0.00081**	21.9	**0.0077**	**2.2**	**0.00085**	
HEC_{99}= 0.0037	**1.4**	**0.0056**	**0.14**	**0.00058**	15.9	**0.0056**	**1.6**	**0.00062**	

Notes:

– MOEs below benchmark MOE indicating risk are denoted in **bold** text. They indicate potential health risks.
– Exposure estimates with/without LEV are found in Table 2-13.

Table 2-33. Acute Non-Cancer Risk Estimates for Residential Uses of TCE-containing degreasers and art/crafts products (Developmental Effects: Congenital Heart Malformations, Johnson et al., 2003)					
Lowest PBPK-derived HECs (ppm) of the developmental toxicity health domain	RESIDENTIAL USE OF DEGREASER PRODUCT MOEs [1]		RESIDENTIAL USE OF ARTS/CRAFTS CLEAR PROTECTIVE COATING SPRAY MOEs [1]		Total UF or Benchmark MOE
	USER [2]	BYSTANDER [3]	USER [2]	BYSTANDER [3]	
HEC_{50}= 0.012	**0.0060**	**0.015**	**0.03**	**0.12**	10
HEC_{95}= 0.0051	**0.0026**	**0.0064**	**0.013**	**0.051**	
HEC_{99}= 0.0037	**0.0019**	**0.0046**	**0.0093**	**0.037**	

Notes:
1 MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks.
2 MOEs for the user categories could be extended to different age groups. EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user while engaging in arts and crafts projects or degreasing.
3 All age categories (<1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20 yrs ; and >21 yrs)

2.7.3 Chronic Non-Cancer and Cancer Risk Estimates for Inhalation Exposures to TCE

Chronic non-cancer and cancer risk estimates for inhalation exposures to TCE were only derived for occupational scenarios since the exposures for consumer uses were not considered chronic in nature.

2.7.3.1 Cancer Risks for Occupational Scenarios

Figures 2-6 and 2-7 present the incremental individual lifetime cancer risks for continuous exposures to TCE occurring during the commercial use of degreaser and spot cleaner products. The cancer risk estimates were calculated by multiplying the EPA's inhalation unit risk for TCE (EPA, 2011e) by the exposure estimate (i.e., LADC) for both direct users and bystanders. Cancer risks were expressed as number of cancer cases per million. Calculations of cancer risks are provided in the supplemental Excel spreadsheet, *TCE OPPT Risk Estimates_061814.xlsx*.

It was assumed that the exposure frequency (i.e., the amount of days per year workers or bystanders are exposed to TCE) was 260 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA/OPPT does not have additional information for further refinement.

EPA typically uses a target cancer risk level between $1x10^{-4}$ and $1x10^{-6}$ for determining the acceptability of the cancer risk in a population. Since the target cancer risk level will be determined during risk management, the occupational cancer risk estimates were compared to three target levels within EPA's acceptability range. The target levels were:

1. $1x10^{-6}$: the probability of 1 chance in 1 million of an individual developing cancer
2. $1x10^{-5}$: the probability of 1 chance in 100,000 of an individual developing cancer, which is equivalent to 10 cancer cases in 1 million
3. $1x10^{-4}$: the probability of 1 chance in 10,000 of an individual developing cancer, which is equivalent to 100 cancer cases in 1 million

All of the degreaser exposure scenarios exceeded the three target cancer levels, with the exception of one of the bystander exposure scenarios (i.e., "*Bystander + LEV—Typical Exposure*"). This particular bystander exposure scenario exceeded the target levels at $1x10^{-5}$ and $1x10^{-6}$ (Figure 2-6).

Likewise, all of the worst case exposures for the spot cleaner scenarios (i.e., both user and bystander scenarios) and one of the typical exposure scenarios with no LEV (i.e., "*Spot Cleaner No LEV—Typical Exposure*") exceeded the three target levels. The remaining spot cleaner scenarios exceeded the target level of $1x10^{-4}$ (i.e., "Spot cleaner + LEV—Typical Exposure"; "Bystander + LEV—Typical Exposure"; and "Bystander No LEV—Typical Exposure") (Figure 2-7).

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Figure 2-6. Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

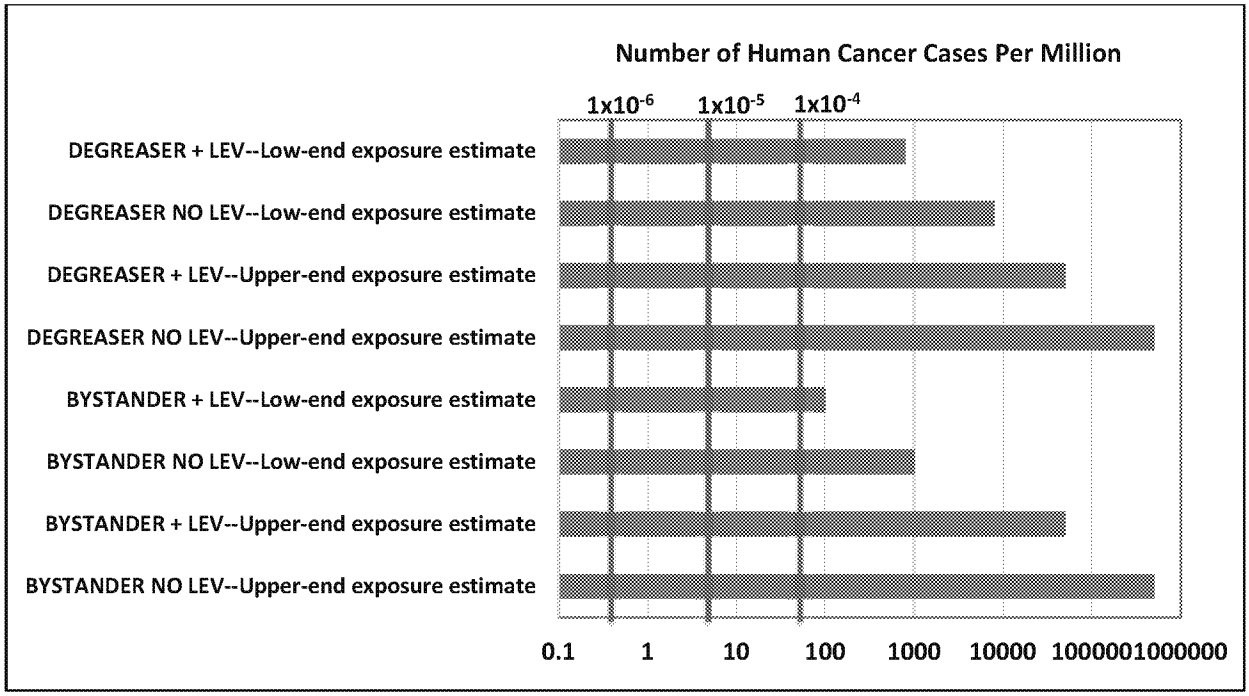
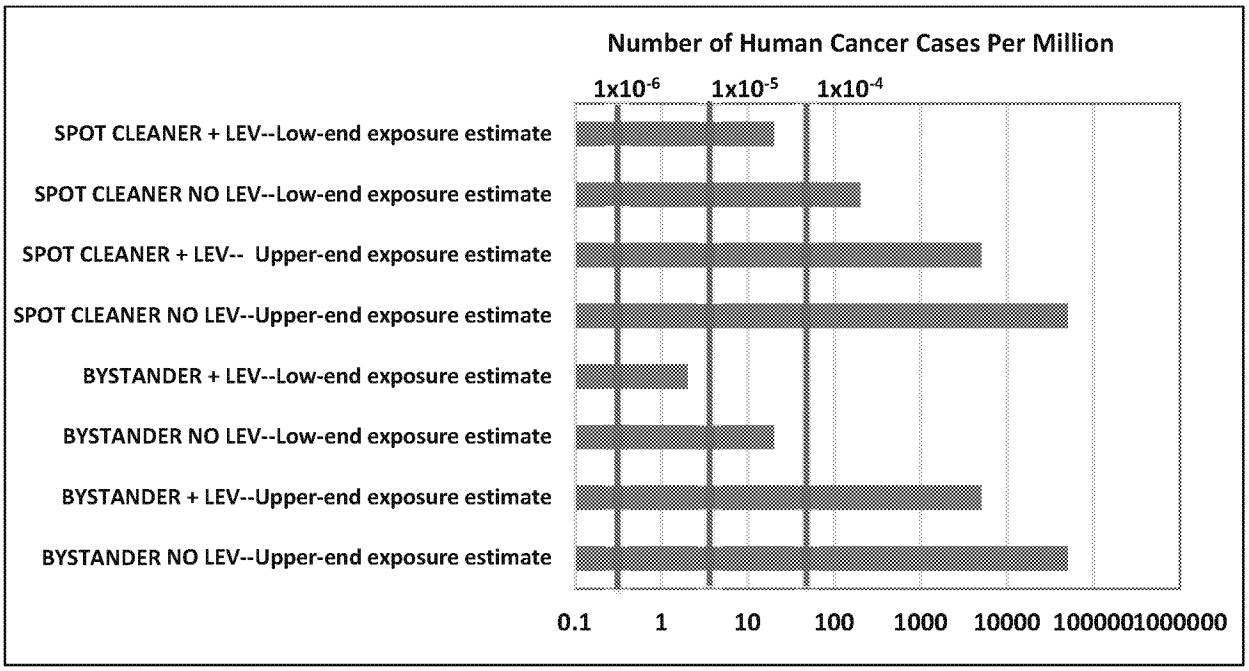


Figure 2-7. Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities



For both degreaser and spot cleaner scenarios, the results indicated that the cancer risk was 10 times greater in scenarios with no local exhaust ventilation that those with room ventilation (+LEV). Moreover, an 8-fold increase in cancer risk was observed in those workers directly using the TCE-containing product when compared to their corresponding bystanders (Figures 2-6 and 2-7). Similarly, a 10-fold increase in cancer risk was reported in those workers using spotting agents containing TCE when compared to their corresponding bystanders indirectly exposed in the dry cleaning facilities (Figure 2-7).

2.7.3.2 Chronic Non-Cancer Risks for Occupational Scenarios

EPA/OPPT estimated chronic non-cancer risks for the occupational use of TCE-containing degreasers and spot cleaners. Since TCE exposure has been associated with a variety of health effects, this assessment estimated human health inhalation chronic risks for developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver toxicity. As previously discussed, the TCE IRIS assessment developed PODs (i.e., HEC_{50}, HEC_{95} or HEC_{99}) for multiple studies that were suitable for dose-response analysis (Appendix L). EPA/OPPT used the lowest POD (or HEC) in each health effects domain for the non-cancer chronic MOE calculations. The risk estimates for the commercial degreaser and spot cleaner uses are presented in Tables 2-34 and 2-35, respectively[30].

Workers in direct contact with the degreaser products and occupational bystanders reported risks (i.e., MOEs<benchmark MOE) for the following chronic non-cancer effects: developmental toxicity, kidney and immunotoxicity. Also, all of the worker scenarios showed risks for reproductive effects and neurotoxicity. These risks were observed in the worker/bystander scenarios regardless of the type of TCE exposure (typical vs. worst case) and the availability of local exhaust ventilation (with LEV vs. no LEV). Moreover, risks for reproductive effects and neurotoxicity were also found in the degreaser bystander scenarios, but only for worst case exposure conditions and typical exposure circumstances with no local exhaust ventilation. Furthermore, risks were also found for liver effects, but only for those degreaser worker/bystander scenarios representing worst case exposure conditions irrespective of the presence of room ventilation (Table 2-34).

The non-cancer chronic risk profile was slightly different for the TCE use in spot cleaners because the TCE exposure concentrations in dry cleaning facilities were 10 to 60-fold lower than those estimated in degreaser small shops. Risks for developmental effects, kidney toxicity and immunotoxic effects were generally observed for all of the spot cleaning worker/bystander exposure scenarios (i.e., typical vs worst case; typical exposure vs worst case) with two exceptions. Non-risk findings were reported for few spot cleaning worker/bystander scenarios under LEV and typical exposure conditions that used the HEC^{50th} percentile for the MOE calculations. Also, the spot cleaning bystander exposure scenario did not report potential non-

[30] Risk estimates were calculated for all of the studies per health effects domain that the EPA's IRIS program identified as suitable for dose-response analysis. These risk estimates are found in the supplemental Excel file "TCE OPPT Risk Estimates_061814".

cancer chronic risks for the aforementioned health effects domains under LEV and typical exposure conditions (Table 2-35).

Risks for reproductive effects and neurotoxicity were less consistently seen across the board with the exception of the spot cleaning worker/bystander exposure scenarios characterizing typical or worst-case exposure condition under no ventilation system. As for risks for liver effects, most of the spot cleaning scenarios showed no risk concern with the exception of the worker/bystander worst case exposure scenarios with no LEV (Table 2-35).

2.7.4 Human Health Risk Characterization Summary

This risk assessment focused on the occupational and consumer uses of TCE-containing degreasers, spot cleaners and clear protective coating spray in arts/crafts. Specifically, the following exposure scenarios were evaluated: small commercial degreasing operations; spot cleaning in dry cleaning facilities; consumer use of an aerosol degreaser; and the consumer use of a clear protective coating spray in an arts/crafts home setting. The population of interest consisted of workers and consumers with direct (users) or indirect (bystander) exposure to TCE. Only the inhalation route of exposure was considered in this risk assessment.

The occupational and consumer exposure assessments generated the TCE exposure levels required to derive non-cancer and cancer risks. Cancer risks were presented as lifetime risks, meaning the risk of developing cancer as a result of the occupational exposure over a normal lifetime of 70 yrs. Lifetime cancer risks from TCE exposure were compared to target risks ranging from 10^{-6} to 10^{-4}.

Many of the degreaser and spot cleaning exposure scenarios exceeded the target cancer risks of 10^{-6}, 10^{-5} and 10^{-4}. This analysis resulted in higher modeled incidences of cancer in the small commercial degreaser than the users of spot cleaners. Thus, the greatest potential for cancer risk came from the occupational exposures to commercial degreasers. Furthermore, higher cancer risks resulted from direct use of the degreaser or lack of local exhaust ventilation at the workplace.

To characterize the risks of adverse health effects other than cancer, MOEs were used to evaluate non-cancer risks for both acute and chronic exposures using the hazard values published in the TCE IRIS assessment (EPA, 2011e). Hazard values based on developmental toxicity (i.e., fetal cardiac defects; Johnson et al., 2003) were used to estimate acute non-cancer risks for occupational and consumer exposures. On the other hand, the chronic non-cancer risks for the worker scenarios were evaluated with the hazard values associated with health effects following long-term exposure to TCE (i.e., developmental toxicity, kidney toxicity, immunotoxicity, reproductive toxicity, neurotoxicity and liver effects). Note that minimal variability (i.e., ≤ 3-fold) exist among the acute and chronic non-cancer hazard values (i.e., HEC_{50}, HEC_{95} or HEC_{99}) used in this assessment.

Most occupational and residential exposure scenarios reported acute risks based on concerns for developmental effects (i.e., cardiac defects) that may occur following a single exposure to TCE during a critical window of susceptibility. Particularly, the degreaser exposure scenarios showed greater acute risks than those reported for the spot cleaning exposure scenarios.

There is a concern for a range of human health effects other than cancer that may appear after chronic exposures to TCE during the occupational use of TCE-containing degreasers and spot cleaning agents. The greatest concern is for developmental effects (i.e., fetal cardiac defects), followed by kidney effects and then immunotoxicity, with an overall higher chronic risk for the degreaser exposure scenarios. In general, the concerns for these three health effects domains occur regardless of the type of exposure (typical vs worst case) and the availability of room ventilation (LEV vs no LEV), although there are some exceptions, particularly in the spot cleaning bystander exposure scenarios.

Potential chronic risks for reproductive effects and neurotoxicity were also observed for degreaser worker exposure scenarios and most of the degreaser bystander exposure scenarios. However, the risks concerns for these effects were reported for fewer spot cleaning worker/bystander scenarios and generally attributed to exposure conditions without room ventilation.

Concerns for liver effects following chronic exposure to TCE are less prominent than the concerns for other health effects domains as chronic risks for liver toxicity were not reported for the majority of the degreaser and spot cleaning worker/bystander scenarios. The exception was the degreaser worker/bystander exposure worst case scenarios and the spot cleaning worker/bystander worst case scenarios with no LEV.

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Table 2-34. Chronic Non-Cancer Risk Estimates for Commercial Use of Degreaser Product at Small Shops

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**0.17**	**0.017**	**0.0025**	**0.0003**	**1.3**	**0.13**	**0.0030**	**0.0003**	10
	HEC95= 0.0051	**0.072**	**0.0072**	**0.0011**	**0.0001**	**0.54**	**0.05**	**0.0013**	**0.0001**	
	HEC99= 0.0037	**0.052**	**0.0052**	**0.0008**	**0.0001**	**0.40**	**0.04**	**0.0009**	**0.0001**	
KIDNEY (NTP, 1998)	HEC50= 0.042	**0.59**	**0.059**	**0.0088**	**0.0009**	**4.4**	**0.4**	**0.01**	**0.001**	10
	HEC95= 0.0085	**0.11**	**0.012**	**0.0018**	**0.0002**	**0.9**	**0.09**	**0.0021**	**0.0002**	
	HEC99= 0.0056	**0.079**	**0.0079**	**0.0012**	**0.0001**	**0.6**	**0.06**	**0.0014**	**0.0001**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**1.3**	**0.1**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.023**	**0.0023**	100
	HEC95= 0.045	**0.6**	**0.06**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.05**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	**1.3**	**0.13**	**0.019**	**0.0020**	**9.7**	**0.97**	**0.022**	**0.0023**	30
	HEC95= 0.045	**0.6**	**0.063**	**0.0095**	**0.0010**	**4.7**	**0.47**	**0.011**	**0.0011**	
	HEC99= 0.033	**0.5**	**0.046**	**0.0069**	**0.0007**	**3.5**	**0.35**	**0.0082**	**0.0008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	**19.7**	**2.0**	**0.3**	**0.03**	147	**15**	**0.35**	**0.034**	30
	HEC95= 0.7	**9.8**	**1.0**	**0.15**	**0.015**	74	**7**	**0.17**	**0.017**	
	HEC99= 0.5	**7.0**	**0.7**	**0.11**	**0.011**	53	**5**	**0.12**	**0.012**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	**183**	**18**	**2.7**	**0.28**	1369	**137**	**3.2**	**0.32**	300
	HEC95= 6.4	**90**	**9**	**1.3**	**0.14**	674	**67**	**1.6**	**0.16**	
	HEC99= 4.8	**67**	**7**	**1.0**	**0.10**	505	**51**	**1.2**	**0.12**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	351	35	**5.3**	**0.53**	2632	263	**6**	**0.61**	10
	HEC95= 12	168	17	**2.5**	**0.26**	1263	126	**3**	**0.29**	
	HEC99= 9.1	128	13	**1.9**	**0.19**	958	96	**2**	**0.22**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-10.

Table 2-35. Chronic Non-Cancer Risk Estimates for Commercial Use of Spotting Agent at Dry Cleaning Facilities

Health Effect Domain and Study	Lowest HEC (ppm) of each health effects domain	WORKER NON-CANCER MOEs [1]				BYSTANDER NON-CANCER MOEs [1]				Total UF or Benchmark MOE
		With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	With LEV--Low-end exposure estimate	No LEV--Low-end exposure estimate	With LEV--Upper-end exposure estimate	No LEV--Upper-end exposure estimate	
DEVELOPMENTAL TOXICITY (Johnson et al., 2003)	HEC50= 0.012	**6.3**	**0.0253**	**0.63**	**0.0027**	72	**0.0253**	**7.2**	**0.0028**	10
	HEC95= 0.0051	**2.7**	**0.0107**	**0.27**	**0.0011**	31	**0.0107**	**3.1**	**0.0012**	
	HEC99= 0.0037	**1.9**	**0.0078**	**0.19**	**0.0008**	22	**0.0078**	**2.2**	**0.0009**	
KIDNEY (NTP, 1998)	HEC50= 0.042	22	**0.088**	**2.2**	**0.0093**	253	**0.0884**	25	**0.0098**	10
	HEC95= 0.0085	**4.5**	**0.018**	**0.45**	**0.0019**	51	**0.0179**	**5.1**	**0.0020**	
	HEC99= 0.0056	**2.9**	**0.012**	**0.29**	**0.0012**	34	**0.0118**	**3.4**	**0.0013**	
IMMUNOTOXICITY Keil et al., 2009 (Decrease in thymus weight and thymus cellularity)	HEC50= 0.092	**48**	**0.194**	**4.8**	**0.020**	554	**0.194**	**55**	**0.022**	100
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
IMMUNOTOXICITY Keil et al., 2009 (Autoimmunity)	HEC50= 0.092	48	**0.194**	**4.8**	**0.020**	554	**0.194**	55	**0.022**	30
	HEC95= 0.045	**24**	**0.095**	**2.4**	**0.010**	271	**0.095**	**27**	**0.011**	
	HEC99= 0.033	**17**	**0.069**	**1.7**	**0.007**	199	**0.069**	**20**	**0.008**	
REPRODUCTIVE TOXICITY (Chia et al. 1996)	HEC50= 1.4	737	**2.9**	74	**0.31**	8423	**2.9**	842	**0.33**	30
	HEC95= 0.7	369	**1.5**	37	**0.16**	4212	**1.5**	421	**0.16**	
	HEC99= 0.5	263	**1.1**	**26**	**0.11**	3008	**1.1**	301	**0.12**	
NEUROTOXICITY (Arito et al., 1994)	HEC50= 13	6844	**27**	684	**2.9**	78214	**27**	7821	**3.0**	300
	HEC95= 6.4	3369	**13**	337	**1.4**	38505	**13**	3851	**1.5**	
	HEC99= 4.8	2527	**10**	**253**	**1.1**	28879	**10**	2888	**1.1**	
LIVER (Kjellstrand et al. 1983)	HEC50= 25	13161	53	1316	**5.5**	150412	53	15041	**5.8**	10
	HEC95= 12	6317	25	632	**2.7**	72198	25	7220	**2.8**	
	HEC99= 9.1	4791	19	479	**2.0**	54750	19	5475	**2.1**	

Notes: (1) MOEs below benchmark MOE indicating risk are denoted in bold text. They indicate potential health risks. (2) Exposure estimates with/without LEV are found in Table 2-13.

2.8 DISCUSSION OF KEY SOURCES OF UNCERTAINTY AND DATA LIMITATIONS

The characterization of variability and uncertainty is fundamental to any risk assessment. Variability refers to "*the true heterogeneity or diversity in characteristics among members of a population (i.e., inter-individual variability) or for one individual over time (intra-individual variability)*" (EPA, 2001c). The risk assessment was designed to reflect critical sources of variability to the extent allowed by available methods and data and given the resources and time available.

On the other hand, uncertainty is "*the lack of knowledge about specific variables, parameters, models, or other factors*" (EPA, 2001c) and can be described qualitatively or quantitatively. Uncertainties in the risk assessment can raise or lower the confidence of the risk estimates. In this assessment, the uncertainty analysis also included a discussion of data gaps/limitations.

The next section describes the uncertainties and data gaps in the exposure, hazard/dose-response and risk characterization.

2.8.1 Uncertainties in the Occupational and Consumer Exposure Assessments

The production volume and release information on TCE are estimates and the actual TCE production or import data may differ from these estimates. The 2011 production volume and use data used in this assessment were published recently and are considered reliable. The vast majority of the TCE used in the U.S. is as an intermediate for the production of a refrigerant (83.6%) and the second highest use (in terms of production volume) is as a degreaser (~14.7%). Confidence in the remaining uses (*i.e.*, <2 percent of the production volume) is less certain.

EPA/OPPT expects dermal exposures under some conditions during the occupational and consumer user of TCE in degreaser and arts/crafts products. However, dermal exposures were not evaluated in this assessment.

2.8.1.1 Small Commercial Degreasing Operations

Releases of and exposures to TCE can vary from one degreasing facility to the next. EPA/OPPT attempted to quantify this uncertainty by evaluating multiple scenarios to establish a range of releases and exposures.

1. ***Releases:*** EPA/OPPT used data from NEI and TRI to estimate releases of TCE into the workplace. EPA/OPPT's estimate was found to be similar in magnitude to release estimates reported in publications and to estimates based on regulatory emission limits.

— This indicates that NEI and TRI are adequate data sources for developing order of magnitude estimates.

— However, rather than just use one release estimate, EPA/OPPT used a range of release estimates (based on the additional sources identified), thus incorporating this uncertainty into its assessment.

2. ***Exposures:*** EPA/OPPT compared its estimated range of exposures to field measurements obtained from OSHA. EPA/OPPT's estimates and OSHA values were of the same order of magnitude (Figure 2-2); EPA/OPPT's exposure range captured approximately 95% of OSHA field measurements with the higher end values of the monitoring data not covered by EPA estimates.

   — EPA/OPPT used a NF/FF mass balance model to estimate workplace exposures. These exposure estimates depend on model inputs. Rather than just use a single value for model inputs, we used ranges for the model inputs.
      - For example, based on data in the literature, ranges were used for parameters such as the room volume, air exchange rate, TCE emissions into the workplace and effectiveness of engineering controls.

      - Based on comments received from external peer review, certain parameter inputs were deemed adequate and thus were not varied; parameters such as the indoor air velocity, the size of the near field region, and hours of operation.

3. ***Population Exposed:*** EPA/OPPT estimated the number of workers and occupational bystanders potentially exposed to TCE based on a NIOSH survey from the 1980s and on the number of small degreasing facilities.

   — Regarding the NIOSH survey, EPA/OPPT normalized these data by estimating the number of workers potentially exposed to TCE on a per facility basis.
      - Use of TCE in degreasing has been on the decline, leading to a decline in the number of facilities.

      - By using a more recent estimate for number of facilities, EPA/OPPT's estimate likely captures this downward trend and provides an adequate order of magnitude estimate. However, this is our judgment and more recent and relevant survey data were not identified for the purposes of comparison.

   — EPA/OPPT estimated the number of degreasing facilities based on EPA's 2006 risk assessment for the halogenated solvent cleaning source category. Since use of TCE in degreasing has been on the decline, this assumption may overestimate the number of facilities and thus the size of the population exposed.

2.8.1.2 Spot Cleaning at Dry Cleaning Facilities

Releases of and exposures to TCE can vary from one dry cleaning facility to the next. EPA/OPPT attempted to quantify this uncertainty by evaluating multiple scenarios to establish a range of releases and exposures.

For this assessment, EPA relied on a 2007 study specific to spot cleaning at dry cleaning facilities in the state of California (CalEPA/EPA, 2007). Dry cleaning facilities in California are assumed to be representative of dry cleaning facilities in the United States. However, this may not be the case; how this assumption impacts EPA's release and exposure assessment is unclear.

1. ***Releases:*** To estimate releases, EPA/OPPT assumed that the entire amount of TCE used for spot cleaning was available for evaporation and thus could be emitted into the workplace. The basis for this assumption is that after spot cleaning, garments are usually queued in a basket prior to the next operation. However, this assumption can overestimate releases of TCE into the workplace.

2. **Exposures:** EPA/OPPT compared its exposure estimates to field measurements performed by NIOSH; these measurements were specific to spot cleaning with TCE. NIOSH measurements were within EPA/OPPT's estimated exposure range.

   — EPA/OPPT used a NF/FF mass balance model to estimate workplace exposures. These exposure estimates depend on model inputs. We used ranges for the model inputs rather than using a single value.
      - For example, based on data in the literature, ranges were used for parameters such as the room volume, air exchange rate, TCE emissions into the workplace and effectiveness of engineering controls.

      - Based on comments received from an external peer review, certain parameter inputs were deemed adequate and thus were not varied; parameters such as the indoor air velocity and the size of the near field region.

3. ***Population Exposed:*** EPA/OPPT estimated the number of workers and occupational bystanders potentially exposed to TCE based on U.S. Census data. Data on number of workers were not adjusted to exclude job categories that likely would not be present at dry cleaning facilities. Thus, EPA/OPPT's estimate likely overestimates the size of the population exposed.

2.8.1.3 Degreaser and Arts/Crafts Uses in Residential Settings

Uncertainties in the consumer exposure assessment arise from the following sources:

1. ***Consumer use information***: Although EPA/OPPT found information about TCE products intended for consumer use, there is some general uncertainty regarding the nature and extent of the consumer use of TCE for the products under the scope of this assessment.

2. ***Model assumptions and input parameters***: The use patterns assumed for the two consumer products, including mass of product used per event, duration of event, and events per year, were hypothetical and not based on consumer product survey data since this was lacking. Therefore, they are likely the source of the greatest uncertainties/data gaps in the exposure estimates for the two hobbyist products. However, there is a high degree of confidence in the consumer product weight fractions identified for the two consumer products evaluated in this assessment. Also, there is a medium to high degree of confidence in certain modeling inputs to the CEM model, including vapor pressure, molecular weight, room volumes, whole house volume, air exchange rate, body weight, and inhalation rate.

   There is no chamber data available for the products modeled in the exposure assessment, thus CEM calculated the mass of TCE entering the room of use by relying on data from a paper that studied the emission rates of solvents off a surface (Chinn, 1981). The spray degreaser results in only TCE being on the surface so it fits well into the Chinn data set, however the spray fixative product does have other components that may affect the evaporation rate of TCE. This introduces uncertainty and a further discussion of this issue is in Appendix I.

3. **Conversion of acute dose rates to air concentrations:** Because the E-FAST2/CEM model outputs for exposure to the user and bystander scenarios are reported in mg/kg-bw/day, it was necessary to convert these values to air concentrations (ppm) in order to perform the non-cancer and cancer risk assessment. This conversion introduces some uncertainty, but it is not apparent whether it may over- or under-estimate exposures.

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2.8.2 Uncertainties in the Hazard and Dose-Response Assessments

2.8.2.1 Uncertainties in the Cancer Hazard/Dose-Response Assessments

The cancer IUR for TCE was based on human kidney cancer risks reported by Charbotel et al. (2006) and adjusted for potential risk for NHL and liver cancer based on human epidemiological data (EPA, 2011e). U.S. EPA has high confidence in the overall derivation of the cancer IUR because it was based on good quality human data and it was similar to unit risk estimates derived from multiple rodent bioassays (EPA, 2011e). Moreover, the assumption of linearity in the relationship between TCE exposure and probability of cancer was based on sufficient weight of evidence supporting a mutagenic mode of action for at least TCE-induced kidney tumors (EPA, 2011e). However, there is insufficient information about the operational modes of actions for the other TCE-induced cancers (e.g., NHL, liver) supporting the default linear approach to estimate cancer risks in the low-dose region (EPA, 2011e).

Although uncertainties arising from animal to human extrapolation were not present in the IUR derivations due to use of human data, other sources of uncertainty exist in the cancer dose-response models and human data used to derive the IUR. These uncertainties are briefly listed and summarized below from information discussed in the TCE IRIS assessment (EPA, 2011e).

1. A source of uncertainty is the cancer dose-response model used to estimate the POD for the IUR derivations. A weighted linear regression model was used to fit the epidemiological data reported by Charbotel et al. (2006). Although a linear model is a good general approach for human studies with limited data, it cannot be ruled out that other alternate model would have performed better than the linear model (EPA, 2011e).

2. There is some evidence that exposure misclassification occurred for some of the cases reported by Charbotel et al. (2006) as a result of retrospectively estimating the cumulative TCE exposures of those that participated in the case-control study. The inhalation unit risk could be under- or overestimated depending on the directional bias of the exposure estimates (EPA, 2011e).

3. Charbotel et al. (2006) accounted for many potential confounding or modifying factors such as exposure to other solvents, lead, ionizing radiation, cutting fluids and other petroleum oils, medical history (e.g., kidney stones, infection, chronic dialysis) and lifestyle information (e.g., smoking, coffee intake). These confounding factors were expected to minimally impact the IUR, but it is possible that other missing factors could influence the cancer slope estimate (EPA, 2011e).

4. There are possible uncertainties associated with the inclusion of a lag period in the analysis of the cancer data. This lag period intended to discount those recent TCE exposures not likely to contribute to the reported cancer incidence in Charbotel et al. (2006). It seems that the lag period might not be an important factor in Charbotel et al. (2006) based on

published (Charbotel et al., 2006) and unpublished analyses (Charbotel et al., 2005) showing similar results in the absence or presence of a lag period (EPA, 2011e).

5. The cancer IUR derived from the Charbotel et al. (2006) renal cancer data was further adjusted to account for other types of cancer (i.e., liver cancer and NHL). There are uncertainties related to the data analysis and assumptions used for the adjustment calculations (EPA, 2011e). For instance, comparisons of the relative contributions to extra cancer risk for two different data sets showed that the results were within 25% of the selected adjustment factor of 4, which shows that the selected factor is reasonable. Also, there are uncertainties related to the association between TCE exposure and increased risks of cancer at multiple sites. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for NHL, but less convincing than for kidney cancer, and more limited for liver cancer (EPA, 2011e). Further support for TCE's carcinogenic characterization comes from positive results in multiple rodent cancer bioassays (EPA, 2011e). Overall, there is sufficient evidence to adjust the IUR for three cancer types. Alternatively, if the IUR would have been derived for two cancer types (i.e., kidney and NHL), the cancer IUR estimate would be reduced by 25%.

2.8.2.2 Uncertainties in the Non-Cancer Hazard/Dose-Response Assessments

EPA/OPPT's risk assessment relied on the PBPK-derived hazard values (i.e., HECs) published in the latest EPA IRIS assessment on TCE (EPA, 2011e). These hazard values were used to estimate acute and chronic risks to various health effects following TCE exposure related to specific TCE uses.

The TCE IRIS assessment conducted a comprehensive discussion of the uncertainties inherent to the data, assumptions and models used to support the derivation of the chronic non-cancer PODs for different health effects domains. Below is a summary of the major uncertainties affecting the non-cancer hazard/dose response approach of this assessment. The reader is referred to the TCE IRIS assessment to obtain details about the non-cancer uncertainty analysis (EPA, 2011e).

Uncertainties in the acute and chronic hazard values stem from the following sources:

1. **Non-cancer hazard values (e.g., NOAELs, LOAELs, BMD):** The TCE IRIS assessment identified PODs from human and animal studies that were suitable for dose-response analysis. The process of identifying PODs for various health effects domains involved the evaluation of the strengths and limitations of the data and the weight of evidence for a particular health effects domain before supporting an association between TCE exposure and various human health effects. The TCE IRIS assessment issued confidence statements for the different health effects domains/studies as part of the uncertainty analysis. However, there are uncertainties about the selected PODs since the values (e.g., NOAEL, LOAEL or BMD) depend on the current available data and could change as additional studies are published (EPA, 2011e).

Also, when selecting a BMD as a POD, the selection of the benchmark dose response (BMR) (e.g., 1%, 5% or 10% level) directly affects the calculation of the BMD. There are uncertainties related to the BMRs since their selection depends on scientific judgments on the statistical and biological characteristics of the dataset and how the BMDs will be finally used (EPA, 2012a).

In addition, there are uncertainties about the appropriate dose-response model used to generate the BMDs. However, these uncertainties should be minimal if the chosen model fits well the observable range of the data, as discussed in the BMDS guidance (EPA, 2012a).

2. **Duration adjustment to continuous exposure:** Most of the PODs used to derive PBPK-derived HECs came from studies that did not expose animals or humans to TCE on a continuous basis. These PODs were then mathematically adjusted to reflect equivalent continuous exposures (daily doses) over the study exposure period under the assumption that the effects are related to concentration × time (C x t), independent of the daily (or weekly) exposure regimen (EPA, 2011e). However, the validity of this assumption is generally unknown, and, if there are dose-rate effects, the assumption of C × t equivalence would tend to bias the POD downwards (EPA, 2011e).

3. **Extrapolation of repeated dose developmental effects to acute scenarios:** There are uncertainties related to whether developmental effects observed in developmental toxicity studies may result from a single exposure to TCE. In this assessment, the acute risk assessment used the hazard value for fetal cardiac defects derived from the Johnson et al. developmental toxicity studies.

   Previously identified uncertainties in the Johnson et al. studies have focused on methodological and reproducibility issues. The author recently published an errata (Johnson, 2014) to update the public record regarding Johnson et al. (2003). However, some questions on that study remain unresolved, i.e., the precise dates that each individual control animal was on study and the detailed results of analytical chemistry testing for dose concentration.

   Additional possible sources of uncertainty identified for the Johnson et al. studies include that the research was conducted over a 6-year period, combined control data were used for comparison to treated groups, and possible imprecision of exposure characterization due to the use of tap water in the Dawson et al. (1993) study and TCE intake values that were derived from water consumption measures of group housed animals.

   On the other hand, the strengths of the Johnson et al. studies include the examination of fetal hearts without knowledge of treatment (or control) group, standardized methods of fetal evaluation, examination of the gross (*in situ*) and internal structure of the fetal hearts by a group of 3 senior researchers, confirmation of cardiac anomalies by consensus agreement, and that the researchers shared individual fetal and litter cardiac abnormality

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data for treated groups with EPA, thereby facilitating independent statistical analysis of the data.

The potential hazard for congenital malformations is supported by a weight of evidence analysis of the weakly suggestive epidemiological data in combination with the findings of the animal and mechanistic studies with TCE and its metabolites (EPA, 2011e). The robustness of the weight of evidence analysis gives greater confidence to the hazard conclusions for fetal cardiac defects (Appendix N).

Furthermore, it is unknown if a higher exposure level of TCE may be required to induce fetal cardiac malformations following a single exposure in light of the short critical window of vulnerability of cardiac development and the absence of data for a very short window of exposure. A single exposure to TCE at a critical window of fetal development may produce adverse developmental effects (EPA, 1991). This was assumed to be a health protective approach.

4. **PBPK model--structure, parameters and model fits:** There are uncertainties associated with the various steps of the model development process of the TCE PBPK model. Most of the assumptions underlying the PBPK model structure are well established for volatile, lipophilic chemicals such as TCE. Thus, these assumptions are unlikely to introduce much bias or inaccuracy in the modeling results. In addition, the model provided reasonable fits to an extraordinarily large database of *in vivo* pharmacokinetic data in rodents and humans (EPA, 2011e).

   Moreover, posterior parameter distributions were generated by Markov Chain Monte Carlo (MCMC) sampling, which employed a hierarchical Bayesian population statistical model and the available *in vivo* data (EPA, 2011e). As stated in EPA (2011e), *"[c]onvergence of the MCMC samples for model parameters was good for mice, and adequate for rats and humans. Evaluation of posterior parameter distributions suggest[ed] reasonable results in light of prior expectations and the nature of the available calibration data"*. Interestingly, the model predictions in rats and humans were consistent with *in vivo* data from many studies that were not used for the calibration process. Furthermore, local sensitivity analyses were conducted and confirmed that most of the scaling parameters were informed by at least some of the calibration data, and those that were not, either were informed by prior data or would not have great impact on dose-metric predictions (EPA, 2011e).

5. **PBPK model—dose metrics:** Dose-response analysis using PBPK modeling prefers dose-metrics that are closely associated with one or more key events that lead to the selected critical effect (i.e., toxic endpoint of concern). Additional uncertainties exist about the appropriate dose-metric for a particular toxic endpoint, although for some effects, there was better information about relevant dose-metrics than for others (EPA, 2011e).

   Moreover, the dose-metric predictions were evaluated for the degree to which the simulations have converged to the true posterior distribution, the combined uncertainty

and population variability, the degree of uncertainty in particular human population percentiles and the degree to which the model predictions are consistent with *in vivo* data (EPA, 2011e).

The analysis showed that the TCE PBPK model appears to be most reliable for the fluxes of total, oxidative, and hepatic oxidative metabolism. In addition, modest uncertainty was found for dose-metrics related to blood levels of TCE and oxidative metabolites, TCOH and TCA. For GSH metabolism, the GSH conjugation predictions had a lower confidence than those dose-metrics based on the parent compound, total metabolism or oxidative metabolites (EPA, 2011e). Predictions for other oxidative metabolism and respiratory oxidative metabolism generally had somewhat more uncertainty than the TCE and metabolism metrics (EPA, 2011e).

6. **PBPK model—population variability:** The TCE PBPK model used a Bayesian population analysis to systematically estimate model parameters and characterize their uncertainty and variability. Although labor intensive, this approach characterized uncertainty and variability in a highly transparent and objective manner (EPA, 2011e). The reader is referred to the TCE IRIS assessment for detailed information about the uncertainties of the PBPK model, specifically Chapters 3 and 6 as well as Appendix A (EPA, 2011e). Below are the highlights of the discussion of the uncertainties of the PBPK modeling approach.

   The predictions of population variability were based on prior and population distributions. These selected distributions may introduce inaccuracies in the predictions of population variability (EPA, 2011e). However, the impact of the chosen distributions was limited to the human variability related to GSH conjugation, which resulted in changes in the dose-metric predictions (EPA, 2011e). There are also uncertainties regarding how the PBPK modeling results address the pharmacodynamic variability of the susceptible human subpopulations exposed to TCE (EPA, 2011e).

   Furthermore, the hierarchical model did not consider certain sources of variability, such as between-animal variability in rodents and between-occasion variability in humans. Instead, they were aggregated with other sources of variability in a residual error term (EPA, 2011e). It seems that this approach did not introduce significant bias in the modeling estimates because the residuals between predictions and data do not overall appear systematically high or low (EPA, 2011e).

7. **PBPK model—developmental toxicity:** The TCE PBPK model does not have a fetus/gestational compartment. The lack of this compartment introduces uncertainty in the modeling estimates (i.e., HECs) for developmental effects. Inclusion of a fetus/gestational compartment would require additional *in vivo* or *in vitro* metabolism data to ensure model identifiability (EPA, 2011e).

8. **PBPK model—route-to-route extrapolation:** PBPK-derived hazard values were based on PODs from either inhalation or oral studies. The TCE PBPK model used interspecies and

route-to-route extrapolation approaches to convert both the inhalation and oral PODs to human internal doses. Then, the model estimated the human equivalent concentrations needed to produce the human internal doses. Since the PBPK model was used, the uncertainties associated with using oral studies for inhalation exposures were minimized.

2.8.3 Uncertainties in the Risk Assessment

The non-cancer acute or chronic risks were expressed in terms of MOEs. MOEs are obtained by comparing the hazard values (i.e., HEC_{50}, HEC_{95} or HEC_{99}) for various TCE-related health effects with the exposure concentrations for the specific use scenarios. Given that the MOE is the ratio of the hazard value divided by the exposure, the confidence in the MOEs is directly dependent on the uncertainties in the hazard/dose-response and exposure assessments that supported the hazard and exposure estimates used in the MOE calculations.

The total UF for each non-cancer PBPK-derived POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The UFs accounted for various endpoint/study-specific uncertainties in the hazard values, such as:

1. **Animal-to-human extrapolation (UF_A):** The UF_A accounts for the uncertainties in extrapolating from rodents to humans. In the absence of data, the default UF_A of 10 is adopted which breaks down to a factor of 3 for toxicokinetic variability and a factor of 3 for pharmacodynamic variability. The TCE PBPK model accounted for the interspecies extrapolation using rodent pharmacokinetic data to estimate internal doses for a particular dose metric, thus reducing the interspecies toxicokinetic uncertainty to 1. Since the PBPK model did not address interspecies toxicodynamic differences, the total UF_A of 3 was retained for all of the PBPK-derived HECs, unless a human study was the source of the POD. In that case, the UF_A was set to 1 (EPA, 2011e).

2. **Inter-individual variation (UF_H):** The UF_H accounts for the variation in sensitivity within the human population. In the absence of data, the default UF_H of 10 is adopted which breaks down to a factor of 3 for toxicokinetic variability and a factor of 3 for pharmacodynamic variability. The TCE PBPK model reduced the human toxicokinetic variability to 1, but not the human toxicodynamic variability. Thus, the total UF_H was 3 for all of the PBPK-derived HECs. This is because the PBPK model does not address the uncertainties regarding the susceptibility of the human subpopulations to TCE exposure and the extent of pharmacodynamics variability (EPA, 2011e).

3. **Database uncertainty factor (UF_D):** The UF_D accounts for deficiencies in the toxicity database that may result in a lower hazard value. The database for TCE toxicity is extensive with studies for many different types of effects, including two-generation reproductive studies, as well as neurological and immunological studies (EPA, 2011e). Thus, a UF_D of 1 was retained for all of the PBPK-derived HECs discussed in the OPPT's risk assessment.

4. **Extrapolation from subchronic to chronic (UF_S):** The UF_S accounts for the uncertainty in extrapolating from a subchronic to a chronic POD. UF_S ranging from 3 to 10 were used in some of the PBPK-derived HECs. Typically, a UF_S of 1 was used to extrapolate a POD from a less-than-chronic developmental toxicity study to a chronic exposure. Developmental PBPK-derived HECs did not use a higher UF_S because the developmental period is recognized as a susceptible life stage where exposure during certain time windows is more relevant to the induction of developmental effects than lifetime exposure (EPA, 1991).

5. **LOAEL-to-NOAEL extrapolation (UF_L):** The UF_L accounts for the uncertainty in extrapolating from a LOAEL to a NOAEL. A value of 10 is the standard default UF_L value, although lower values (e.g., 3) can be used if the effect is considered minimally adverse at the LOAEL or is an early marker for an adverse effect (EPA, 2011e). UF_L ranging from 3 to 30 (i.e., 3, 10 or 30) were used in the PBPK-derived HECs. For one of the kidney PODs (NCI, 1976), a UF_L value of 30 was used because the incidence rate for the adverse effect was ≥90% at the LOAEL (EPA, 2011e).

Unlike cancer risks, an MOE exceeding the benchmark MOEs is an indicator that there is a potential risk and cannot be translated to a probability that certain adverse health effects would occur. Also, those MOEs that exceed but remain close to the benchmark MOE do not necessarily mean that adverse effects would occur.

The chronic non-cancer risks for the occupational scenarios assumed that the human health risks are constant for a working lifetime based on the exposure assumptions used in the occupational exposure assessment. However, the risks could be under- or over-estimated depending on the variations to the exposure profile of the workers and occupational bystanders using TCE-containing degreasers and spot cleaners.

Regarding exposure to TCE through the skin, the impact of dermal exposures on human health risks was not assessed in this assessment for the consumer and occupational scenarios. Exclusion of dermal exposures is expected to underestimate the risks of the selected TCE uses. This would likely be an issue of concern in those exposure scenarios that resulted in a "no-risk" finding, especially those that reported MOEs close to the benchmark MOE, but still above the benchmark.

As discussed previously, the cancer risk estimates were based on the assumption of linearity in the relationship between TCE exposure and probability of cancer. Uncertainties are introduced in the cancer risks when there is limited information justifying the liner cancer dose-response model when compared to other available models. In the case of TCE, the cancer IUR was based on reliable data supporting a mutagenic mode of action for at least TCE-induced kidney tumors (EPA, 2011e). The IUR was adjusted to account for other types of TCE-induced cancers (e.g., NHL, liver). There is some uncertainty about the validity of the linear approach for these other cancers since there was insufficient information about the modes of actions underlying the onset of these cancers following chronic exposure to TCE (EPA, 2011e).

2.9 CONCLUSIONS OF THE HUMAN HEALTH RISK ASSESSMENT

EPA/OPPT's risk assessment focused on uses of TCE as a degreaser both in small commercial settings and consumers, the commercial use of TCE as a spotting agent in dry cleaning shops, and the consumer use of TCE in a clear protective coating spray by individuals in the arts/crafts field. In this assessment, EPA/OPPT estimated the size of the population at risk as:

- Approximately 30,000 workers and occupational bystanders at small commercial degreasing operations.
- Approximately 300,000 workers and occupational bystanders at dry cleaning operations.
- No data were available to estimate the number of consumers and bystanders exposed to TCE during the use of degreasers and arts/crafts clear protective coating spray.

In summary, the risk assessment showed the following risk findings:

Cancer Risks

1. There are cancer risk concerns for users and bystanders occupationally exposed to TCE when using TCE-containing degreasers and spot cleaners in small commercial shops and dry cleaning facilities, respectively.
2. Many of the degreaser and spot cleaning exposure scenarios exceed the target cancer risks of 10^{-6}, 10^{-5} and 10^{-4}.
3. The occupational exposures to commercial degreasers show the greatest cancer risk when compared to the spot cleaning exposure scenarios.

Acute Non-Cancer Risks:

1. There are acute non-cancer risks for developmental effects (i.e., cardiac defects) for most occupational and residential exposure scenarios (i.e., MOEs were below the benchmark MOE of 10).
2. The degreaser exposure scenarios show greater acute risks for developmental effects than those reported for the spot cleaning exposure scenarios.

Chronic Non-Cancer Risks:

1. There are chronic non-cancer risks for a range of human health effects in both occupational degreaser and spot cleaning exposure scenarios (i.e., MOEs were below the benchmark MOE).

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2. The greatest concern is for developmental effects (i.e., fetal cardiac defects), followed by kidney effects and then immunotoxicity, with an overall higher chronic risk for the degreaser exposure scenarios. In general, this concern is irrespective of the type of exposure (typical vs worst case) and the availability of room ventilation (LEV vs no LEV).

3. There are chronic risks for reproductive effects and neurotoxicity for degreaser worker exposure scenarios and most of the degreaser bystander exposure scenarios. However, the risks concerns for these effects are reported for fewer spot cleaning worker/bystander scenarios and generally attributed to exposure conditions without room ventilation.

4. There are chronic risks for liver effects although the risks are less prominent than those reported for other health effects domains. These risks are found only in the degreaser worker/bystander exposure worst case scenarios and the spot cleaning worker/bystander worst case scenarios with no LEV.

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3 References

Arito, H., M. Takahashi, and T. Ishikawa. 1994. *Effect of Subchronic Inhalation Exposure to Low-Level Trichloroethylene on Heart Rate and Wakefulness-Sleep in Freely Moving Rats.* Sangyo Igaku/Japanese Journal of Industrial Health (Japan), 36(1), 1-8. (as cited in EPA, 2011e).

Ash, M., and I. Ash. 2009. 1,1,2-Trichloroethylene. In Ash, M. , and I. Ash, *Handbook of Industrial Chemical Additives* (2nd ed., Vol. 2). Synapse Information Resources.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. *Toxicological Profile for Trichloroethylene*. Division of Toxicology, Toxicology Information Branch, Atlanta, GA. http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf.

ATSDR (Agency for Toxic Substances and Disease Registry). 1998. *Volatile Organic Compounds in Drinking Water and Adverse Pregnancy Outcomes. United States Marine Corps Base, Camp Lejeune, NC*. PB98-156540. Atlanta, GA. http://www.atsdr.cdc.gov/hs/lejeune/. (as cited in EPA, 2011e).

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. *Update on the Status of the Superfund Substance-Specific Applied Research Program*. 64 Federal Register 10 (January 15, 1999), pp. 2760-2790.

ATSDR (Agency for Toxic Substances and Disease Registry). 2001. *Final Report: Evaluation of Priority Health Conditions in a Community with Historical Contamination by Trichloroethylene*. U.S. Department of Health and Human Services, Atlanta, GA. (as cited in EPA, 2011e).

ATSDR (Agency for Toxic Substances and Disease Registry). 2006. *Health Consultation: Endicott Area Investigation: Health Statistics Review: Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York*. U.S. Department of Health and Humans Services, Atlanta, GA. http://www.atsdr.cdc.gov/HAC/pha/EndicottAreaInvestigation/EndicottHealthStatsReviewHC052606.pdf. (as cited in EPA, 2011e).

ATSDR (Agency for Toxic Substances and Disease Registry). 2008. *Health Consultation: Health Statistics Review Follow-Up: Cancer and Birth Outcome Analysis: Endicott Area Investigation, Endicott Area, Town of Union, Broome County, New York*. U.S. Department of Health and Human Services, Atlanta, GA. http://www.atsdr.cdc.gov/hac/pha//EndicottAreaInvestigationFollowUp/EndicottAreaHC051508.pdf. (as cited in EPA, 2011e).

ATSDR (Agency for Toxic Substances and Disease Registry). 2011. *Priority List of Hazardous Substances*. Division of Toxicology and Environmental Medicine, Atlanta, GA. http://www.atsdr.cdc.gov/SPL/.

Baldwin, P. E., and A. D. Maynard. 1998. *A Survey of Wind Speeds in Indoor Workplaces*. Annals of Occupational Hygiene, 42(5), 303-313.

Bernad, P. G., S. Newell, and D. A. Spyker. 1987. *Neurotoxicity and Behavior Abnormalities in a Cohort Chronically Exposed to Trichloroethylene*. Veterinary and Human Toxicology, 29(6), 475. (as cited in EPA, 2011e).

Blossom, S. J., C. A. Cooney, S. B. Melnyk, J. L. Rau, C. J. Swearingen, and W. D. Wessinger. 2013. *Metabolic Changes and DNA Hypomethylation in Cerebellum Are Associated with Behavioral Alterations in Mice Exposed to Trichloroethylene Postnatally*. Toxicology and Applied Pharmacology, 269(3), 263-269.

Blossom, S. J., S. Melnyk, C. A. Cooney, K. M. Gilbert, and S. J. James. 2012. *Postnatal Exposure to Trichloroethylene Alters Glutathione Redox Homeostasis, Methylation Potential, and Neurotrophin Expression in the Mouse Hippocampus*. Neurotoxicology, 33(6), 1518-1527.

BLS (Bureau of Labor Statistics). 2012. *Occupational Employment Statistics: Laundry and Dry-Cleaning Workers*. U.S. Department of Labor, Washington, DC. http://www.bls.gov/oes/current/oes516011.htm (accessed on January 7, 2014).

Bove, F. J. 1996. *Public Drinking Water Contamination and Birthweight, Prematurity, Fetal Deaths, and Birth Defects*. Toxicology and Industrial Health, 12(2), 255-266. (as cited in EPA, 2011e).

Bove, F. J., M. C. Fulcomer, J. B. Klotz, J. Esmart, E. M. Dufficy, and J. E. Savrin. 1995. *Public Drinking Water Contamination and Birth Outcomes*. American Journal of Epidemiology, 141(9), 850-862. (as cited in EPA, 2011e).

Boyer, A., W. Finch, and R. Runyan. 2000. *Trichloroethylene Inhibits Development of Embryonic Heart Valve Precursors in Vitro*. Toxicological Sciences, 53(1), 109-117. (as cited in EPA, 2011e).

Bross, G., D. DiFranceisco, and M. E. Desmond. 1983. *The Effects of Low Dosages of Trichloroethylene on Chick Development*. Toxicology, 28(4), 283-294. (as cited in EPA, 2011e).

Buben, J. A., and E. J. O'Flaherty. 1985. *Delineation of the Role of Metabolism in the Hepatotoxicity of Trichloroethylene and Perchloroethylene: A Dose-Effect Study*. Toxicology and Applied Pharmacology, 78, 105-122. (as cited in EPA, 2011e).

Burg, J., and G. Gist. 1997. *The Potential Impact on Women from Environmental Exposures.* Journal of Women's Health, 6(2), 159-161. (as cited in EPA, 2011e).

Caldwell, P. T., P. A. Thorne, P. D. Johnson, S. Boitano, R. B. Runyan, and O. Selmin. 2008. *Trichloroethylene Disrupts Cardiac Gene Expression and Calcium Homeostasis in Rat Myocytes*. Toxicological Sciences, 104(1), 135-143. (as cited in EPA, 2011e).

CalEPA/EPA (California Environmental Protection Agency/U.S. Environmental Protection Agency). 2007. *Spotting Chemicals: Alternatives to Perchloroethylene and Trichloroethylene in the Textile Cleaning Industry*. Report prepared for CalEPA/U.S.EPA by K. Wolf and M. Morris from the Institute for Research and Technical Assistance. http://www.irta.us/reports/DTSC%20Spotting%20Chemical%20for%20Web.pdf.

Carney, E. W., B. A. Thorsrud, P. H. Dugard, and C. L. Zablotny. 2006. *Developmental Toxicity Studies in Crl:CD (SD) Rats Following Inhalation Exposure to Trichloroethylene and Perchloroethylene*. Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 77(5), 405-412. (as cited in EPA, 2011e).

Charbotel, B., J. Fevotte, M. Hours, J. L. Martin, and A. Bergeret. 2005. *Case-Control Study on Renal Cell Cancer and Occupational Trichloroethylene Exposure, in the Arve Valley (France)*. Institut Universitaire de Médecine du Travail, UMRESTTE, Université Claude Bernard, Lyon, France. http://hal.archives-ouvertes.fr/docs/00/54/59/80/PDF/charbotel_octobre_05.pdf. (as cited in EPA, 2011e).

Charbotel, B., J. Fevotte, M. Hours, J. L. Martin, and A. Bergeret. 2006. *Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part 2: Epidemiological Aspects*. Annals of Occupational Hygiene, 50(8), 777-787. (as cited in EPA, 2011e).

Chia, S., C. Ong, M. Tsakok, and A. Ho. 1996. *Semen Parameters in Workers Exposed to Trichloroethylene*. Reproductive toxicology, 10(4), 295-299. (as cited in EPA, 2011e).

Chinn, K. S. K. 1981. *A Simple Model for Predicting Chemical Agent Evaporation*. U.S. Department of Defense, Defense Technical Information Center, Cameron Station, Alexandria, VA. http://www.epa.gov/opptintr/exposure/presentations/efast/chinn_1981_a_simple_method_for_predicting.pdf.

Chiu, W. A., S. Micallef, A. C. Monster, and F. Y. Bois. 2007. *Toxicokinetics of Inhaled Trichloroethylene and Tetrachloroethylene in Humans at 1 Ppm: Empirical Results and Comparisons with Previous Studies*. Toxicological Sciences, 95(1), 23-36. (as cited in EPA, 2011e).

Chiu, W. A., M. S. Okino, and M. V. Evans. 2009. *Characterizing Uncertainty and Population Variability in the Toxicokinetics of Trichloroethylene and Metabolites in Mice, Rats, and Humans Using an Updated Database, Physiologically Based Pharmacokinetic (PBPK) Model, and Bayesian Approach*. Toxicology and Applied Pharmacology, 241(1), 36-60. (as cited in EPA, 2011e).

Coble, J. (Occupational Safety and Health Administration). *OSHA IMIS TCE Exposure Data*. Personal Communication with: Choudhary, R. (U.S. Environmental Protection Agency, Washington, DC), November 26, 2013. EPA/OPPT request on TCE related data from OSHA.

Collier, J. M., O. Selmin, P. D. Johnson, and R. B. Runyan. 2003. *Trichloroethylene Effects on Gene Expression During Cardiac Development*. Birth Defects Research, Part A: Clinical and Molecular Teratology, 67(7), 488-495. (as cited in EPA, 2011e).

Culver, T. B., C. A. Shoemaker, and L. W. Lion. 1991. *Impact of Vapor Sorption on the Subsurface Transport of Volatile Organic Compounds: A Numerical Model and Analysis*. Water Resources Research, 27(9), 2259-2270.

Daubert, T. E., and R. P. Danner. 1989. *Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation.* New York, NY: Hemisphere Publishing Corporation, American Institute of Chemical Engineers, Design Institute for Physical Property Data.

Dawson, B., P. Johnson, S. Goldberg, and J. Ulreich. 1990. *Cardiac Teratogenesis of Trichloroethylene and Dichloroethylene in a Mammalian Model.* Journal of the American College of Cardiology, 16(5), 1304-1309. (as cited in EPA, 2011e).

Dawson, B., P. Johnson, S. Goldberg, and J. Ulreich. 1993. *Cardiac Teratogenesis of Halogenated Hydrocarbon-Contaminated Drinking Water*. Journal of the American College of Cardiology, 21(6), 1466-1472. (as cited in EPA, 2011e).

Dekant, W., M. Metzler, and D. Henschler. 1984. *Novel Metabolites of Trichloroethylene through Dechlorination Reactions in Rats, Mice and Humans*. Biochemical Pharmacology, 33(13), 2021-2027. (as cited in EPA, 2011e).

DHHS (Department of Health and Human Services). 2012. *Household Products Database*. Bethesda, MD. http://householdproducts.nlm.nih.gov/ (accessed on April 9, 2014).

Dilling, W. L., N. B. Tefertiller, and G. J. Kallos. 1975. *Evaporation Rates and Reactivities of Methylene Chloride, Chloroform, 1,1,1-Trichloroethane, Trichloroethylene, Tetrachloroethylene, and Other Chlorinated Compounds in Dilute Aqueous Solutions*. Environmental Science and Technology, 9(9), 833-838.

Drake, V., S. Koprowski, J. Lough, N. Hu, and S. Smith. 2006. *Trichloroethylene Exposure During Cardiac Valvuloseptal Morphogenesis Alters Cushion Formation and Cardiac Hemodynamics in the Avian Embryo*. Environmental Health Perspectives, 114(6), 842-847. (as cited in EPA, 2011e).

Drake, V. J., S. L. Koprowski, N. Hu, S. M. Smith, and J. Lough. 2006. *Cardiogenic Effects of Trichloroethylene and Trichloroacetic Acid Following Exposure During Heart Specification of Avian Development*. Toxicological Sciences, 94(1), 153-162. (as cited in EPA, 2011e).

DuTeaux, S., T. Berger, R. Hess, B. Sartini, and M. Miller. 2004. *Male Reproductive Toxicity of Trichloroethylene: Sperm Protein Oxidation and Decreased Fertilizing Ability*. Biology of Reproduction, 70, 1518-1526. (as cited in EPA, 2011e).

ECB (European Chemicals Bureau). 2000. *IUCLID Dataset for Trichloroethylene*. European Chemical Substances Information System, Joint Research Centre, Institute for Health and Consumer Protection, European Chemicals Bureau, Helsinki, Finland. http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/79016.pdf.

ECB (European Chemicals Bureau). 2004. *European Union Risk Assessment Report: Trichloroethylene (Cas No 79-01-6)*. EINECS No: 201-167-4. Joint Research Center, Institute for Health and Consumer Protection,European Chemicals Bureau, Helsinki, Finland.

Elovaara, E., K. Hemminki, and H. Vainio. 1979. *Effects of Methylene Chloride, Trichloroethane, Trichloroethylene, Tetrachloroethylene and Toluene on the Development of Chick Embryos*. Toxicology, 12(2), 111-119. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1979. *Water-Related Environmental Fate of 129 Priority Pollutants. Volume 2: Halogenated Aliphatic Hydrocarbons, Halogenated Ethers, Monocyclic Aromatics, Phthalate Esters, Polycyclic Aromatic Hydrocarbons, Nitrosamines, and Miscellaneous Compounds*. EPA-440/4-79-029B. Office of Water, Planning and Standards, Washington, DC.

EPA (U.S. Environmental Protection Agency). 1980. *Fate of Toxic and Hazardous Materials in the Air Environment*. EPA-600/3-80-084. Office of Research and Development, Research Triangle Park, NC.

EPA (U.S. Environmental Protection Agency). 1982. *Steam Electric Power Generating Point Source Category; Effluent Limitations Guidelines, Pretreatment Standards and New Source Performance Standards, Final Rule*. 47 Federal Register 224 (November 19, 1982), pp. 52290-52309.

EPA (U.S. Environmental Protection Agency). 1985a. *Assessment of Trichloroethylene as a Potentially Toxic Air Pollutant, Proposed Rule*. 50 Federal Register 246 (December 23, 1985), pp. 52422-52425.

EPA (U.S. Environmental Protection Agency). 1985b. *National Primary Drinking Water Regulations; Volatile Synthetic Organic Chemicals, Final Rule*. 50 Federal Register 219 (November 13, 1985), pp. 46880-46901.

EPA (U.S. Environmental Protection Agency). 1986a. *Clarification and Correction of Previously Published Notice on the Assessment of Trichloroethylene as a Potentially Toxic Air Pollutant*. 51 Federal Register 43 (March 5, 1986), pp. 7714.

EPA (U.S. Environmental Protection Agency). 1986b. *Guidelines for Mutagenicity Risk Assessment*. EPA/630/R-98/003. Risk Assessment Forum, Washington, DC. http://www.epa.gov/iris/backgrd.html. (as cited in EPA, 2011e).

EPA (U.S. Environmental Agency). 1986c. *Guidelines for the Health Risk Assessment of Chemical Mixtures*. EPA/630/R-98/002. Risk Assessment Forum, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1987a. *Household Solvent Products: A National Usage Survey*. Office of Toxic Substances, Washington, DC. http://www.epa.gov/oppt/exposure/presentations/efast/westat_1987b_household_solvent_products.pdf.

EPA (US Environmental Protection Agency). 1987b. *National Primary Drinking Water Regulations. Synthetic Organic Chemicals. Monitoring for Unregulated Contaminants, Final Rule*. 52 Federal Register 130 (Wednesday, July 8, 1987), pp. 25690-25696.

EPA (U.S. Environmental Protection Agency). 1987c. *Organic Chemicals and Plastics and Synthetic Fibers Category Effluent Limitations Guidelines, Pretreatment Standards, and New Source Performance Standards, Final Rule*. 52 Federal Register 214 (November 5, 1987), pp. 42522-42584.

EPA (U.S. Environmental Protection Agency). 1988a. *Recommendations for and Documentation of Biological Values for Use in Risk Assessment*. EPA/600/6-87/008. Office of Research and Development, Cincinnati, OH. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1988b. *Underground Injection Control Program: Hazardous Waste Disposal Injection Restrictions; Amendments to Technical Requirements for Class I Hazardous Waste Injection Wells. Additional Monitoring Requirements Applicable to All Class I Wells, Final Rule*. 53 Federal Register 143 (July 26, 1988), pp. 28118-28157.

EPA (U.S. Environmental Protection Agency). 1989. *Reportable Quantity Adjustments. Delisting of Ammonium Thiosulfate, Final Rule*. 54 Federal Register 155 (August 14, 1989), pp. 33426-33484.

EPA (U.S. Environmental Protection Agency). 1991. *Guidelines for Developmental Toxicity Risk Assessment*. EPA/600/FR-91/001. Risk Assessment Forum, Washington, DC. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=4560.

EPA (U.S. Environmental Protection Agency). 1992. *TCE Removal from Contaminated Soil and Groundwater*. EPA/540/S-92-002. Office of Research and Development and Office of Solid Waste and Emergency Response. Prepared by H.H. Russell, J.E. Matthews and G.W. Sewell, Washington, DC. http://www.epa.gov/superfund/remedytech/tsp/download/tce.pdf.

EPA (U.S. Environmental Protection Agency). 1994a. *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity Studies*. Office of Pesticide Products, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=186068. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1994b. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*. EPA/600/8-90/066F. Office of Research and Development, Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1994c. *National Emission Standards for Hazardous Air Pollutants for Source Categories. Organic Hazardous Air Pollutants from the Synthetic Organic Chemical Manufacturing Industry and Other Processes Subject to the Negotiated Regulation for Equipment Leaks, Final Rule*. 59 Federal Register 208 (October 28, 1994), pp. 54131-54132.

EPA (U.S. Environmental Protection Agency). 1994d. *National Emission Standards for Hazardous Air Pollutants: Halogenated Solvent Cleaning, Final Rule and Test Method*. 59 Federal Register 231 (December 2, 1994), pp. 61801-61828.

EPA (U.S. Environmental Protection Agency). 1994e. *Notice of Opportunity to Initiate Negotiations for TSCA-Section 4. Enforceable Consent Agreements; Solicitation of Testing Proposals for ATSDR Chemicals*. 59 Federal Register 189 (September 30, 1994), pp. 49934-49938.

EPA (U.S. Environmental Protection Agency). 1995a. *EPA Office of Compliance Sector Notebook Project. Profile of the Dry Cleaning Industry*. EPA/310-R-95-001. Office of Compliance, Office of Enforcement and Compliance Assurance, Washington, DC.

http://www.epa.gov/compliance/resources/publications/assistance/sectors/notebooks/index.html.

EPA (U.S. Environmental Protection Agency). 1995b. *Final Water Quality Guidance for the Great Lakes System, Final Rule*. 60 Federal Register 56 (March 23, 1995), pp. 15366-15425.

EPA (U.S. Environmental Protection Agency). 1995c. *The Use of the Benchmark Dose Approach in Health Risk Assessment*. EPA/630/R-94/007. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/useof-bda-healthrisk.htm. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1996. *Guidelines for Reproductive Toxicity Risk Assessment*. EPA/630/R-96/009. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/pdfs/REPRO51.PDF. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1997. *Exposure Factors Handbook*. EPA/600/P-95/002F a-c. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12464.

EPA (U.S. Environmental Protection Agency). 1998a. *Guidelines for Neurotoxicity Risk Assessment*. EPA/630/R-95/001F. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/pdfs/NEUROTOX.PDF. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 1998b. *Hazardous Waste Combustors; Revised Standards; Final Rule- Part 1: RCRA-Comparable Fuel Exclusion; Permit Modifications for Hazardous Waste Combustion Units; Notification of Intent to Comply; Waste Minimization and Pollution Prevention Criteria for Compliance Extensions*. 63 Federal Register 118 (June 19, 1998), pp. 33782-33829.

EPA (U.S. Environmental Protection Agency). 1998c. *Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft)*. EPA/600/R-98/051. Office of Research and Development, Washington, DC.

EPA (U.S. Environmental Protection Agency). 1998d. *National Emission Standards for Hazardous Air Pollutants: Wood Furniture Manufacturing Operations, Final Rule*. 63 Federal Register 248 (December 28, 1998), pp. 71376-71385.

EPA (U.S. Environmental Protection Agency). 1998e. *National Primary Drinking Water Regulations. Consumer Confidence Reports, Final Rule*. 63 Federal Register 160 (August 19, 1998), pp. 44512-44536.

EPA (U.S. Environmental Protection Agency). 1999. *Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances.* 64 Federal Register 213 (November 4, 1999), pp. 60194-60204.

EPA (U.S. Environmental Protection Agency). 2000a. *Benchmark Dose Technical Guidance Document [External Review Draft].* EPA/630/R-00/001. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/benchmark-dose-doc-draft.htm. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2000b. *Science Policy Council Handbook: Risk Characterization.* EPA/100/B-00/002. Office of Science Policy, Washington, DC. http://www.epa.gov/osa/spc/pdfs/rchandbk.pdf. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2000c. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures.* EPA/630/R-00/002. Risk Assessment Forum, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2000d. *Voluntary Children's Chemical Evaluation Program.* 65 Federal Register 248 (December 26, 2000), pp. 81700-81718.

EPA (U.S. Environmental Protection Agency). 2001a. *Draft Generic Scenario- Use of Vapor Degreasers.* Office of Pollution Prevention and Toxics, Chemical Engineering Branch, Washington, DC.

EPA (U.S. Environmental Protection Agency). 2001b. *National Emission Standards for Pharmaceuticals Production, Final Rule.* 66 Federal Register 149 (August 2, 2001), pp. 40121-40137.

EPA (U.S. Environmental Protection Agency). 2001c. *Risk Assessment Guidance for Superfund: Volume 3 - Part a, Process for Conducting Probabilistic Risk Assessment.* EPA/540-R-02-002. Office of Emergency and Remedial Response, Washington, DC. http://www.epa.gov/oswer/riskassessment/rags3adt/.

EPA (U.S. Environmental Protection Agency). 2002a. *National Emission Standards for Hazardous Air Pollutants for Friction Materials Manufacturing Facilities.* 67 Federal Register 202 (October 18, 2002), pp. 64498-64512.

EPA (U.S. Environmental Protection Agency). 2002b. *A Review of the Reference Dose and Reference Concentration Processes.* EPA/630/P-02/002F. Risk Assessment Forum, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=51717. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2003. *National Emission Standards for Hazardous Pollutants; Printing, Coating, and Dyeing of Fabrics and Other Textiles; Final Rule*. 68 Federal Register 103 (May 29, 2003), pp. 32172-32229.

EPA (U.S. Environmental Protection Agency). 2004a. *Air Toxics Risk Assessment Reference Library. Volume 1. Technical Resource Manual*. EPA-453-K-04-001A. Office of Air Quality Planning and Standards, Research Triangle Park, NC. www.epa.gov/ttn/fera/risk_atra_vol1.html.

EPA (U.S. Environmental Protection Agency). 2004b. *National Emission Standards for Hazardous Air Pollutants: Organic Liquids Distribution (Non-Gasoline)*. 69 Federal Register 22 (February 3, 2004), pp. 5038-5087.

EPA (U.S. Environmental Protection Agency). 2005a. *Guidelines for Carcinogen Risk Assessment*. EPA/630/P-03/001F. Risk Assessment Forum, Washington, DC. http://www.epa.gov/cancerguidelines/. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2005b. *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*. EPA/630/R-03/003F. Risk Assessment Forum, Washington, DC. http://www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2006a. *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment*. EPA/600/R-05/043F. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668.

EPA (U.S. Environmental Protection Agency). 2006b. *A Framework for Assessing Health Risk of Environmental Exposures to Children*. EPA/600/R-05/093F. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2006c. *Peer Review Handbook (3rd Edition)*. EPA/100/B-06/002. Science Policy Council, Washington, DC. http://www.epa.gov/peerreview/pdfs/peer_review_handbook_2006.pdf. (as cited in EPA, 2011e).

EPA (U.S. Environmental Protection Agency). 2006d. *Risk Assessment for the Halogenated Solvent Cleaning Source Category Web Site*. Washington, DC. http://yosemite.epa.gov/ee/epa/ria.nsf/vwRef/A.2006.10?OpenDocument (accessed on November 8, 2012).

EPA (U.S. Environmental Protection Agency). 2007a. *Economic Impact Analysis of the Halogenated Solvent Cleaners Residual Risk Standard*. EPA-452/R-07-005. Office of Air Quality Planning and Standards, Health and Environmental Impacts Division, Air Benefits and Costs Group, Research Triangle Park, NC. http://www.epa.gov/ttnecas1/regdata/EIAs/hsceconanalysisreportfinaldraft60000.pdf.

EPA (U.S. Environmental Protection Agency). 2007b. *Exposure and Fate Assessment Screening Tool (E-FAST). Version 2.0. Documentation Manual*. Office of Pollution Prevention and Toxics, Exposure Assessment Branch, Washington, DC. www.epa.gov/oppt/exposure/pubs/efast2man.pdf.

EPA (U.S. Environmental Protection Agency). 2007c. *National Air Emission Standards for Hazardous Air Pollutants: Halogenated Solvent Cleaning*. 72 Federal Register 85 (May 3, 2007), pp. 25138-25159.

EPA (U.S. Environmental Protection Agency). 2007d. *Protection of Stratospheric Ozone: Listing of Substitutes for Ozone-Depleting Substances- N-Propyl Bromide in Solvent Cleaning*. 72 Federal Register 103 (May 30, 2007), pp. 30142-30167.

EPA (U.S. Environmental Protection Agency). 2008. *National Emissions Inventory Data and Documentation Web Site*. Washington, DC. http://www.epa.gov/ttn/chief/net/2008inventory.html (accessed on August 16, 2008).

EPA (US Environmental Protection Agency). 2009. *National Emission Standards for Hazardous Air Pollutants for Chemical Manufacturing Area Sources; Final Rule*. 74 Federal Register 208 (October 29, 2009), pp. 56008-56056.

EPA (U.S. Environmental Protection Agency). 2010. *National Primary Drinking Water Regulations. Announcement of the Results of EPA Review of Existing Drinking Water Standards and Request for Public Comment and/or Information on Related Issues. Notice, Request for Comments*. 75 Federal Register 59 (March 29, 2010), pp. 15500-15572.

EPA (U.S. Environmental Protection Agency). 2011a. *Exposure Factors Handbook*. EPA/600R-090052F. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

EPA (U.S. Environmental Protection Agency). 2011b. *Integrated Risk Information System (IRIS) Glossary*. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary (accessed on March 1, 2014).

EPA (U.S. Environmental Protection Agency). 2011c. *Review of EPA Draft Assessment Entitled "Toxicological Review of Trichloroethylene" (October 2009)*. EPA-SAB-11-002. Science Advisory Board. http://yosemite.epa.gov/sab/sabproduct.nsf/0/b73d5d39a8f184bd85257817004a1988/$FILE/EPA-SAB-11-002-unsigned.pdf.

EPA (U.S. Environmental Protection Agency). 2011d. *Toxic Chemical Release Inventory Reporting Forms and Instructions. Revised 2011 Version*. EPA 260-R-10-001. Washington, DC. http://www2.epa.gov/sites/production/files/documents/ry2011rfi.pdf.

EPA (U.S. Environmental Protection Agency). 2011e. *Toxicological Review of Trichloroethylene (CAS No. 79-01-6)*. EPA/635/R-09/011F. Integrated Risk Information System, Office of Research and Development, Washington, DC. http://www.epa.gov/iris/supdocs/0199index.html.

EPA (U.S. Environmental Protection Agency). 2012a. *Benchmark Dose Technical Guidance*. EPA/100/R-12/001. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf.

EPA (U.S. Environmental Protection Agency). 2012b. *Estimation Programs Interface (EPI) Suite Download Web Site*. Washington, DC. http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm (accessed on November 7, 2012).

EPA (U.S. Environmental Protection Agency). 2012c. *Toxic Release Inventory (TRI) Program Web Site*. Washington, DC. http://www.epa.gov/tri/index.htm (accessed on April 30, 2012).

EPA (U.S. Environmental Protection Agency). 2012d. *TSCA Work Plan Chemicals: Methods Document*. Office of Pollution Prevention and Toxics, Washington, DC. http://www.epa.gov/oppt/existingchemicals/pubs/wpmethods.pdf.

EPA (U.S. Environmental Protection Agency). 2013a. *2012 Chemical Data Report (CDR)*. Washington, DC. http://www.epa.gov/tri/index.htm (accessed in November 2013).

EPA (U.S. Environmental Protection Agency). 2013b. *Final Peer Review Comments for the OPPT Trichloroethylene (TCE) Draft Risk Assessment*. Office of Pollution Prevention and Toxics, Washington, DC. http://www.scgcorp.com/tcl2013/prcomments.asp.

Epstein, D. L., G. A. Nolen, J. L. Randall, S. A. Christ, E. J. Read, J. A. Stober, and M. K. Smith. 1992. *Cardiopathic Effects of Dichloroacetate in the Fetal Long-Evans Rat*. Teratology, 46(3), 225-235. (as cited in EPA, 2011e).

Ettema, J. H., R. L. Zielhuis, E. Burer, H. A. Meier, L. Kleerekoper, and M. A. de Graaf. 1975. *Effects of Alcohol, Carbon Monoxide and Trichloroethylene Exposure on Mental Capacity*. International Archives of Occupational and Environmental Health, 35(2), 117-132. (as cited in NAC, 2008).

Evans, M. V., W. A. Chiu, M. S. Okino, and J. C. Caldwell. 2009. *Development of an Updated PBPK Model for Trichloroethylene and Metabolites in Mice, and Its Application to Discern the Role of Oxidative Metabolism in TCE-Induced Hepatomegaly*. Toxicology and Applied Pharmacology, 236(3), 329-340. (as cited in EPA, 2011e).

Ferguson, R. K., and R. J. Vernon. 1970. *Trichloroethylene in Combination with Cns Drugs. Effects on Visual-Motor Tests*. Archives of Environmental Health, 20, 462-467. (as cited in NAC, 2008).

Fisher, J., S. Channel, J. Eggers, P. Johnson, K. MacMahon, C. Goodyear, G. Sudberry, D. Warren, J. Latendresse, and L. Graeter. 2001. *Trichloroethylene, Trichloroacetic Acid, and Dichloroacetic Acid: Do They Affect Fetal Rat Heart Development*. International Journal of Toxicology, 20(5), 257-267. (as cited in EPA, 2011e).

Fogel, M. M., A. R. Taddeo, and S. Fogel. 1986. *Biodegradation of Chlorinated Ethenes by a Methane-Utilizing Mixed Culture*. Applied and Environmental Microbiology, 51(4), 720-724.

Forand, S. P., E. L. Lewis-Michl, and M. I. Gomez. 2012. *Adverse Birth Outcomes and Maternal Exposure to Trichloroethylene and Tetrachloroethylene through Soil Vapor Intrusion in New York State*. Environ Health Perspect, 120(4), 616-621.

Forkert, P., L. Lash, V. Nadeua, R. Tardif, and A. Simmonds. 2002. *Metabolism and Toxicity of Trichloroethylene in Epididymis and Testis*. Toxicology and Applied Pharmacology, 182, 244-254. (as cited in EPA, 2011e).

Fredriksson, A., B. Danielsson, and P. Eriksson. 1993. *Altered Behaviour in Adult Mice Orally Exposed to Tri- and Tetrachloroethylene as Neonates*. Toxicology Letters, 66, 13-19. (as cited in EPA, 2011e).

Gash, D. M., K. Rutland, N. L. Hudson, P. G. Sullivan, G. Bing, W. A. Cass, J. D. Pandya, M. Liu, D. Choi, R. L. Hunter, G. A. Gerhardt, C. D. Smith, J. T. Slevin, and T. S. Prince. 2008. *Trichloroethylene: Parkinsonism and Complex 1 Mitochondrial Neurotoxicity*. Annals of Neurology, 63, 184-192. (as cited in EPA, 2011e).

Gay, B. W., P. L. Hanst, J. J. Bufalini, and R. C. Noonan. 1976. *Atmospheric Oxidation of Chlorinated Ethylenes*. Environmental Science and Technology, 10(1), 58-67.

Gilboa, S. M., T. A. Desrosiers, C. Lawson, P. J. Lupo, T. J. Riehle-Colarusso, P. A. Stewart, E. van Wijngaarden, M. A. Waters, A. Correa, and S. National Birth Defects Prevention. 2012. *Association between Maternal Occupational Exposure to Organic Solvents and Congenital Heart Defects, National Birth Defects Prevention Study, 1997-2002.* Occupational and Environmental Medicine, 69(9), 628-635.

Glauser, J., and C. Funda. 2012. IHS Global Inc. Chemical Economics Handbook. . In *CEH Marketing Research Report: C2 Chlorinated Solvents*, January 2012.

Goldberg, S. J., M. D. Lebowitz, E. J. Graver, and S. Hicks. 1990. *An Association of Human Congenital Cardiac Malformations and Drinking Water Contaminants*. Journal of the American College of Cardiology, 16(1), 155-164. (as cited in EPA, 2011e).

Green, T., and M. S. Prout. 1985. *Species Differences in Response to Trichloroethylene: Part 2. Biotransformation in Rats and Mice*. Toxicology and Applied Pharmacology, 79(3), 401-411. (as cited in EPA, 2011e).

Hamburger, V., and H. L. Hamilton. 1951. *A Series of Normal Stages in the Development of the Chick Embryo*. Journal of Morphology, 88, 49-92.

Hansch, C., A. Leo, and D. Howkman. 1995. Hydrophobic, Electronic and Steric Constants. In *Exploring QSAR* (pp. 4). American Chemical Society, Washington, DC.

Hardin, B. D., G. P. Bond, M. R. Sikov, F. D. Andrew, R. P. Beliles, and R. W. Niemeier. 1981. *Testing of Selected Workplace Chemicals for Teratogenic Potential.* Scandinavian Journal of Work, Environment and Health, 7(Suppl 4), 66-75. (as cited in EPA, 2011e).

Hassoun, E., C. Kariya, and F. E. Williams. 2005. *Dichloroacetate-Induced Developmental Toxicity and Production of Reactive Oxygen Species in Zebrafish Embryos*. Journal of Biochemical and Molecular Toxicology, 19(1), 52-58.

Healy, T., T. Poole, and A. Hopper. 1982. *Rat Fetal Development and Maternal Exposure to Trichloroethylene 100 Ppm*. British Journal of Anaesthesia, 54, 337-341. (n).

Hill, A. B. 1965. *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine, 58(5), 295-300.

Horvath, A. L., F. W. Getzen, and Z. Maczynska. 1999. *Iupac-Nist Solubility Data Series 67. Halogenated Ethanes and Ethenes with Water*. JPCRD, 28(2), 395-627.

Howard, P. H., R. S. Boethling, W. M. Jarvis, W. M. Meylan, and E. M. Michalenko. 1991. *Handbook of Environmental Degradation Rates.* Boca Raton, FL: Lewis Publishers/CRC Press.

HSDB (Hazardous Substances Data Bank). 1992. *Trichloroethylene*. National Library of Medicine, Bethesda, MD. http://toxnet.nlm.nih.gov/. (as cited in NAC, 2008).

HSDB (Hazardous Substances Data Bank). 2012. *Trichloroethylene*. National Library of Medicine, Bethesda, MD. http://toxnet.nlm.nih.gov/ (accessed on August 15, 2012).

Hunter, E., E. Rogers, J. Schmid, and A. Richard. 1996. *Comparative Effects of Haloacetic Acids in Whole Embryo Culture*. Teratology, 54(2), 57-64. (as cited in EPA, 2011e).

Hutter, G. M., G. R. Brenniman, and R. J. Anderson. 1992. *Measurement of the Apparent Diffusion Coefficient of Trichloroethylene in Soil*. Water Environment Research, 64(1), 69-77.

IARC (International Agency for Research on Cancer). 2014. *Monographs on the Evaluation of Carcinogenic Risks to Humans: Cadmium, Trichloroethylene, Tetrachloroethylene, and Some Chlorinated Agents, Volume 106*. World Health Organization, Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol106/mono106.pdf.

Iavicoli, I., A. Marinaccio, and G. Carelli. 2005. *Effects of Occupational Trichloroethylene Exposure on Cytokine Levels in Workers*. Journal of Occupational and Environmental Medicine, 47(5), 453-457. (as cited in EPA, 2011e).

ICIS. 2010. *Inorganics News in Brief, October 25, 2010*. http://www.icis.com/Articles/2010/10/25/9403851/inorganics-news-in-brief.html (accessed on November 6, 2012).

ICIS. 2012. *Inorganics News in Brief, January 23, 2012*. http://www.icis.com/Articles/2012/01/23/9525488/inorganics-news-in-brief.html (accessed on November 6, 2012).

Ikeda, M. 1977. *Metabolism of Trichloroethylene and Tetrachloroethylene in Human Subjects*. Environmental Health Perspectives, 21, 239-245. (as cited in EPA, 2011e).

Ikeda, M., and T. Imamura. 1973. *Biological Half-Life of Trichloroethylene and Tetrachloroethylene in Human Subjects*. International Archives of Occupational and Environmental Health, 31(3), 209-224. (as cited in EPA, 2011e).

Isaacson, L., S. Spohler, and D. Taylor. 1990. *Trichloroethylene Affects Learning and Decreases Myelin in the Rat Hippocampus*. Neurotoxicology and Teratology, 12, 375-381. (as cited in EPA, 2011e).

Jacob, S., M. Hery, J. C. Protois, J. Rossert, and B. Stengel. 2007. *New Insight into Solvent-Related End-Stage Renal Disease: Occupations, Products and Types of Solvents at Risk*. Occupational and Environmental Medicine, 64, 843–848. (as cited in EPA, 2011e).

Jayjock, M. A., T. Armstrong, and M. Taylor. 2011. *The Daubert Standard as Applied to Exposure Assessment Modeling Using the Two-Zone (NF/FF) Model Estimation of Indoor Air Breathing Zone Concentration as an Example*. Journal of Occupational and Environmental Hygiene, 8(11), D114-D122.

Johnson, P., S. Goldberg, S. Mays, and B. Dawson. 2005. *Correction: Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat*. Environmental Health Perspectives, 113, A18. (as cited in EPA, 2011e).

Johnson, P. D. 2014. *Erratum: Erratum for Johnson Et Al. [Environ Health Perspect 113: A18 (2005)]*. Environmental Health Perspectives, 10.1289/ehp.122-A94.

Johnson, P. D., B. V. Dawson, and S. J. Goldberg. 1998a. *Cardiac Teratogenicity of Trichloroethylene Metabolites*. Journal of the American College of Cardiology, 32(2), 540-545.

Johnson, P. D., B. V. Dawson, and S. J. Goldberg. 1998b. *A Review: Trichloroethylene Metabolites: Potential Cardiac Teratogens*. Environmental Health Perspectives, 106 (Suppl 4), 995-999.

Johnson, P. D., S. J. Goldberg, M. Z. Mays, and B. V. Dawson. 2003. *Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat*. Environmental Health Perspectives, 111(3), 289-292. (as cited in EPA, 2011e).

Jollow, D. J., J. V. Bruckner, D. C. McMillan, J. W. Fisher, D. G. Hoel, and L. C. Mohr. 2009. *Trichloroethylene Risk Assessment: A Review and Commentary*. Critical Reviews in Toxicology, 39(9), 782-797. (as cited in EPA, 2011e).

Kan, F. W. K., P. G. Forkert, and M. G. Wade. 2007. *Trichloroethylene Exposure Elicits Damage in Epididymal Epithelium and Spermatozoa in Mice*. Histology and Histopathology, 22, 977-988. (as cited in EPA, 2011e).

Kaneko, T., M. Saegusa, K. Tasaka, and A. Sato. 2000. *Immunotoxicity of Trichloroethylene: A Study with Mrl-Lpr/Lpr Mice*. Journal of Applied Toxicology : JAT, 20, 471-475. (as cited in EPA, 2011e).

Kao, A. S. 1994. *Formation and Removal Reactions of Hazardous Air Pollutants*. Journal of the Air and Waste Management Association, 44, 683-696.

Kao, C. M., and J. Prosser. 1999. *Intrinsic Bioremediation of Trichloroethylene and Chlorobenzene: Field and Laboratory Studies*. Journal of Hazardous Materials, 69(1), 67-79.

Keil, C. B., C. E. Simmons, and A. T. Renee. 2009. *Mathematical Models for Estimating Occupational Exposure to Chemicals* (2nd ed.) American Industrial Hygiene Association (AIHA).

Keil, D. E., M. M. Peden-Adams, S. Wallace, P. Ruiz, and G. S. Gilkeson. 2009. *Assessment of Trichloroethylene (TCE) Exposure in Murine Strains Genetically-Prone and Non-Prone to Develop Autoimmune Disease*. Journal of Environmental Science and Health. Part A, Toxic/hazardous Substances & Environmental Engineering, 44(5), 443-453. (as cited in EPA, 2011e).

Kezic, S., A. C. Monster, J. Kruse, and M. M. Verberk. 2000. *Skin Absorption of Some Vaporous Solvents in Volunteers*. International Archives of Occupational and Environmental Health, 73(6), 415-422.

Kjellstrand, P., B. Holmquist, P. Alm, M. Kanje, S. Romare, I. Jonsson, L. Mansson, and M. Bjerkemo. 1983. *Trichloroethylene: Further Studies of the Effects on Body and Organ Weights and Plasma Butyrylcholinesterase Activity in Mice*. Acta Pharmacologica et Toxicologica, 53, 375-384. (as cited in EPA, 2011e).

Kjellstrand, P., M. Kanje, and M. Bjerkemo. 1987. *Regeneration of the Sciatic Nerve in Mice and Rats Exposed to Trichloroethylene*. Toxicology Letters, 38(1-2), 187-191. (as cited in EPA, 2011e).

Koontz, M. D., and H. E. Rector. 1995. *Estimation of Distributions for Residential Air Exchange Rates. Final Report*. Washington, DC (as cited in US EPA 2011a).

Kumar, P., A. Prasad, B. Maji, U. Mani, and K. Dutta. 2001. *Trichloroethylene Induced Testicular Toxicity in Rats Exposed by Inhalation*. Human & Experimental Toxicology, 20, 585-589. (as cited in EPA, 2011e).

Kumar, P., A. Prasad, D. Saxena, U. Manu, B. Maji, and K. Dutta. 2000. *Fertility and General Reproduction Studies in Trichloroethylene Exposed Rats*. Indian Journal of Occupational Health, 43, 117-126. (as cited in EPA, 2011e).

Lagakos, S. W., B. J. Wessen, and M. Zelen. 1986. *An Analysis of Contaminated Well Water and Health Effects in Woburn, Massachusetts*. Journal of the American Statistical Association, 81(395), 583-596. (as cited in EPA, 2011e).

Lehmann, I., M. Rehwagen, U. Diez, A. Seiffart, U. Rolle-Kampczyk, M. Richter, H. Wetzig, M. Borte, and O. Herbarth. 2001. *Enhanced in Vivo Ige Production and T Cell Polarization*

toward the Type 2 Phenotype in Association with Indoor Exposure to VOC: Results of the Lars Study. International Journal of Hygiene and Environmental Health, 204(4), 211-221. (as cited in EPA, 2011e).

Lehmann, I., A. Thoelke, M. Rehwagen, U. Rolle-Kampczyk, U. Schlink, R. Schulz, M. Borte, U. Diez, and O. Herbarth. 2002. *The Influence of Maternal Exposure to Volatile Organic Compounds on the Cytokine Secretion Profile of Neonatal T Cells*. Environmental Toxicology, 17(3), 203-210. (as cited in EPA, 2011e).

Lindstrom, A. B., and J. D. Pleil. 1996. *A Methodological Approach for Exposure Assessment Studies in Residences Using Volatile Organic-Compound-Contaminated Water*. J Air Waste Manage Assoc, 46(11), 1058-1066.

Loeber, C., M. Hendrix, S. Diez De Pinos, and S. Goldberg. 1988. *Trichloroethylene: A Cardiac Teratogen in Developing Chick Embryos*. Pediatric Research, 24(6), 740-744. (as cited in EPA, 2011e).

Loffredo, C., C. Ferencz, and A. Correa-Villasenor. 1991. *Organic Solvents and Cardiovascular Malformations in the Baltimore-Washington Infant Study [Abstract]*. Teratology, 43, 450.

Luhring, D., and N. Marks. 2000. *How Dry Cleaning Works*. HowStuffWorks.com. http://home.howstuffworks.com/dry-cleaning.htm (accessed on January 6, 2014).

Maltoni, C., and G. Cotti. 1986. *Results of Long-Term Carcinogenicity Bioassays of Tetrachloroethylene on Sprague-Dawley Rats Administered by Ingestion*. Acta Oncologica (Italy), 7(1), 11-26. (as cited in EPA, 2011e).

McCarty, P. L. 1996. Biotic and Abiotic Transformations of Chlorinated Solvents in Ground Water. In *Symposium in Natural Attenuation of Chlorinated Organics in Ground Water (EPA/540/R-96/509)* (pp. 5-9). Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC.

Mishima, N., S. Hoffman, E. G. Hill, and E. L. Krug. 2006. *Chick Embryos Exposed to Trichloroethylene in an Ex Ovo Culture Model Show Selective Defects in Early Endocardial Cushion Tissue Formation*. Birth Defects Research, Part A: Clinical and Molecular Teratology, 76(7), 517-527. (as cited in EPA, 2011e).

Mu, D. Y., and K. M. Scow. 1994. *Effect of Trichloroethylene (TCE) and Toluene Concentrations on TCE and Toluene Biodegradation and the Population Density of TCE and Toluene Degraders in Soil*. Applied and Environmental Microbiology, 60(7), 2661-2665.

NAC (National Advisory Committee for AEGLs). 2008. *Interim Acute Exposure Guideline Levels (AEGL) for Trichloroethylene (CAS Reg. No. 70-01-6)*. Washington, DC. http://www.epa.gov/oppt/aegl/pubs/trichloroethylene_interim_dec_2008_v1.pdf.

Narotsky, M., E. Weller, V. Chinchilli, and R. Kavlock. 1995. *Nonadditive Developmental Toxicity in Mixtures of Trichloroethylene, Di(2-Ethylhexyl) Phthalate, and Heptachlor in a 5 X 5 X 5 Design*. Toxicological sciences : an official journal of the Society of Toxicology, 27, 203-216. (cited in EPA, 2011e).

Narotsky, M. G., and R. J. Kavlock. 1995. *A Multidisciplinary Approach to Toxicological Screening: Ii. Developmental Toxicity*. Journal of Toxicology and Environmental Health, 45(2), 145-171. (as cited in EPA, 2011e).

NCI (National Cancer Institute). 1976. *Carcinogenesis Bioassay of Trichloroethylene (NCI-CG-TR-2)*. National Institutes of Health, U.S. Department of Health, Education, and Welfare, Public Health Service, Bethesda, MD. (cited in EPA 2011e).

NIOSH (National Institute for Occupational Safety and Health). 1997a. *Control of Health and Safety Hazards in Commercial Drycleaners: Chemical Exposures, Fire Hazards, and Ergonomic Risk Factors*. Publication Number 97-150. Centers for Disease Control and Prevention, Atlanta, GA. http://www.cdc.gov/niosh/docs/97-150/#controls.

NIOSH (National Institute for Occupational Safety and Health). 1997b. *Control of Spotting Chemical Hazards in Commercial Drycleaning*. Publication Number 97-158. Centers for Disease Control and Prevention, Atlanta, GA. http://www.cdc.gov/niosh/docs/hazardcontrol/hc20.html.

NITE (National Institute of Technology and Evaluation). 2012. *1,1,2-Trichloroethene. CAS No. 79-01-6. Biodegradation and Bioconcentration of the Existing Chemical Substances under the Chemical Substances Control Law*. Incorporated Administrative Agency. Chemical Risk Information Platform, Japan. http://www.safe.nite.go.jp/english/sougou/view/ComprehensiveInfoDisplay_en.faces.

NRC (National Research Council). 1983. *Risk Assessment in the Federal Government: Managing the Process*. National Academy Press, Washington, DC. http://www.nap.edu/openbook.php?record_id=366&page=R1. (as cited in EPA, 2011e).

NRC (National Research Council). 2001. *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals*. National Academy Press, Washington, DC. http://www.nap.edu/catalog.php?record_id=10122.

NRC (National Research Council). 2006. *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*. National Academies Press, Washington, DC. http://www.nap.edu/openbook.php?record_id=11707&page=R1.

NRC (National Research Council). 2009. *Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects*. National Academy Press, Washington, DC. http://www.nap.edu/catalog.php?record_id=12618.

NTP (National Toxicology Program). 1986. *Trichloroethylene: Reproduction and Fertility Assessment in F344 Rats When Administered in the Feed (NTP-86-085)*. National Institute of Environmental Health Sciences Research Triangle Park, NC. (cited in US EPA 2011e as George et al. 1986).

NTP (National Toxicology Program). 1988. *Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel--Gavage Studies)*. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (as cited in EPA, 2011e).

O'Neil, M. J., A. Smith, and P. E. Heckelman. 2001. Trichloroethylene. In *The Merck Index* (13th ed., pp. 1718). Merck & Co., Inc, Whitehouse Station, NJ.

Opdam, J. J. 1989. *Intra and Interindividual Variability in the Kinetics of a Poorly and Highly Metabolising Solvent*. British Journal of Industrial Medicine, 46(12), 831-845. (as cited in EPA, 2011e).

Parfitt, K., S. C. Sweetman, P. S. Blake, and A. V. Parsons (Editors). 1999. *Martindale: The Complete Drug Reference* (32nd ed.). London: Pharmaceutical Press. (as cited in NAC, 2008).

Peden-Adams, M. M., J. G. Eudaly, L. M. Heesemann, J. Smythe, J. Miller, G. S. Gilkeson, and D. E. Keil. 2006. *Developmental Immunotoxicity of Trichloroethylene (TCE): Studies in B6c3f1 Mice*. Journal of Environmental Science and Health. Part A, Toxic/hazardous Substances & Environmental Engineering, 41(3), 249-271. (as cited in EPA, 2011e).

Prout, M. S., W. M. Provan, and T. Green. 1985. *Species Differences in Response to Trichloroethylene: I. Pharmacokinetics in Rats and Mice*. Toxicology and Applied Pharmacology, 79(3), 389-400. (as cited in EPA, 2011e).

Radican, L., D. Wartenberg, G. Rhoads, D. Schneider, R. Wedeen, P. Stewart, and A. Blair. 2006. *A Retrospective Occupational Cohort Study of End-Stage Renal Disease in Aircraft Workers Exposed to Trichloroethylene and Other Hydrocarbons*. Journal of Occupational and Environmental Medicine, 48(1), 1-12. (as cited in EPA, 2011e).

Richards, A. A., and V. Garg. 2010. *Genetics of Congenital Heart Disease*. Curr Cardiol Rev, 6(2), 91-97.

Ruckart, P. Z., F. J. Bove, and M. Maslia. 2013. *Evaluation of Exposure to Contaminated Drinking Water and Specific Birth Defects and Childhood Cancers at Marine Corps Base Camp Lejeune, North Carolina: A Case-Control Study*. Environ Health, 12, 104.

Rufer, E. S., T. Hacker, J. Lough, and S. M. Smith. 2008. *Low-Dose Trichloroethylene Exposure During Valvuloseptal Morphogenesis Causes Ventricular Septal Defects in Hatched Chicks*. Toxicologist, 102(S-1), 314. (as cited in EPA, 2011e).

Rufer, E. S., T. A. Hacker, G. R. Flentke, V. J. Drake, M. J. Brody, J. Lough, and S. M. Smith. 2010. *Altered Cardiac Function and Ventricular Septal Defect in Avian Embryos Exposed to Low-Dose Trichloroethylene*. Toxicological Sciences, 113(2), 444-452. (as cited in EPA, 2011e).

Ruijten, M. W., M. M. Verberk, and H. J. Sallé. 1991. *Nerve Function in Workers with Long Term Exposure to Trichloroethene*. British Journal of Industrial Medicine, 48(2), 87-92. (as cited in EPA, 2011e).

Saillenfait, A. M., I. Langonne, and J. P. Sabate. 1995. *Developmental Toxicity of Trichloroethylene, Tetrachloroethylene and Four of Their Metabolites in Rat Whole Embryo Culture*. Archives of Toxicology, 70(2), 71-82. (as cited in EPA, 2011e).

Sanders, V. M., A. N. Tucker, K. L. White, B. M. Kauffman, P. Hallett, R. A. Carchman, J. F. Borzelleca, and A. E. Munson. 1982. *Humoral and Cell-Mediated Immune Status in Mice Exposed to Trichloroethylene in the Drinking Water*. Toxicology and Applied Pharmacology, 62, 358-368. (as cited in EPA, 2011e).

Sato, A., T. Nakajima, Y. Fujiwara, and N. Murayama. 1977. *A Pharmacokinetic Model to Study the Excretion of Trichloroethylene and Its Metabolites after an Inhalation Exposure*. British Journal of Industrial Medicine, 34(1), 56-63. (as cited in EPA, 2011e).

Schwetz, B. A., B. K. J. Leong, and P. J. Gehring. 1975. *The Effect of Maternally Inhaled Trichloroethylene, Perchloroethylene, Methyl Chloroform, and Methylene Chloride on Embryonal and Fetal Development in Mice and Rats*. Toxicology and Applied Pharmacology, 32(1), 84-96. (as cited in EPA, 2011e).

Selmin, O. I., P. A. Thorne, P. T. Caldwell, and M. R. Taylor. 2008. *Trichloroethylene and Trichloroacetic Acid Regulate Calcium Signaling Pathways in Murine Embryonal Carcinoma Cells P19*. Cardiovascular toxicology, 8(2), 47-56. (as cited in EPA, 2011e).

Smith, M. K., J. L. Randall, E. J. Read, and J. A. Stober. 1989. *Teratogenic Activity of Trichloroacetic Acid in the Rat*. Teratology, 40(5), 445-451. (as cited in EPA, 2011e).

Smith, M. K., J. L. Randall, E. J. Read, and J. A. Stober. 1992. *Developmental Toxicity of Dichloroacetate in the Rat*. Teratology, 46(3), 217-223. (as cited in EPA, 2011e).

SRC (Syracuse Research Corporation). 2012. *The Physical Properties Database (PHYSPROP).* Syracuse, NY. http://www.srcinc.com/what-we-do/product.aspx?id=133.

Stewart, R. D., E. D. Baretta, H. C. Dodd, and T. R. Torkelson. 1970. *Experimental Human Exposure to Trichloroethylene*. Archives of Environmental Health, 20, 224-229. (as cited in NAC, 2008).

Taskinen, H., A. Anttila, M. L. Lindbohm, M. Sallmén, and K. Hemminki. 1989. *Spontaneous Abortions and Congenital Malformations among the Wives of Men Occupationally Exposed to Organic Solvents*. Scandinavian Journal of Work, Environment and Health, 15(5), 345-352. (as cited in EPA, 2011e).

Taskinen, H., P. Kyyronen, and K. Hemminki. 1994. *Laboratory Work and Pregnancy Outcome*. Journal of Occupational Medicine, 36(3), 311-319. (as cited in EPA, 2011e).

Taylor, D. H., K. E. Lagory, D. J. Zaccaro, R. J. Pfohl, and R. D. Laurie. 1985. *Effect of Trichloroethylene on the Exploratory and Locomotor Activity of Rats Exposed During Development*. Science of the Total Environment, 47, 415-420. (as cited in EPA, 2011e).

Tibaldi, R., W. ten Berge, and D. Drolet. 2014. *Dermal Absorption of Chemicals: Estimation by Ih Skinperm*. J Occup Environ Hyg, 11(1), 19-31.

Tikkanen, J., and O. P. Heinonen. 1988. *Cardiovascular Malformations and Organic Solvent Exposure During Pregnancy in Finland*. American Journal of Industrial Medicine, 14(1), 1-8.

Tikkanen, J., and O. P. Heinonen. 1991. *Maternal Exposure to Chemical and Physical Factors During Pregnancy and Cardiovascular Malformations in the Offspring*. Teratology, 43(6), 591-600.

USCB (United States Census Bureau). 2011. *County Business Patterns (CPB): County Business Patterns and Zip Code Business Patterns.* Washington, DC. http://www.census.gov/econ/cbp/index.html (accessed on January 10, 2014).

USDOC (U.S. Department of Commerce). 2008. *North American Industry Classification System. Introduction to NAICS Web Site*. U.S. Census Bureau. http://www.census.gov/eos/www/naics/ (accessed on November 9, 2012).

Vernon, R. J., and R. K. Ferguson. 1969. *Effects of Trichloroethylene on Visual Motor Performance*. Archives of Environmental Health, 18, 894-900. (as cited in NAC, 2008).

von Grote, J., C. Hurlimann, M. Scheringer, and K. Hungerbuhler. 2003. *Reduction of Occupational Exposure to Perchloroethylene and Trichloroethylene in Metal Degreasing*

over the Last 30 Years: Influences of Technology Innovation and Legislation. J Expo Anal Environ Epidemiol, 13(5), 325-340.

von Grote, J., C. Hürlimann, M. Scheringer, and K. Hungerbühler. 2006. *Assessing Occupational Exposure to Perchloroethylene in Dry Cleaning*. Journal of Occupational and Environmental Hygiene, 3(11), 606-619.

Wackett, L. P., G. A. Brusseau, S. R. Householder, and R. S. Hanson. 1989. *Survey of Microbial Oxygenases: Trichloroethylene Degradation by Propane-Oxidizing Bacteria*. Applied and Environmental Microbiology, 55(11), 2960-2964.

Wadden, R. A., P. A. Scheff, and J. E. Franke. 1989. *Emission Factors for Trichloroethylene Vapor Degreasers*. American Industrial Hygiene Association Journal, 50(9), 496-500.

Wakeham, S. G., A. C. Davis, and J. L. Karas. 1983. *Mesocosm Experiments to Determine the Fate and Persistence of Volatile Organic Compounds in Coastal Seawater*. Environmental Science and Technology, 17(10), 611-617.

Weast, R. C., and S. M. Selby. 1966. Ethene, Trichloro-. In Weast, R. C., *Handbook of Chemistry and Physics* (47th ed., pp. C-314). The Chemical Rubber, Co., Cleaveland, OH.

White, R. F., R. G. Feldman, I. I. Eviator, J. F. Jabre, and C. A. Niles. 1997. *Hazardous Waste and Neurobehavioral Effects: A Developmental Perspective*. Environmental Research, 73(1-2), 113-124. (as cited in EPA, 2011e).

Williams, F. E., T. J. Sickelbaugh, and E. Hassoun. 2006. *Modulation by Ellagic Acid of Dca-Induced Developmental Toxicity in the Zebrafish (Danio Rerio)*. Journal of Biochemical and Molecular Toxicology, 20(4), 183-190.

Wilson, J. T., and B. H. Wilson. 1985. *Biotransformation of Trichloroethylene in Soil*. Applied and Environmental Microbiology, 49(1), 242-243.

Woolhiser, M., S. Krieger, J. Thomas, and J. Hotchkiss. 2006. *Trichloroethylene (TCE): Immunotoxicity Potential in CD Rats Following a 4-Week Vapor Inhalation Exposure*. The Dow Chemical Company, Unpublished Report, Midland, MI. (as cited in EPA, 2011e).

Xu, H., N. Tanphaichitr, P. G. Forkert, A. Anupriwan, W. Weerachatyanukul, R. Vincent, A. Leader, and M. G. Wade. 2004. *Exposure to Trichloroethylene and Its Metabolites Causes Impairment of Sperm Fertilizing Ability in Mice*. Toxicological Sciences, 82(2), 590-597.

Xu, J. Q., K. D. Kochanek, S. L. Murphy, and B. Tejada-Vera. 2010. *Deaths: Final Data for 2007*. National Center for Health Statistics, Hyattsville, MD. http://www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_19.pdf. (as cited in EPA, 2011a).

Yauck, J. S., M. E. Malloy, K. Blair, P. M. Simpson, and D. G. McCarver. 2004. *Proximity of Residence to Trichloroethylene-Emitting Sites and Increased Risk of Offspring Congenital Heart Defects among Older Women*. Birth Defects Research Part A: Clinical and Molecular Teratology, 70(10), 808-814.

APPENDICES

Appendix A PRODUCTION VOLUME AND INVENTORY UPDATE RULE DATA

In 2011, global consumption of TCE was 945 million lbs with expected growth at about 1.5 percent annually over the next five years. The corresponding U.S. consumption was 255 million lbs (Glauser and Funda, 2012)[31]. here were two U.S. producers for TCE as of 2011: The Dow Chemical Company in Freeport, TX and PPG Industries, Inc. in Lake Charles, LA (Glauser and Funda, 2012). Exports of TCE from the U.S. have increased along with similar increases for all chlorinated solvents (80 percent in 2011, 72 percent in 2010) (ICIS, 2010, 2012).

TCE production volume of 224.7 million lbs were reported to EPA in the 2012 Chemical Data Report (CDR). Seven companies reported using TCE in industrial/manufacturing activities: Dow Chemical, Greenchem, PPG Industries Inc., Shin Etsu, Solvchem Inc., Triinternational Inc., and Vinmar Overseas LTD, plus two other companies (EPA, 2013a). There were two other companies that reported to 2012 CDR, but much of this information was claimed confidential business information (CBI) and cannot be made available to the public. Data in tables A-5 to A-7 were extracted from the 2012 CDR records (EPA, 2013a).

Table A-1. National Chemical Information for TCE from 2012 CDR	
Production Volume (aggregate)	224.7 million lbs
Maximum Concentration (at manufacture or import site)	>90%
Physical form(s)	Liquid
Number of reasonably likely to be exposed industrial manufacturing, processing, and use workers (aggregated)	>1,000
Was industrial processing or use information reported?	Yes
Was commercial or consumer use information reported?	Yes

[31] This source material includes data or information derived from IHS Products provided to the U.S. EPA. IHS products have been provided to the U.S. EPA for its internal use and in the context of a license agreement. By receiving and accessing this material, you agree that IHS is not liable to you or any third party for your use of and/or reliance on the IHS data and information contained in this document, and any such use shall be at your own risk.

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Table A-2. Summary of Industrial TCE Uses from 2012 CDR		
Industrial Sector (Based on NAICS)	**Industrial Function**	**Type of Processing**
All Other Basic Organic Chemical Manufacturing	Intermediates	Processing as a reactant
Industrial Gas Manufacturing	Functional fluids (closed systems)	Processing as a reactant
Wholesale and Retail Trade	Solvents (for cleaning or degreasing)	Processing as a reactant
Agriculture, Forestry, Fishing and Hunting	Agricultural chemicals (non-pesticidal)	Processing as a reactant
All Other Basic Organic Chemical Manufacturing	Solvents (for cleaning or degreasing)	Processing-repackaging
All Other Chemical Product and Preparation Manufacturing	Not Known or Reasonably Ascertainable	Use-non-incorporative activities
All Other Chemical Product and Preparation Manufacturing	Solvents (which become part of product formulation or mixture)	Processing-incorporation into formulation, mixture, or reaction product
All Other Basic Organic Chemical Manufacturing	Not Known or Reasonably Ascertainable	Processing-repackaging
Primary Metal Manufacturing	Solvents (for cleaning or degreasing)	Processing-incorporation into formulation, mixture, or reaction product

Table A-3. TCE Commercial/Consumer Use Category Summary		
Commercial/Consumer Product Category	**Intended for Commercial and /or Consumer Uses or Both**	**Intended for Use in Children's Products in Related Product Category**
Adhesives and Sealants	Both	No

Appendix B REGULATORY HISTORY OF TCE AT THE USEPA AND RELATED ACTIONS

B-1 Regulatory History of TCE at the U.S. EPA

The purpose of this section is to provide a brief regulatory history of TCE from the perspective of the EPA. TCE has been subject to 25 final rules and notices issued by the Agency from 1979 to 2009 that were relevant or significant with regard to TCE. These 25 rules and notices were promulgated by EPA's Office of Air and Radiation (OAR), the Office of Solid Waste and Emergency Response (OSWER), the Office of Water (OW) and the Office of Pollution Prevention and Toxics (OPPT).

EPA/OW initially identified TCE as a "toxic pollutant" in 1979 (EPA, 1979). TCE was classified as a "priority pollutant" in 1982 and no discharges of TCE were allowed from steam electric power generating point sources (EPA, 1982). EPA/OW then established a non-enforceable maximum contaminant level goal (MCLG) of 0 mg/L for TCE in 1985 (EPA, 1985b). Two years later, EPA/OW set a maximum contaminant level (MCL) of 0.005 mg/L for drinking water (EPA, 1987b) and set an effluent limitation of 69 µg/L maximum daily average and 26 µg/L maximum monthly average for new and existing sources discharging to POTWs from the organic chemicals, plastics, and synthetic fibers industrial category (EPA, 1987c). The following year, EPA/OW prohibited injection of TCE into class I underground injection wells (EPA, 1988b). TCE was identified by EPA/OW as a bioaccumulative chemical of concern pollutant in 1995 for a final water quality guidance for the great lakes system. This established water quality criteria for protection of human health by setting a human cancer value (HCV) of 29 µg/L for drinking water and 370 µg/L for non-drinking water for the Great Lakes system (EPA, 1995b). In 1998, EPA/OW identified TCE as a possible human carcinogen by establishing a national primary drinking water regulation that specified the following consumer confidence report health effect language: "*some people who drink water containing trichloroethylene in excess of the MCL [0.005 mg/L] over many years could experience problems with their liver and may have an increased risk of getting cancer*" (EPA, 1998e). EPA/OW identified TCE's major sources in drinking water originating from "discharge from metal degreasing sites and other factories (EPA, 1998)." EPA/OW is currently evaluating and revising TCE's MCL based upon analytical feasibility (EPA, 2010).

EPA/OAR has listed TCE as a HAP from several different industrial emission sources in multiple rules (EPA, 1985a, 1986a, 1994c, 1994d, 1998d, 2001b, 2002a, 2003, 2004b, 2007c, 2009), including solvent cleaning operations (EPA, 1994d, 2007c) as well as a "probable or possible human carcinogen" from operations including printing, coating, and dyeing of fabrics and other textiles (EPA, 2003). EPA/OAR classified TCE as a group I chemical for emission standards for equipment leaks in the synthetic organic chemical manufacturing industry (EPA, 1994c). In addition, EPA/OAR identified TCE as a substitute for two ozone depleting chemicals, methyl chloroform and CFC–113, for metals, electronics, and precision cleaning, in 2007 (EPA, 2007d).

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EPA/OSWER set a reportable quantity of 100 lbs (45.4 kg) for releases of TCE from vessels or facilities in 1989 (EPA, 1989). EPA/OSWER also set a minimum required detection limit for TCE of 37 mg/kg for hazardous waste combustors in 1998 (EPA, 1998b).

Although EPA/OPPT has only issued two notices relevant to TCE (EPA, 1994e, 2000d), other voluntary information collection activities for TCE have occurred in the past. These activities were primarily the result of two separate but related voluntary information collection activities: data gaps identified by ATSDR (EPA, 1994e) and data gaps identified for pilot chemicals for EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) (EPA, 2000d).

EPA/OPPT published a notice for voluntary solicitation of testing proposals in order to be considered for an enforceable consent agreement (ECA) negotiation in 1994 for 12 substances, including TCE (EPA, 1994e). This notice was based on data gaps identified by ATSDR in coordination with EPA. After ATSDR updated its data needs for TCE in 1999 (ATSDR, 1999), the Halogenated Solvents Industry Alliance, Inc. (HSIA) responded with its intent to fulfill four of seven identified data needs. These four data needs included developmental neurotoxicity, developmental toxicity, immunotoxicity, and neurotoxicity via the oral route. HSIA entered into a memorandum of understanding (MOU) with ATSDR in June of 2001 to fulfill these four data needs.

Over the course of the next several years, from 2001 to 2007, HSIA completed and submitted two studies to the Agency: a developmental toxicity and an immunotoxicity study via the inhalation route in rats. These two studies had been planned to be extrapolated to the human oral route using PBPK modeling. HSIA had also planned to fulfill the data need for neurotoxicity via the oral route using PBPK modeling of existing published data from the inhalation route. In addition, HSIA had planned to conduct a developmental neurotoxicity study in rats via the oral route. HSIA did not fulfill its MOU for these four planned studies due to several factors, including problems securing an appropriate lab, discontinuation of a strain of rat previously used in their completed studies, and discrepancies with ATSDR regarding the completeness of the three aforementioned studies using PBPK modeling.

Since 2008, no further action has been taken by EPA/OPPT with regard to TCE and its existing data gaps identified by ATSDR.

B-2 Other Regulatory Actions in the U.S. and Abroad

TCE is listed on California's Safer Consumer Products regulations candidate chemicals list and the Proposition 65 list of chemicals. California also lists TCE as a designated chemical for biomonitoring because it has the potential to pose higher exposure rates in California in comparison to other states. Minnesota classifies TCE as a chemical of high concern, while other states, like Washington and Maine, have considered TCE for similar chemical listings. Several additional states have various regulatory actions that range from reporting requirements to contamination limits and use reduction efforts. Some examples include Massachusetts, New

York, Ohio, Colorado and Michigan as they evaluate and monitor exposure to mitigate health risks.

TCE is listed in the European Union Authorisation List owing to its classification as carcinogen (category 1B), with a sunset date of April 21, 2014. In 2004, the United Kingdom completed a Risk Assessment of TCE on behalf of the European Union. In March 2010, France presented a proposal on the identification of TCE as substance of very high concern because of its carcinogenic properties. A dossier was circulated to Member States and was made available on the ECHA website. Comments were received by Member States and interested parties on the proposal. The dossier was referred to the Member State Committee and on June 2010 the Member State Committee agreed to identify TCE as substance meeting the criteria of for a Candidate List of Substance of Very High Concern owing to its classification as carcinogen (category 2).

In Canada, the first Priority Substances List (PSL1) was published in the Canada Gazette in 1989, and the assessments of risks to human health or the environment posed by the 44 substances on the list were completed within the legislated time frame of five years. Options to reduce exposure for those substances determined to be "toxic" were and are being considered, in consultation with stakeholders. Canada assessed TCE in 1993 and considered it as a "toxic" under section 11 of the 1988 Canadian Environmental Protection Act (CEPA 1988). The TCE assessment concluded that "trichloroethylene occurs at concentrations that may be harmful to the environment, and that may constitute a danger in Canada to human life or health. It has been concluded that trichloroethylene occurs at concentrations that do not constitute a danger to the environment on which human life depends."

In Japan, TCE is consider a Class II substance (Class II Specified Chemical Substances are substances that may pose a risk of long-term toxicity to humans or to flora and fauna in the human living environment, and that have been, or in the near future are reasonably likely to be, found in considerable amounts over a substantially extensive area of the environment). Japan also controls air emissions and water dischargers containing TCE, as well as aerosol products for household use and household cleaners containing TCE.

TCE is listed in the Australian National Pollutant Inventory (NPI), a programme run cooperatively by the Australian, State and Territory governments to monitor common pollutants and their levels of release to the environment. Reporting obligations may apply to this chemical. This chemical is included on Australia's High Volume Industrial Chemicals List (HVICL) because it is manufactured or imported in large quantities (1000 tonnes or more). Australia requires a secondary notification if significant new information about TCE's health and/or environmental effects becomes available, for example new data on the mutagenic or reproductive effects. Notification will also be required if it is used in wool scouring or any other new use resulting in a significant increase in the quantities imported into Australia. Australia classifies TCE as a health, physicochemical and/or ecotoxicological hazard, according to the National Occupational Health and Safety Commission (NOHSC) Approved Criteria for Classifying Hazardous Substances. TCE has also been reviewed as a part of the

Australia National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Priority Existing Chemical (PEC) assessment process. The report is available here: http://www.nicnas.gov.au/__data/assets/pdf_file/0004/4369/PEC_8_Trichloroethylene_Full_Report_PDF.pdf

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Appendix C ENVIRONMENTAL FATE OF TCE

C-1 Environmental Fate

Knowledge of the environmental fate (transport and transformation) of a compound is important to understanding its potential impact on specific environmental media (e.g., water, sediment, and soil) and exposures to target organisms of concern.

TCE is a volatile liquid with high vapor pressure, moderate water solubility, and high mobility in soil. Most reported environmental releases of TCE are to air with much lower releases to landfills and very little released to water (see Chapter 2, Section 2.2, *Overview of Environmental Fate and Releases of TCE*). If released to air, degradation by sunlight and reactants in the atmosphere is slow. If released to water, sediment, or soil, the fate of TCE is influenced by volatilization from the water surface or from moist soil and by microbial biodegradation under some conditions. The biodegradation of TCE in the environment is dependent on a variety of factors and so a wide range of degradation rates have been reported (ranging from days to years). TCE is not expected to bioconcentrate in aquatic organisms due to measured bioconcentration factors of less than 1000.

C-1-1 Fate in Air

TCE does not absorb light greater than 290 nm very well; therefore, degradation of TCE by direct exposure to light, if it is released to the atmosphere, is not expected to be an important fate process (EPA, 1979). TCE is expected to undergo relatively slow atmospheric hydroxy radical oxidation with an estimated atmospheric half-life of about 13 days (using Version 4.10 of EpiSuite, EPA, 2012b). Half-life estimates using measured rate data have been reported in the range of 1 – 11 days using hydroxy radical concentrations expected in relatively polluted and pristine air, respectively (Howard et al., 1991). Phosgene, dichloroacetyl chloride (DCAC), chloroform, and formyl chloride can be formed from the reaction of TCE with hydroxyl radicals (EPA, 1980; Gay et al., 1976; Kao, 1994).

C-1-2 Fate in Water

Volatilization from water surfaces will be an important fate process based upon TCE's measured Henry's Law constant. However, its density may cause it to sink in the water column, potentially increasing the aquatic residence time of TCE. Volatilization half-lives in an experimental field mesocosm consisting of seawater, planktonic, and microbial communities ranged from 10.7 to 28 days (Wakeham et al., 1983). In contrast, half-lives of evaporation from laboratory water surfaces (distilled water) have been reported to be on the order of several minutes to hours, depending upon the turbulence (Culver et al., 1991; Hutter et al., 1992). TCE achieved only 19 percent of its theoretical biochemical oxygen demand (BOD) over the course of a 28-day incubation period using the closed bottle (Organisation for Economic Co-operation and Development [OECD] 301D) test, and thus is not considered readily biodegradable. It achieved 2.4 percent of its theoretical BOD using an activated sludge inoculum in the modified

Ministry of International Trade and Industry test (MITI, OECD 301C) over the course of a 14-day incubation period. It was not inherently biodegradable in a Zahn-Wellens test (OECD 302B). These studies suggest that TCE will biodegrade slowly in surface waters. However, slow photooxidation in water has been reported (half-life of 10.7 months) (Dilling et al., 1975). Based on these studies, biodegradation and hydrolysis in surface waters are not expected to be important environmental fate processes.

C-1-3 Fate in Soil, Sediment, and Groundwater

TCE is expected to have high mobility in soil based on measured soil organic carbon partition coefficients ranging from 72 to 148. Volatilization of TCE from moist soil surfaces is expected to be an important fate process given its relatively high Henry's Law constant. TCE is expected to volatilize from dry soil surfaces based upon its high vapor pressure.

Both laboratory tests and field studies in the environment show wide variation in TCE biodegradation rates. In some cases, laboratory studies have shown rapid biodegradation. TCE has been shown to biodegrade under aerobic conditions by methanotrophic microbes in the presence of other substrates and under anaerobic conditions (in suitable reducing environments) in the presence of other organic matter. Without competent microorganisms that can degrade TCE and favorable environmental conditions, TCE can persist in the environment on the order of years.

Aerobic biodegradation of TCE by specialized communities of microorganisms has been reported (Wackett et al., 1989). Biodegradation of TCE has also been shown to occur under conditions where additional substrates have been added to the medium (Kao and Prosser, 1999; Mu and Scow, 1994; Wilson and Wilson, 1985). Mixed microbial cultures of methane-utilizing bacteria have been shown to degrade TCE in two days under aerobic conditions (Fogel et al., 1986). However, there are several factors that can limit the aerobic biodegradation of TCE, including TCE 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 TCE in aerobic soils.

Biodegradation of TCE also occurs under anaerobic conditions. Under these conditions, as might be seen in flooded soils, sediment, or aquifer environments, TCE is biodegraded via reductive dechlorination; the extent and rate of degradation are dependent upon the strength of the reducing environment and other factors (McCarty, 1996). TCE half-lives in the field for aquifer studies range from 35 days to over six years. Major products of biodegradation of TCE in groundwater include dichloroethylene, chloromethane, and vinyl chloride (HSDB, 2012).

TCE contamination exists in the subsurface environment as a result of spills and leaking transfer lines/storage tanks. Because of its density and low Koc, TCE will ultimately move downward in the soil until an impermeable barrier is reached. This may occur when a TCE spill is of sufficient magnitude or deep enough in soil for volatilization to be restricted. Once in soil, TCE can become associated with soil pore water, enter the gas phase because of its Henry's Law

constant, or exist as a nonaqueous phase liquid (NAPL). It is possible that upward or downward movement of TCE can occur in each of these three phases, thereby increasing the areal extent of the original spill. Nonaqueous phase concentrations of TCE which are large enough to overcome capillary forces will move downward into the aquifer. Once the water table is penetrated, lateral flow may be mediated by the regional ground-water flow. Due to its high density, the movement of free-phase TCE is still directed vertically until lower permeability features are encountered. Once an impermeable layer is encountered, horizontal movement will occur. Such movement may even be directed against the natural ground-water flow by the effects of gravity. Since permeability is a function of the liquid as well as the medium, the vertical movement of TCE through an aquifer is determined by geological properties of the aquifer material; i.e., granular size of sand or clay lenses. TCE will tend to pool near these impermeable features. Water passing over and around these pools may solubilize TCE so that it can be spread throughout the aquifer. This pattern of release and distribution in aquifers and TCE persistence have led to the widespread detection of TCE in groundwater and drinking water supplies derived from the contaminated groundwater (EPA, 1992).

C-1-4 Bioconcentration

TCE is not expected to bioconcentrate in fish, with measured bioconcentration factors (BCFs) in carp ranging from four to 17. TCE's low measured BCF value suggests that bioconcentration in aquatic organisms is low (NITE, 2012). The estimated upper trophic level bioaccumulation factor (BAF) for TCE is 24 (EPA, 2012b). Table C-2 provides a summary of the environmental fate information for TCE.

C-1-5 Conclusions on Environmental Fate

TCE is a volatile liquid and if released to air, will be slowly degraded by atmospheric hydroxy radicals. If released to water, volatilization to the atmosphere will be an important fate process and biodegradation will be slow. In soil, TCE does not bind strongly to soil organic matter and if not biodegraded at an appreciable rate, TCE can migrate through soil to groundwater. Based on the experimental evidence and environmental fate data available, TCE is expected to have low bioaccumulation potential in aquatic organisms (bioconcentration/bioaccumulation factor less than 1000) and moderate persistence in the environment (environmental half-life of greater than two months but less than six months).

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Table C-1. Environmental Fate Characteristics of TCE[a]	
Property	**Value**
CASRN	79-01-6
Photodegradation half-life	13.2 days (estimated)
Hydrolysis half-life	Does not hydrolyze under environmental conditions[b]
Biodegradation	19% after 28 days (not readily biodegradable)[b]; 4% after 28 days (not inherently biodegradable)[b]; 100% after 2 days (anaerobic conditions using mixed march cultures)[b]; 2.4% after 14 days (not readily biodegradable)[c]
Bioconcentration	BCF = 4.3-17 (measured in carp at 0.070 mg/L)[c]; BCF = 4-16 (measured in carp at 0.007 mg/L)[c]; BCF = 17 (measured in freshwater fish at 0.0087 mg/L)[c]; BAF = 23.7 (estimated)[a]
Log K_{oc}	2.17 (measured in silty clay Nebraska loam)[c]; 1.94 (measured in silty clay Nevada loam)[c]; 1.86 (measured in a forest soil)[c]; 1.8 (estimated)
Fugacity (Level III Model)[b] Air (%) Water (%) Soil (%) Sediment (%)	 35.4 54.2 10.1 0.3
Persistence[d]	P2 (moderate)
Bioaccumulation[d]	B1 (low)

Sources:
[a] EPA (2012b)
[b] ECB (2000)
[c] NITE (2012)
[d] EPA (1999)

Appendix D NAICS CODES FOR TCE DEGREASING

An analysis of the North American Industry Classification System (NAICS) identified 78 different industries that primarily use TCE as a degreaser (NAICS codes are listed in Table D-1).

Table D-1. TCE Used as a Degreaser Primarily in These Industries (USDOC, 2008)

NAICS Codes							
33121	321113	332112	332721	332999	334417	335929	339114
33272	323116	332116	332722	333132	334419	335999	339992
33341	325188	332117	332811	333298	334513	336321	339995
33422	325998	332211	332812	333311	334515	336340	339999
33512	326299	332212	332813	333415	335121	336411	488111
33531	331111	332311	332912	333921	335211	336413	493110
33634	331210	332313	332913	333994	335312	336414	811310
33641	331419	332431	332919	333999	335313	336510	928110
33999	331421	332510	332994	334413	335911	337125	
314999	332111	332618	332996	334414	335921	337127	

Each number listed is a different industry that may be associated with TCE/degreasing operations. Those interested may go to the following URL and type in a code - http://www.census.gov/eos/www/naics/ (USDOC, 2008). For example, the following results are seen when the listed numbers are searched:

33121:

1. 33121: Iron and Steel Pipe and Tube Manufacturing from Purchased Steel
2. 331210: Iron and Steel Pipe and Tube Manufacturing from Purchased Steel

332811 (results below slightly edited for simplicity):

1. Metal Heat Treating - This U.S. industry comprises establishments primarily engaged in heat treating, such as annealing, tempering, and brazing, and cryogenically treating metals and metal products for the trade.
2. Establishments primarily engaged in both fabricating and heat treating metal products are classified in the Manufacturing sector according to the product made.
3. Annealing metals and metal products for the trade
4. Brazing (i.e., hardening) metals and metal products for the trade
5. Burning metals and metal products for the trade
6. Cold treating metals for the trade
7. Cryogenic treating metals for the trade
8. Hardening (i.e., heat treating) metals and metal products for the trade
9. Heat treating metals and metal products for the trade
10. Shot peening metal and metal products for the trade
11. Tempering metals and metal products for the trade

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Appendix E ESTIMATION OF TCE EMISSION RATE AT SMALL DEGREASING FACILITIES

1 NEI Point Sources (PS)

1. Point sources (PS) assumed to represent large facilities
2. Data obtained from: 2008neiv2_facility_process.zip
3. Filter data by 1) pollutant name, 2) relevant NAICS codes, 3) source classification codes (SCC) for "Solvent-Degreasing" sector and 4) unit type code (430)
4. Results for large facilities
   a. TCE Air Emissions (1.48 Mlbs per year)
   b. Number of TCE-emitting facilities (154 based on number of unique EIS identifiers)
   c. Number of TCE-emitting degreasing units (180 based on number of unique EIS Unit Identifiers)
   d. Number of degreasing units per facility (180/154 = 1.2)

2 NEI Nonpoint Sources (NPS)

1. Nonpoint sources (NPS) assumed to represent small facilities
2. Data obtained from: 2008neiv2_nonpoint.zip
3. Filter data by 1) pollutant name and 2) source classification codes (SCC) for "Solvent-Degreasing" sector
4. Results for small facilities
   a. TCE Air Emissions (2.86 Mlbs per year)
   b. Number of NPS (1,779)
   c. Based on EPA's 2006 risk assessment for the halogenated solvent cleaning source category, total number of facilities expected to be approximately 1,900. Number of TCE-emitting facilities = 1,900 – 154 = 1,746
   d. Assume one (1) degreasing unit per facility; smaller facilities (NPS) are expected to have less degreasing units per facility than larger (PS) facilities.

3 TRI

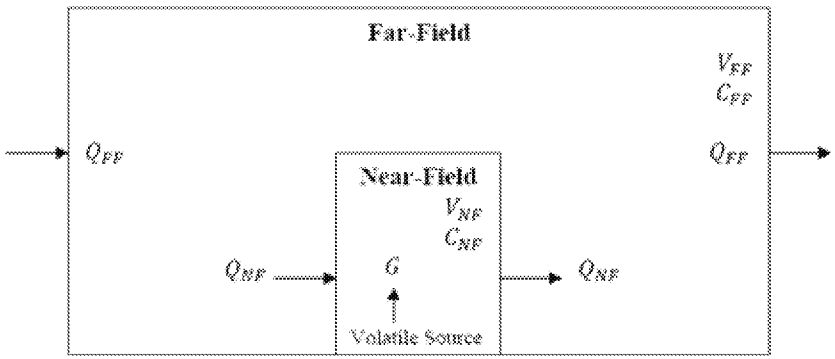
1. Filter TRI data by relevant NAICS codes
2. 2008 TRI: total TCE air emissions ~2.55 Mlbs per year
3. 2008 NEI: total TCE air emission ~4.34 (1.48 + 2.86) Mlbs per year
4. NEI TCE air emissions are about 2 times (2X) those reported in TRI (4.34/2.55 = 2)
5. Use more recent data from 2011 TRI but adjust TRI TCE air emissions (1.69 Mlbs per year) by 2X = 3.38 Mlbs per year
6. Based on 2008 NEI, small facilities account for 66% of total air emissions
   a. Total TCE air emissions from small facilities (66% of 3.38 Mlbs per year = 2.23 Mlbs per year)
   b. Release per small facility (2.23/1,746 = 1,277 lbs per year)

4 TCE Emission Rate

1. EPA's draft Generic Scenario on Use of Vapor Degreasers
   a. Small facilities expected to operate 260 days per year for 2 hours per day (31,200 minutes per year)
   b. Solvent-to-Air interface can vary from 0.28 to 0.87 m^2
   c. Operating TCE emissions can range from 5 to 10 grams per minute.
2. Local exhaust ventilation (LEV) can reduce potential TCE emissions by 90% (Wadden, et al., 1989). Based on NEI and TRI:
   a. Potential TCE emissions escaping into work place with no LEV (1,277*454/31,200 = 19 grams per minute)
   b. Potential TCE emissions escaping into work place with LEV (10% of 19 grams per minute = 1.9 grams per minute)
3. Overall NESHAP emission limit is 150 kg/m^2/month
   a. Based on this limit, potential TCE emissions escaping into work place can vary from 16 to 50 grams per minute (2,600 minutes per month; Solvent-to-Air interface of 0.28 to 0.87 m^2).

Appendix F ESTIMATION OF TCE EXPOSURES AT SMALL DEGREASING FACILITIES

1 Solvent degreasing facility is partitioned into two zones: Near-Field / Far-Field



2 Results of Near-Field / Far-Field approximation

"Workers" are directly involved with degreasing operations; "Occupational Bystanders" have the potential to be exposed to TCE but they are not directly involved with degreasing operations; TWA = Time Weighted Average; LEV = local exhaust ventilation; the OSHA PEL for TCE is 100 ppm (537 mg/m^3); number of small facilities = 1,746.

		Small Industrial / Commercial Facilities		
		With LEV	No LEV	Number of Workers
Workers	Inhalation Exposure (8 hr TWA, ppm)	0.3 to 20	3 to 197	8,730
Occupational Bystanders		0.04 to 17	0.4 to 172	20,952

3 Potential worker exposures to TCE

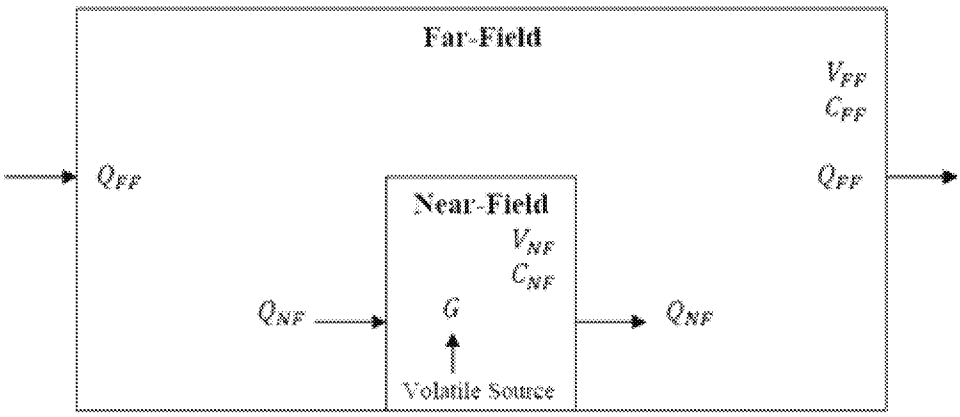
1. Exposure monitoring data for TCE:
   a. OSHA monitoring data from 2003 to 2010 was available; data was specific to TCE; this data was filtered by relevant NAICS codes; 39 personal breathing zone time-weighted average (TWA) measurements were available. Exposure values ranged from 0.06 to 380 ppm (average: 45 ppm; median: 17 ppm; 95th percentile: ~170 ppm)
   b. EPA's exposure estimates are similar to OSHA's data, being of the same order of magnitude.
2. Number of workers and bystanders potentially exposed to TCE:
   a. Based on (ASTDR, 1997), approximately 17 workers per facility are potentially exposed to TCE; this estimate is understood to include both, workers that are and are not (occupational bystanders) directly involved with solvent cleaning operations.
   b. Based on EPA's draft Generic Scenario on Use of Vapor Degreasers, the number of workers expected to be directly involved with solvent cleaning operations is estimated to be 5 workers per facility.
   c. Occupational bystanders (17 – 5 = 12 occupational bystanders per facility)

Appendix G CALCULATION OF TCE EXPOSURES AT SMALL DEGREASING FACILITIES

In Figure G-1, a solvent degreasing facility is partitioned into two zones: the near-field and the far-field (Keil, C. B. et al., 2009). In occupational settings, this is done because contaminant levels in the near-field are considered to provide a better representation of a worker's personal breathing zone than those in the far-field. In other words, potential worker exposures depend on how close a worker is to the emission source. For this risk assessment, the far-field exposures represented those exposures received by occupational bystanders. That is to say, those individuals who would be in the building (and perhaps even the room), but not physically close to the volatile source as shown in Figure G-1.

Figure G- 1. Illustration of an Imperfectly Mixed Room: Near-Field/Far-Field Approximation of a Solvent Cleaning Facility

Note: Potential Worker Exposures Depend on How Close a Worker is to the Emission (Volatile) Source.



Near-Field Mass Balance

$$V_{NF}\frac{dC_{NF}}{dt} = C_{FF}Q_{NF} - C_{NF}Q_{NF} + G \qquad \text{[G-1]}$$

Far-Field Mass Balance

$$\boldsymbol{V_{FF}\frac{dC_{FF}}{dt} = C_{NF}Q_{NF} - C_{FF}Q_{NF} - C_{FF}Q_{FF}} \qquad \textbf{[G-2]}$$

Where:

V_{NF} = near-field volume
V_{FF} = far-field volume
Q_{NF} = near-field ventilation rate
Q_{FF} = far-field ventilation rate
C_{NF} = average near-field concentration
C_{FF} = average far-field concentration
G = average generation rate
t = time

At steady-state, Equations [G-1] and [G-2] can be reduced to the following:

$$\boldsymbol{C_{NF} = \frac{G}{Q_{NF}\left(1 - \frac{Q_{NF}}{Q_{NF} + Q_{FF}}\right)}} \qquad \textbf{[G-3]}$$

$$\boldsymbol{C_{FF} = \frac{C_{NF}Q_{NF}}{Q_{NF} + Q_{FF}}} \qquad \textbf{[G-4]}$$

Equations [G-1] and [G-2] can be solved for the time-varying concentrations in the near-field and far-field (Keil, C. B. et al., 2009).

$$C_{NF} = G\left(k_1 + k_2 e^{\lambda_1 t} - k_3 e^{\lambda_2 t}\right) \qquad \textbf{[G-5]}$$

$$C_{FF} = G\left(\frac{1}{Q_{FF}} + k_4 e^{\lambda_1 t} - k_5 e^{\lambda_2 t}\right) \qquad \textbf{[G-6]}$$

Where:

$$k_1 = \frac{1}{\left(\frac{Q_{NF}}{Q_{NF} + Q_{FF}}\right) Q_{FF}} \qquad \textbf{[G-7]}$$

$$k_2 = \frac{Q_{NF}Q_{FF} + \lambda_2 V_{NF}(Q_{NF} + Q_{FF})}{Q_{NF}Q_{FF}V_{NF}(\lambda_1 - \lambda_2)} \qquad \textbf{[G-8]}$$

$$k_3 = \frac{Q_{NF}Q_{FF} + \lambda_1 V_{NF}(Q_{NF} + Q_{FF})}{Q_{NF}Q_{FF}V_{NF}(\lambda_1 - \lambda_2)} \quad \textbf{[G-9]}$$

$$k_4 = \left(\frac{\lambda_1 V_{NF} + Q_{NF}}{Q_{NF}}\right) k_2 \quad \textbf{[G-10]}$$

$$k_5 = \left(\frac{\lambda_2 V_{NF} + Q_{NF}}{Q_{NF}}\right) k_3 \quad \textbf{[G-11]}$$

$$\lambda_1 = 0.5\left[-\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right) + \sqrt{\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right)^2 - 4\left(\frac{Q_{NF}Q_{FF}}{V_{NF}V_{FF}}\right)}\right] \quad \textbf{[G-12]}$$

$$\lambda_2 = 0.5\left[-\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right) - \sqrt{\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right)^2 - 4\left(\frac{Q_{NF}Q_{FF}}{V_{NF}V_{FF}}\right)}\right] \quad \textbf{[G-13]}$$

Time-weighted-average (TWA) concentrations in the near-field and far-field can be calculated as follows:

$$C_{NF,TWA} = \frac{\int_{t_1}^{t_2} C_{NF}\, dt}{\int_{t_1}^{t_2} dt} = \frac{\int_{t_1}^{t_2} G\left(k_1 + k_2 e^{\lambda_1 t} - k_3 e^{\lambda_2 t}\right) dt}{(t_2 - t_1)} = \frac{\left(G\left(k_1 t_2 + \frac{k_2 e^{\lambda_1 t_2}}{\lambda_1} - \frac{k_3 e^{\lambda_2 t_2}}{\lambda_2}\right) - G\left(k_1 t_1 + \frac{k_2 e^{\lambda_1 t_1}}{\lambda_1} - \frac{k_3 e^{\lambda_2 t_1}}{\lambda_2}\right)\right)}{(t_2 - t_1)} \quad \textbf{[G-14]}$$

$$C_{FF,TWA} = \frac{\int_{t_1}^{t_2} C_{FF}\, dt}{\int_{t_1}^{t_2} dt} = \frac{\int_{t_1}^{t_2} G\left(\frac{1}{Q_{FF}} + k_4 e^{\lambda_1 t} - k_5 e^{\lambda_2 t}\right) dt}{(t_2 - t_1)}$$

$$= \frac{\left(G\left(\frac{t_2}{Q_{FF}} + \frac{k_4 e^{\lambda_1 t_2}}{\lambda_1} - \frac{k_5 e^{\lambda_2 t_2}}{\lambda_2}\right) - G\left(\frac{t_1}{Q_{FF}} + \frac{k_4 e^{\lambda_1 t_1}}{\lambda_1} - \frac{k_5 e^{\lambda_2 t_1}}{\lambda_2}\right)\right)}{(t_2 - t_1)} \quad \textbf{[G-15]}$$

As indicated in section 2.2.2, for the purposes of this assessment, small industrial/commercial degreasing processes are expected to operate 260 days per year for 2 hrs per day (EPA, 2001a). In addition, EPA/OPPT assumed that there is no exposure at small industrial/commercial degreasing facilities for 6 hrs per day. Thus, in order to calculate 8-hr TWA concentrations, the results from Equations [G-14] and [G-15] were multiplied by a factor of 0.25.

For the purposes of mass transfer from and to the Near-Field, the Free Surface Area, FSA, is defined to be the surface area that is available for mass transfer and is not necessarily equal to the surface area of the Near-Field. For instance, if the Near-Field is defined to be a rectangular region, as illustrated in Figure G-1, the Near-Field floor would not be available for mass transfer. Thus, FSA would be less than the actual surface area of the Near-Field:

$$FSA = 2(L_{NF} * H_{NF}) + 2(W_{NF} * H_{NF}) + (L_{NF} * W_{NF}) \quad \textbf{[G-16]}$$

Where: L_{NF}, W_{NF}, H_{NF} are the length, width, and height of the Near-Field, respectively.
If the Near-Field indoor wind speed, v_{NF}, is known and the area for mass transfer into and from the Near-Field is equal, then the Near-Field ventilation rate, Q_{NF}, is given by:

$$Q_{NF} = \frac{1}{2} * FSA * v_{NF} \quad \textbf{[G-17]}$$

If the Far-Field volume, V_{FF}, and the air exchange rate, AER, are known, then the Far-Field ventilation rate, Q_{FF}, is given by:

$$Q_{FF} = V_{FF} * AER \quad \textbf{[G-18]}$$

Based on the model inputs in Table G-1, potential workplace TCE inhalation exposure values can be estimated for workers in the near-field and for bystanders in the far-field (see Table G-2).

Table G-1. Model Inputs for Small / Industrial Commercial Degreasing Facilities			
Parameter	**Units**	**Parameter Values**	**Comments**
V_{FF}	ft^3 (m^3)	10,593 to 70,620 (300 to 2,000)	Values supported by von Grote et al. (2003)
AER	1/hr	2 to 15	Values supported by von Grote et al. (2003) and EPA (2013b)
v_{NF}	cm / s (m/hr)	10 (360)	Value is ~50th percentile supported by Baldwin and Maynard (1998)
L_{NF}	ft (m)	10 (3.05)	Assumes volatile source is centered in the near-field and worker activities are within 5 feet of the emitting source
W_{NF}	ft (m)	10 (3.05)	
H_{NF}	ft (m)	6 (1.83)	Adequate height to capture a typical worker's breathing zone
FSA	ft^2 (m^2)	340 (32)	Equation [G-16]
t_1	hr	0	Starting time for Equations [G-14] and [G-15]
t_2	hr	2	Ending time for Equations [14] and [15]; as indicated earlier, small commercial/industrial degreasing processes are expected to operate for 2 hrs per day (EPA, 2001a)
G	g / min (mg/hr)	5 to 50 (3E+5 to 3E+6)	No local exhaust ventilation (LEV; see Table 2-8 in section 2.3.2 in the main document
		0.5 to 5 (3E+4 to 3E+5)	With LEV; potential operating TCE emissions reduced by 90% (Wadden et al., 1989)

Table G-2. Potential Workplace TCE Inhalation Exposures and Number of Workers Exposed						
Type of Facility	Potential Workplace TCE Inhalation Exposures (8-hr TWA)					
	Near-Field			Far-Field		
	LEV (ppm)	No LEV (ppm)	Number of Workers	LEV (ppm)	No LEV (ppm)	Number of Workers
Small commercial degreasing facility	0.3 (low-end estimate) 20 (upper-end estimate)	3 (low-end estimate) 197 (upper-end estimate)	8,730	0.04 (low-end estimate) 17 (upper-end estimate)	0.4 (low-end estimate) 172 (upper-end estimate)	20,952

Appendix H CALCULATION OF TCE EXPOSURES FROM SPOT CLEANING AT DRY CLEANING FACILITIES

For background information on the Near-Field/Far-Field mass balance model, please refer to Appendix G. Based on the model inputs in Table H-1, potential workplace TCE inhalation exposures from spot cleaning at dry cleaning facilities were estimated for workers in the near-field and for occupational bystanders in the far-field (see Table H-2).

Table H-1. Model Inputs for Dry Cleaning Facilities

Parameter	Units	Parameter Values	Comments
V_{FF}	ft^3 (m^3)	7,062 to 70,620 (200 to 3,000)	Values supported by von Grote et al. (2006)
AER	1/hr	1 to 19	Values supported by von Grote et al. (2006) and EPA (2013b)
v_{NF}	cm / s (m/hr)	10 (360)	Values is ~50th percentile supported by Baldwin and Maynard (1998)
L_{NF}	ft (m)	10 (3.05)	Assumes volatile source is centered in the near-field and worker activities are within 5 feet of the emitting source
W_{NF}	ft (m)	10 (3.05)	
H_{NF}	ft (m)	6 (1.83)	Adequate height to capture a typical worker's breathing zone
FSA	ft^2 (m^2)	340 (32)	See Equation [G-16] in Appendix G
t_1	hr	0	Starting time for Equations [G-14] and [G-15] (see equations in Appendix G)
t_2	hr	8	Ending time for Equations [14] and [15] (see equations in Appendix G); as indicated earlier, dry cleaning facilities are expected to operate for 8 hrs per day (BLS, 2012)
G	g / min (mg/hr)	0.037 to 0.37 (2.22E+3 to 2.22E+4)	No local exhaust ventilation (LEV); see Table 2-11 in section 2.4.2 in the main document
		0.0037 to 0.037 (222 to 2.22E+3)	With LEV; TCE emissions reduced by 90% (Wadden et al., 1989)

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Table H-2. Potential Workplace TCE Inhalation Exposures and Number of Workers Exposed						
Type of Facility	Potential Workplace TCE Inhalation Exposures (8-hr TWA)					
	Near-Field			Far-Field		
	With LEV (ppm)	No LEV (ppm)	Number of Workers	With LEV (ppm)	No LEV (ppm)	Number of Workers
Dry Cleaning Facility	0.008 (low-end estimate) 2 (upper-end estimate)	0.08 (low-end estimate) 19 (upper-end estimate)	36,000	0.0007 (low-end estimate) 2 (upper-end estimate)	0.007 (low-end estimate) 18 (upper-end estimate)	252,000

Appendix I EFAST2/CEM INDOOR MODELING, CONSUMER BEHAVIOR PARAMETERS AND MODEL COMPARISONS

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) performs assessments of exposures to common products to consumers. This section describes the values that were chosen for the modeling parameters in CEM to provide more support for the TCE exposure assessment. This material is also described in the E-FAST2 manual available on the EPA's webpage. The first section describes house and emission properties, the second section describes the consumer use patterns and the final section will discuss comparisons of CEM with other exposure models.

The default parameters used for household characteristics were all set to mean or median values based on data found in the available literature and these were used in the TCE assessment. Consumer behavior patterns were not set to EFAST2's default settings, which were high -end values. Alternatively, a hypothetical scenario was created for the user of two products containing TCE. Westat survey data provided some indication that the values used were below mean or median for the mass but above the mean for the time spent in the room of use. However, the Westat survey categories were not completely aligned with the description of the products chosen to model in the exposure assessment section.

I-1 Default parameters used in CEM for emission and household characteristics

Table I-1 summarizes the selection and justification of exposure parameters for CEM for the purposes of estimation of indoor air concentrations of TCE.

I-1-1 Air Exchange Rate

The air exchange rate used by OPPT for the TCE model runs was the E-FAST/CEM default value of 0.45 air changes per hour (ACH). This choice is consistent with the recommended central value per the current and prior editions of the Exposure Factors Handbook (EFH) (Figure I-1) (EPA, 1997, 2011a).

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Table I-1. Summary of CEM Parameters for Estimation of TCE Indoor Air Concentrations			
S. No	**Modeling Input**	**Value**	**Justification/Source**
1	Air exchange rate (air exchanges/hr)	0.45	Recommended 50th percentile value of residential air exchange rate for all regions within the United States (Koontz and Rector, 1995)
2	Overspray fraction (unitless)	0.01	Selection based on professional judgment (US EPA 2007a).
3	Whole House volume (m^3)	369	Value was obtained from EPA (1997). Although the updated EFH (EPA, 2011a) provides a larger number (492 m^3), the older value was retained in order to provide more conservative estimates.
4	Emission rate (hrs^{-1})	101.06	Estimated using Chinn's algorithm (Chinn, 1981) based on E-FAST model documentation. This algorithm utilizes molecular weight and vapor pressure to estimate emission rates.
5	Inhalation rate (m^3/hr)	0.74 – During use 0.61 – After use	*During product use:* 0.74 m^3/hr based on short-term exposure at light activity level (EPA, 2011a) *After product use:* 0.611 m^3/hr (EPA, 2011a) Short term inhalation values during light activity (male and female combined) were taken from the following age groups and averaged to create an estimate for inhalation rate during product use. 21 to <31 years; 31 to <41 years; 41 to <51 years; 51 to <61 years; 61 to <71 years; and 71 to <81 years.
6	Body weight (kg)	80	Mean value of body weights for all adults (≥21 yrs), male and female combined. Value based on EPA analysis of NHANES 1999–2006 data (EPA, 2011a)
7	Interzonal airflow rate (m^3/hr)	81.73	Air flow rate between the room of use (utility room or zone 1) and the rest of the house (zone 2 (Koontz and Rector, 1995)

Figure I-1. Screen capture of Summary of Recommended Values for Residential Building Parameters from the Exposure Factors Handbook (EPA, 2011a)

Table 19-1. Summary of Recommended Values for Residential Building Parameters

	Mean	10th Percentile	Source
Volume of Residence[a]	492 m^3 (central estimate)[b]	154 m^3 (lower percentile)[c]	U.S. EPA 2010 analysis of U.S. DOE, 2008a
Air Exchange Rate	0.45 ACH (central estimate)[d]	0.18 ACH (lower percentile)[e]	Koontz and Rector, 1995

[a] Volumes vary with type of housing. For specific housing type volumes, see Table 19-6.
[b] Mean value presented in Table 19-6 recommended for use as a central estimate for all single family homes, including mobile homes and multifamily units.
[c] 10th percentile value from Table 19-8 recommended to be used as a lower percentile estimate.
[d] Median value recommended to be used as a central estimate based across all U.S. census regions (see Table 19-24).
[e] 10th percentile value across all U.S. census regions recommended to be used as a lower percentile value (see Table 19-24).
ACH = Air changes per hour.

I-1-2 Overspray fraction

The selection of a default overspray fraction of 0.01 in CEM was based on professional judgment (EPA, 2007b). For the scenarios that were modeled, the E-FAST inhalation exposure metrics were not sensitive to the overspray/aerosolized fraction. For example, for the TCE run labeled "ID Number: 1 fixative user 21-78" the modeled peak concentration (Cp_{pot}) was 66.97 mg/m^3. If this fraction was changed to 0.25, then a nearly identical modeled peak concentration of 67.04 mg/m^3 was obtained. Here we are only using the peak concentration as a model diagnostic, not as a tool to understand exposures for any time scale longer than 10 seconds.

I-1-3 Emission Rate

The emitted mass was handled in CEM in two ways. When an aerosol product is used, some of the product does not reach the intended application surface but remains in the air. This portion, commonly known as the overspray, is assumed to be 1% of the product emitted during use. This results in the constant emission of TCE to the room air over the duration of use (0.5 hrs or 1 hour depending on the scenario). The remaining fraction (99%) that is striking the intended application surface forms a film. This film is treated as an incremental source, as described below (Figure I-2).

Figure I-2. Screen capture of E-FAST equations for estimation of emission rate

For a **product that is applied to surface**, such as a general purpose cleaner or a latex paint, an incremental source model is used. This model assumes a constant application rate over the specified duration of use; each instantaneously applied segment has an emission rate that declines exponentially over time, at a rate that depends on the chemical's molecular weight (MW) and vapor pressure (VP).

In the case of a general purpose cleaner, the equation for exponentially declining emissions for each instantaneously applied segment is as follows:

$$E(t) = E(0) \times \exp(-kt) \qquad \text{(Eq. 3-41)}$$

where E (t) is the emission rate (mass/time) at time t (in hours), E (0) is the initial emission rate at time 0, k is a first-order rate constant for the emissions decline (inverse hours), and t is elapsed time (hours). The value of k is determined from an empirical relationship, developed by Chinn (1981), between the time (in hours) required for 90 percent of a pure chemical film to evaporate (EvapTime) and the chemical's molecular weight and vapor pressure:

$$EvapTime = \frac{145}{(MW \times VP)^{0.9546}} \qquad \text{(Eq. 3-42)}$$

The value of k is determined from the 90 percent evaporation time as follows:

$$k = \frac{\ln(10)}{EvapTime} \qquad \text{(Eq. 3-43)}$$

Using Equation 3-42 to calculate *EvapTime*:

$$EvapTime = \frac{145}{(131.4 \times 73.46)^{0.9546}}$$

Where,

Molecular weight (MW) = 131.4 g/mole

Vapor Pressure (VP) = 73.46 torr

Hence, *EvapTime* = 0.023 hrs or 1.36 min

Using Equation 3-43 to calculate *Emission Rate (k):*

$$k = \frac{\ln(10)}{1.36}$$

Hence, *Emission Rate (k)* = 101.06 hrs^{-1} or 1.68 min^{-1}

Because Chinn's algorithm assumes a pure chemical film, it tends to produce a lower-bound estimate of the evaporation time; thus, overestimates the peak concentration. In products that are a mixture of chemicals, interaction forces between the different chemicals could alter the evaporation rate of individual constituents. However, this is only a concern for the spray fixative since the degreaser use results in only TCE on the surface, which is consistent with Chinn's study (Chinn, 1981).

In the simulation done for this assessment, the outcome was not expected to be strongly dependent on the exact value of *k* due to the long time period the consumer spent in the room of use after the period of product application. All of the TCE mass was expected to enter the air before the user leaves the room even if the k value was adjusted to be less conservative. Currently the evaporation time for 90% of the TCE in the film on the application surface (0.023 hrs or 1. 36 min) was much less than the 2 hrs the user spent in the room of use, about two orders of magnitude. Even if this value were to increase, due to intermolecular interactions within a more complicated mixture decreasing the emission rate, it would likely still be less than the 2 hrs spent in the room of use.

I-1-4 House Volume and movement within the home

CEM currently uses a default house volume (369 m^3) that is based on the mean value from the 1997 edition of the EFH (EPA, 1997). The 2011 edition of the EFH recommends a larger value of 492 m^3 in recognition of the trend toward larger houses over the time between successive editions (EPA, 2011a; see Table 19-1 extract on page 1). The 50th% value (median) in the 2011 EFH edition is 395 m^3, so the mean volume used from the 1997 EFH is still close to the most recent median value.

Examination of tables 19-8 and 19-9 of the 2011 EFH indicate that the increased mean house volume is mostly due to the increase in the volume of the homes at the high end of the distribution (75th percentile and above), whereas the homes in the lower 50th percentile are relatively unchanged (EPA, 2011a). The lower value that was used would tend to produce more conservative exposure estimates, other things being equal, due to the smaller volume available for dispersal/dilution of the emitted TCE.

However the exposure values for the user could be more impacted by the size of the room selected during use. The volume assigned to the room of use was 20 m^3 for a utility room. The utility room in this case served as a proxy for a hobby/craft room that might be represented, for example, by a 9 ft x 10 ft room. With a ceiling height of 8 ft, the room volume would be 720 ft^3 or ~ 20.4 m^3. This room is zone 1 in the CEM simulations for the two products; zone 2 is the rest of the house (349 m^3). The user and bystander move about the home according to a hypothetical behavior pattern constructed to represent a day spent mostly indoors. Since the behavior patterns do not involve the residents entering the hobby room except to use the product, the user spends the rest of the time either in zone 2 or outside (where there is no chemical exposure) and the bystander spends the entire 24 hrs either in zone 2 or outside.

I-1-5 Inhalation rate and body weight

We used the 2011 EFH to obtain the inhalation rate and body weight values for the simulation (EPA, 2011a). These values were based on the NHANES data (1999-2006) and correspond to the age groups reported in the 2011 EFH. It is important to note that in the exposure assessment only the exposure doses will be affected by these parameters. Indoor air concentrations are determined by the product use patterns, the volume of the room and of the house, and the physical-chemical properties of TCE. Body weight and inhalation rate do not change the indoor air concentrations that the model calculates. The indoor air concentrations are the only part of the exposure assessment that is used in the final risk assessment.

I-2 Consumer behavior patterns

E-FAST2/CEM requires the input of consumer behavior pattern information, including mass of product used, duration of use, time spent in the room of use and the volume of the room of use. By default, E-FAST2/CEM uses pre-set, high-end values for a variety of consumer use scenarios when use information is not available for specific products. Under these conditions, the model results tend to over predict the exposure.

EPA/OPPT did not have consumer behavior pattern information for the products being evaluated in this assessment. Instead of using the E-FAST2/CEM's default inputs, EPA/OPPT used professional judgment to inform the selection of hypothetical input parameters and assumptions representing the consumers' behavior patterns.

Commenters suggested that EPA/OPPT should look through the Westat survey data (EPA, 1987a)[32] to look for information that could be used within the TCE assessment. EPA/OPPT frequently uses the 1987 Westat survey data for consumer modeling because the report provides information about a range of product categories. A closer examination of the Westat data revealed that the Westat survey categories were not well aligned with either of the products modeled in this assessment.

Table I-2 provides a summary of the information provided in the Westat survey and how it compares to the values used in this assessment. The spray degreaser product had some similarity with two categories from the survey: solvent type cleaning fluids or degreasers and brake cleaners/quieters. Although the survey values were not used in the TCE's consumer model assessment, the Westat data supplies an indication that the product masses used for the degreaser scenario and that the room of use are not unreasonable high (i.e. overly conservative). The time spent in the room of use is potentially closer to a 90th percentile value.

[32] The Westat study was prepared for EPA by Battelle EPA (1987a).

Table I-2. Comparison of Westat Survey Data and EPA's TCE Degreaser Simulation Values				
Westat data for solvent type cleaning fluids or degreasers				**EPA TCE Degreaser Simulation values**
	Mean	**Median (50th%)**	**90th %**	
Time spent using product	29.48 min	15.0 min	60.0 min	60 min
Time spent in room after use	33.29 min	3.0 min	60.0 min	60 min
Amount of product per event	9.45 oz (268 g)	3.3 oz (94 g)	16.0 oz (454 g)	0.85 oz (24 g)
	Household location			
Room of use	Garage 12.2% Outside 28.0% **Inside room 49.1 %**			Utility room
Westat data for brake cleaners/quieters				**Simulation values**
	Mean	**Median (50th%)**	**90th %**	
Time spent using product	23.38 min	15.0 min	49.5 min	60 min
Time spent in room after use	10.27 min	0.0 min	30.0 min	60 min
Amount of product per event	6.26 oz (177 g)	4.0 oz (113 g)	12.0 oz (340 g)	0.85 oz (24 g)
	Household location			
Room of use	Garage 17.7% **Outside 77.1 %** Inside room 5.2 %			Utility room

I-2-1 Westat data for solvent type cleaning fluids

The description of the Westat data for solvent-type cleaning fluids matched well with the intended use of the spray degreaser product that EPA/OPPT modeled as seen in Table I-2. Unfortunately, a majority of the respondents in the Westat survey stated that they were describing their use of a liquid product (74.4%), not an aerosol product (25.6 %). EPA/OPPT had difficulties in making direct comparisons of the survey's masses to those used in the exposure simulations.However, it is the only currently available data that EPA/OPPT found closely relating to the products under evaluation.

The mass of product (24 g) that EPA/OPPT used was well below the mean and median values reported by survey respondents. E-FAST2/CEM is highly sensitive to the mass of product used suggesting that the EPA/OPPT's simulated exposure would be potentially less conservative (i.e. show lower air concentrations) if users of the TCE degreaser fit into similar use patterns to the Westat survey.

The plurality of Westat-surveyed users (49.1%) also stated that they used the product in a room inside the house that was not the basement or the living room, making it plausible that the modeled room have a relatively small volume. This supports the selection of the utility room for the spray degreaser scenario in this exposure assessment. The time of use selected for the simulation is at the high end of the survey data (90th%), which would result in more conservative exposures (i.e. higher exposures) since the selected value was twice the mean value reported by Westat.

I-2-2 Westat data for brake cleaners/quieters

The description of this product category in the survey matches less well than the previous survey group. The description for the chosen product in the TCE assessment does not describe use in an automotive setting but the function and chemical composition of the product may be similar and a large section of the respondents in the Westat survey for this category stated that they had used an aerosol product (65.6%). As before the mass used in the TCE simulations was well below both the mean and median survey values. Since this is an automotive product category a large fraction of the respondents used the product outdoors or in the garage. If users are outdoors it would significantly decrease exposures, but it is not clear what fraction of the chosen product's users take this precaution. The time of use chosen in the simulation was also larger than the surveyed data for this category.

I-2-3 Summary of Westat data

The survey data provided an indication that the room of use was appropriate and that the mass used in the simulations was potentially on the low end. The time of use and the subsequent time spent in the room after use were the only parameters in the simulation that could be properly described as high-end from comparisons with the survey data. All of these comparisons suffer from the absence of a Westat survey category that matches well with the two products selected for the TCE assessment, a solvent spray degreaser and a spray fixative.

I-3 Comparison of EFAST CEM with MCCEM

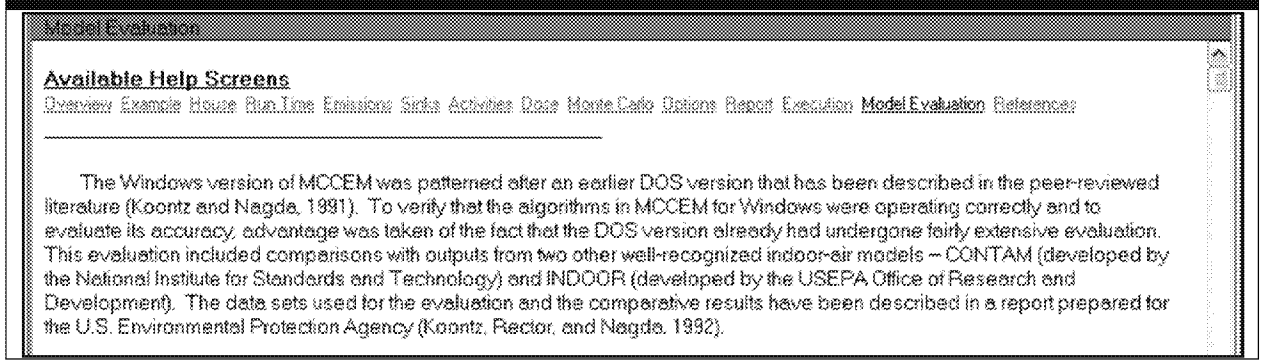
Peer reviewers recommended that EPA/OPPT attempt to use other models besides CEM, such as the Multichamber Concentration and Exposure Model (MCCEM) to calculate exposures for the TCE assessment. Reviewers also were interested if CEM had been validated or compared to other models that simulate indoor exposures to chemicals. Thus, EPA/OPPT compared the E-FAST2/CEM model with MCCEM to address peer review comments.

The inhalation exposures determined by E-FAST2/CEM use the same calculation engine as MCCEM. MCCEM is a peer-reviewed model that EPA/OPPT uses for assessing consumer inhalation exposure. MCCEM is considered to be a higher tier model than CEM as it is able to use measured chamber data for mass released due to product use to calculate exposures. An earlier, DOS-based version of MCCEM was formally presented to the modeling community in a 1991 issue of the *Indoor Air* journal. In 1998, EPA peer reviewed a Windows-based version of MCCEM. Unfortunately, chamber data were not available for the TCE-containing products that

were chosen in this assessment. Thus, EPA/OPPT could not run the MCCEM model for the characterization of consumer exposures.

MCCEM was the subject of a model evaluation effort for EPA (Figure I-3) whereby its outputs were compared with those from two other well-recognized indoor-air models. These two models were CONTAM developed by National Institute of Standards and Technology (NIST), and INDOOR developed by EPA's Indoor Environmental Management Branch (IEMB) in Research Triangle Park, NC. Results from all three of the models were in very close agreement for cases/scenarios that were included in the evaluation effort. Lastly, a quick comparison of the two models (EFAST's CEM and MCCEM) yielded almost identical results, for the same set of input values.

Figure I-3. Screen Capture of MCCEM Model Evaluation Efforts


Model Evaluation

Available Help Screens

Overview Example House Run Time Emissions Sinks Activities Dose Monte Carlo Options Report Execution Model Evaluation References

The Windows version of MCCEM was patterned after an earlier DOS version that has been described in the peer-reviewed literature (Koontz and Nagda, 1991). To verify that the algorithms in MCCEM for Windows were operating correctly and to evaluate its accuracy, advantage was taken of the fact that the DOS version already had undergone fairly extensive evaluation. This evaluation included comparisons with outputs from two other well-recognized indoor-air models – CONTAM (developed by the National Institute for Standards and Technology) and INDOOR (developed by the USEPA Office of Research and Development). The data sets used for the evaluation and the comparative results have been described in a report prepared for the U.S. Environmental Protection Agency (Koontz, Rector, and Nagda, 1992).

Appendix J CONVERTING E-FAST ADRs TO AIR CONCENTRATIONS

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) performs assessments of exposures to common products to consumers. The exposure values generated using the E-FAST/CEM models are in mg/kg-bw/day (Table J-1). The only output in the acute exposure scenario expressed as a concentration was the peak concentration, which represented the maximum concentration in air calculated by the model during any 10-second time step during (in this case) 24 hrs. This value did not realistically describe a 24-hr exposure, even as a worst-case scenario (all peak concentrations can be found in documents cited in the supplementary documents containing the CEM runs.).

Table J-1. Estimated TCE Potential Acute Dose Rates from the Residential Indoor Use of Solvent Degreasers or Clear Protecting Coating Sprays

Age (yrs)	Clear Protective Coating Spray User ADR_{pot} (mg/kg-bw/day)	Clear Protective Coating Spray Bystander ADR_{pot} (mg/kg-bw/day)	Solvent Degreaser User ADR_{pot} (mg/kg-bw/day)	Solvent Degreaser Bystander ADR_{pot} (mg/kg-bw/day)
<1	NA	0.5	NA	3
1-2		0.4		3
3-5		0.4		2
6-10		0.3		2
11-15		0.2		1
16-20	0.5	0.2	3	1
21-78	0.4	0.1	3	0.8

Notes: ADR_{pot} = potential acute dose rate; NA = not applicable

Thus, to convert the E-FAST CEM outputs from mg/kg-bw/day to ppm, we used the equation for the potential acute dose rate reported in the E-FAST manual (EPA, 2007b). The general expression for the potential acute dose rate (ADR_{pot}) is as follows:

$$ADRpot = \frac{(Cair \times InhR \times FQ \times DEv \times ED)}{BW \times AT}$$

where:

ADR_{pot} = potential acute dose rate (mg/kg-bw/day)
Cair = exposure concentration (mg/m^3)
InhR = inhalation rate (m^3/hr)
FQ = frequency of product use (events/year)
DEv = duration of an event (hour/event)
ED = exposure duration (years of product usage)
BW = body weight (kg)
AT = averaging time (days)

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Rearranging and simplifying this equation to calculate *an approximation* for C_{air} over the 24-hr averaging time for the ADR_{POT} results in the following equation:

$$Cair \approx \frac{ADRpot \ x \ BW}{InhR \ x \ 24}$$

This simplification is reasonable since the averaging time for acute exposure is one day (24 hrs). In both scenarios, the frequency is just once per day. Although the duration of the event for the two consumer scenarios is either one hour (degreaser) or 0.5 hrs (clear protective coating spray)[33], for the purposes of this exercise and to convert the model output to a more useable exposure value to compare to the hazard value, there is no correction for this difference. This assumption is still conservative since the values generated were reasonably high exposures that probably overestimated the actual exposures.

An example calculation is presented below, since the final value is in mg/m^3 and the desired units will be in ppm. All calculated values are presented in Table J-2.

For the clear protective coating spray use, 21- to 78-yr-old user:

ADR_{pot} = 0.45 mg/kg-bw/day
InhR (during use; 0.5 hrs) = 0.74 m^3/hr
InhR (other times; 23.5 hrs) = 0.611 m^3/hr
BW = 80 kg [using 2011 Exposure Factors Handbook; EPA (2011a)]

$$C_{air} = \frac{(0.45 \text{ mg/kg-bw/day}) \ (80 \text{ kg})}{[0.74 \text{ m}^3\text{/hr x } 0.5 \text{ hr}) + [0.611 \text{ m}^3\text{/hr x } 23.5 \text{ m}^3\text{/hr})}$$

= 2.4 mg/m^3; converting to ppm[34] = 0.446 ppm (rounded to 0.4 ppm to use a single significant figure given the assumptions in the back-calculation).

[33] However, for the user in both scenarios, the inhalation rates were slightly higher during use of the product, as stipulated in the model outputs. Thus, for the degreaser use, an inhalation rate of 0.74 m^3/hr (for 21 to 78 year olds, 0.72 m^3/hr for the 16 to 20 year olds) was used for one hour, and 0.611 m^3/hr (for 21 to 78 yr olds, 0.679 m^3/hr for the 16 to 20 yr olds) for the remaining 23 hrs. For the clear protective coating spray use, the higher, user inhalation rate was used for 0.5 hrs, with the "normal" rate used for 23.5 hrs. This correction was not done for any bystander scenario.

[34] 1 ppm = 5.374 mg/m^3.

Table J-2. Estimated TCE Inhalation Calculated Concentration in Air (Over Course of Day) from Use of Two Consumer Products Indoors at Residences				
Ages	**Clear Protective Coating Spray User ADR_{pot} (ppm)**	**Clear Protective Coating Spray Bystander ADR_{pot} (ppm)**	**Solvent Degreaser User ADR_{pot} (ppm)**	**Solvent Degreaser Bystander ADR_{pot} (ppm)**
<1	NA	0.1	NA	0.8
1-2	NA	0.1	NA	0.8
3-5	NA	0.1	NA	0.8
6-10	NA	0.1	NA	0.8
11-15	NA	0.1	NA	0.8
16-20	0.4	0.1	2	0.8
>21	0.4	0.1	2	0.8

Notes:
- NA = not applicable
- 1 ppm = 5.374 mg/m^3

As seen in the table J-2, each age group is exposed to the same modeled air concentrations and therefore all age group have the same ADR_{pot} (ppm). The conversion from dose to air concentrations resulted in 24-hr time averaged indoor air concentrations for TCE (ppm) that were not sensitive to user specific characteristics such as body weight or respiration rate. This is why the same value was present throughout each column in Table J-2. Values in Table J-2 were the only values used in the risk assessment.

The age groups are present in Tables J-1 and J-2 and model output sheets in the supplementary documents, which reflect the output values of the CEM model. Note that CEM also assumes that the user will be over 16. However, Table J-2 shows that the age groups are irrelevant for the calculated concentrations of TCE in the air. In section 2.5.4 of the risk assessment, age groups were collapsed within each user or bystander use scenario. Since there is not sufficiently refined data to create different consumer behavior patterns for different age groups, EPA/OPPT assumed that younger users (<16) of degreaser and arts/crafts products would be exposed to the same concentrations as older users (>16).

Appendix K RISK ASSESSMENT GUIDELINES, LITERATURE SEARCH STRATEGY, STUDY SELECTION AND DATA QUALITY CRITERIA FOR THE TCE IRIS TOXICOLOGICAL REVIEW AND OPPT STUDY REVIEW

K-1 Risk Assessment Guidelines

The description below was extracted from the TCE IRIS assessment published in September 2011 (EPA, 2011e, Chapter 1, pages 1-1 to 1-2).

Development of these hazard identification and dose-response assessments for TCE has followed the general guidelines for risk assessment as set forth by the National Research Council (NRC, 1983). U.S. Environmental Protection Agency (U.S. EPA) Guidelines and Risk Assessment Forum Technical Panel Reports that may have been used in the development of this assessment include the following:

1. *Guidelines for the Health Risk Assessment of Chemical Mixtures (EPA, 1986c)*
2. *Guidelines for Mutagenicity Risk Assessment (EPA, 1986b)*
3. *Recommendations for and Documentation of Biological Values for Use in Risk Assessment (EPA, 1988a)*
4. *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991)
5. *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (EPA, 1994a)*
6. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA, 1994b)*
7. *Use of the Benchmark Dose Approach in Health Risk Assessment (EPA, 1995c)*
8. *Guidelines for Reproductive Toxicity Risk Assessment (EPA, 1996)*
9. *Guidelines for Neurotoxicity Risk Assessment* (EPA, 1998a)
10. *Science Policy Council Handbook: Risk Characterization* (EPA, 2000b)
11. *Benchmark Dose Technical Guidance Document* (EPA, 2000a)
12. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA, 2000c)
13. *A Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002b)
14. *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a)
15. *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005b)
16. *Science Policy Council Handbook: Peer Review* (EPA, 2006c)
17. *A Framework for Assessing Health Risks of Environmental Exposures to Children* (EPA, 2006b)

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K-2 Literature Search Strategy

When developing the TCE IRIS assessment, the literature search strategy was based on the chemical name, Chemical Abstracts Service Registry Number (CASRN), and multiple common synonyms (EPA, 2011e). Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

Primary, peer-reviewed literature identified through December 2010 was included where that literature was determined to be critical to the assessment. The relevant literature included publications on TCE which were identified through Toxicology Literature Online (TOXLINE), the U.S. National Library of Medicine's MEDLINE, the Toxic Substance Control Act Test Submission Database (TSCATS), the Registry of Toxic Effects of Chemical Substances (RTECS), the Chemical Carcinogenesis Research Information System (CCRIS), the Developmental and Reproductive Toxicology/Environmental Teratology Information Center (DART/ETIC), the Environmental Mutagens Information Center (EMIC) and Environmental Mutagen Information Center Backfile (EMICBACK) databases, the Hazardous Substances Data Bank (HSDB), the Genetic Toxicology Data Bank (GENE-TOX), Chemical abstracts, and Current Contents. Other information, including health assessments developed by other organizations, review articles, and independent analyses of the health effects data were retrieved and included in the assessment when appropriate (EPA, 2011e).

K-3 Study Selection and Data Quality Criteria Which Served As the Basis for This Assessment

- *Epidemiology data*: Study quality evaluation criteria and a general format for the capture of epidemiology study data and characterization have previously been developed in the IRIS program and have been presented in the *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991). These factors include the study power, potential bias in data collection, selection bias, measurement biases associated with exposure and outcome, and consideration of potential confounding and effect modification. This format was used to summarize study information and observed strengths, biases, and confounding factors for each study (Figure K-1).

- *Animal toxicology data*: Study quality evaluation criteria for *in vivo*, *in vitro*, and *in ovo* toxicology studies were developed.These criteria included considerations described in (EPA, 1991) and focused on the adequacy of study design and documentation of information on the test animals (e.g., species, strain, source, sex, age/lifestage/embryonic stage), environment (e.g., husbandry, culture medium), test substance (e.g., identification, purity, analytical confirmation of stability and concentration), treatment (e.g., dose levels, controls, vehicle, group sizes, duration, route of administration), endpoints evaluated (e.g., schedule of evaluation, randomization and blinding procedures, assessment methods), and reporting (quality and completeness) (Figure K-2). Analyses of the study strengths and limitations were also conducted.

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Figure K-1. Study Quality Considerations for Epidemiological Studies

Feature		Example Questions
Selection	Participants	• Were inclusion and exclusion criteria applied consistently across study groups?
	Comparability	• Are baseline characteristics similar between groups? If not, did the analysis control for differences? • Is the comparison group appropriate, including having both exposed and non-exposed subjects drawn from the same population:
Attrition	Attrition Rate	• Was the attrition rate uniformly low?
	Length of Follow-Up	• In cohort studies: Dose the length of follow-up differ between groups? • In case-control studies: Is the time period between exposure between exposure/intervention and outcome the same for cases and controls? • Was follow-up long enough to assess the outcome of interest?
Detection	Exposure Characteristics	• What is the level of exposure misclassification? • Is there an adequate level of exposure variability to detect an effect? • Are there adequate numbers of persons exposed at various exposure levels to detect a dose-response effect? • What is the extent of reliance on imputed exposure levels?
	Outcome Assessment	• Were the outcome assessors blinded to the exposure or intervention status of participants? • Is there confidence that the outcome of interest preceded exposure?
	Confounding Variables or Exposure	• Are confounding variables assessed using reliable and consistent measures? • Did researchers adjust or control for other exposures or interventions that are anticipated to bias results?
	Statistical Tests	• Are statistical analyses performed with reliable tests and implemented consistently?

Figure K- 2. Study Quality Considerations for Animal Studies

Feature	Example Questions	
Exposure Quality	•Were the exposures well designed and tightly controlled? •Was the test article/formulation adequately identified and characterized? Are co-exposures expected as a result of test article composition? •Is the administration route relevant to human exposure? •Are the exposure levels relevant? •Inhalation exposure: Were analytical concentrations in the test animals' breathing zone measured and reported (i.e., not just target or nominal concentrations)? •Inhalation exposure: For aerosol studies, were the mass median aerodynamic diameter and geometric standard deviation reported?	•Inhalation exposure: Was the chamber type appropriate? Dynamic chambers should be used; static chambers are not recommended. •Inhalation exposure: Were appropriate methods used to generate the test article and measure the analytical concentration? •Diet/Water Exposure: Was consumption measured to allow for accurate dose determinations? Were stability and homogeneity of the test substance maintained? Was palatability an issue? •Gavage Exposure: Was an appropriate vehicle used? Are there any toxicokinetic differences due to bolus dosing? Consider relevance to human exposures.
Test Animals	•Were the test animals appropriate for evaluation of the specified effect(s)? •Were the species, strain, sex, and/or age of the test animals appropriate for the effect(s) measured? •Were the control and exposed populations matched in all aspects other than exposure?	•Were an appropriate number of animals examined, based on what is known about the particular endpoint(s) in question? •Were there any notable issues regarding animal housing or food and water consumption?
Study Design	•Is the study design appropriate for the effect(s) and chemical analyzed? •Were exposure frequency and duration appropriate for the effect(s) measured? •Were anticipated confounding factors caused by selection bias controlled for in the study design (e.g., correction for potential litter bias; randomization of treatment groups)? •Was the timing of the endpoint evaluation (e.g., latency from exposure) appropriate? •Was it a Good Laboratory Practices (GLP) study?	•Was it designed according to established guidelines (e.g., EPA, OECD)? Was it designed to specifically test the endpoint(s) in question? •Did the study design include other experimental procedures (e.g., surgery) that may influence the results of the toxicity endpoint(s) in question? Were they controlled for? •Was the study design able to detect the most sensitive effects in the most sensitive population(s)? •Were multiple exposure groups tested? Was justification for exposure group spacing given? Was recovery or adaptation tested?
Toxicity Endpoints	•Are the protocols used for evaluating a specific endpoint reliable and the study endpoints chosen relevant to humans? •Are the endpoints measured relevant to humans? Do the endpoints evaluate an adverse effect on the health outcome in question? •Were the outcomes evaluated according to established protocols? If not, were the approaches biologically sound? Were any key protocol details omitted?	•Were all necessary control experiments performed to allow for selective examination of the endpoint in question? •As appropriate, were steps taken to minimize experimenter bias (e.g., blinding)? •Does the methodology employed represent the most appropriate and discriminating option for the chosen endpoint?
Data Presentation and Analysis	•Were statistical methods and presentation of data sufficient to accurately define the direction and magnitude of the observed effect(s)? •Are the statistical methods and comparisons appropriate? •Was sufficient sampling performed to detect a biologically relevant effect (e.g., appropriate number of slides examined)?	•Does the data present pooled groups that should be displayed separately (e.g., pooled exposure groups; pooled sexes) and/or analyzed separately? •Was an unexpectedly high/low level of within-study variability and/or variation from historical measures reported or explained? •As appropriate, were issues such as systemic and maternal toxicity (e.g., body weight) considered?
Reporting	•Are descriptions of study methods and results for all endpoints sufficient to allow for study quality evaluations? •Were the details of the exposure protocols and equipment provided? •Were test animal specifics adequately presented? •Are the protocols for all study endpoints clearly described? Is sufficient detail provided to reproduce the experiment(s)?	•Are the statistical methods applied for data analysis provided and applied in a transparent manner? Was variability reported? •Did the study evaluate a unique cohort of animals (i.e., are multiple studies linked)? •Are group sizes and results reported quantitatively for each exposure group, time-point, and endpoint examined?

Appendix L LIST OF ORAL AND INHALATION STUDIES SUITABLE FOR NON-CANCER DOSE-RESPONSE ANALYSIS IN THE TCE IRIS ASSESSMENT

L-1 Liver Effects

Target Organ	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Liver	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures, variable time periods for 30-120 days	$BMDL_{10}$= 21.6 ppm	Increased liver/body weight ratio	25	12	9.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (male)	Oral (gavage)	100 to 3,200 mg/kg-bw/day	6 weeks	$BMDL_{10}$= 82 mg/kg-bw/day		32	15	11	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Buben and O'Flaherty (1985)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 25 ppm		53	24	19	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-2 Kidney Effects

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Kidney	Rat (female)	Oral (gavage)	500 to 1,000 mg/kg-bw/day	5 days/week for 104 weeks	$BMDL_{05}$ = 9.45 mg/kg-bw/day	Toxic nephropathy	0.042	0.0085	0.0056	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	NTP (1988)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hr/day, 5 days/week for 4 weeks	$BMDL_{10}$= 15.7 ppm	Increased kidney weight/body weight ratio	0.099	0.020	0.013	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Woolhiser et al. (2006)
	Rat (male)	Oral (gavage)	50 to 250 mg/kg-bw/day	4-5 days/week for 52 weeks	$BMDL_{10}$ = 34 mg/kg-bw/day	Pathology changes in renal tubule	0.19	0.038	0.025	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Rat (male)	Inhalation	100 to 600 ppm	7 hrs/day, 5 days/week for 2 years	$BMDL_{10}$= 40.2 ppm	Pathology changes in renal tubule	0.28	0.057	0.038	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Maltoni and Cotti (1986)
	Mouse (male)	Inhalation	37 to 3,600 ppm	Continuous and intermittent exposures for 30-120 days	$BMDL_{10}$ = 34.7 ppm	Increased kidney weight/body weight ratio	0.88	0.18	0.12	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; *Total UF=10*	Kjellstrand et al. (1983)
	Mouse (female)	Oral (gavage)	869 to 1,739 mg/kg-bw/day	5 days/week, TWA during exposure period (78 weeks), animals observed for 90 weeks	LOAEL = 620 mg/kg-bw/day	Pathology changes in renal tubule (toxic nephrosis)	3.9	0.77	0.5	UF_S=1; UF_A= 3; UF_H=3; UF_L=30; *Total UF=300*	NCI (1976)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

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L-3 Neurotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Nervous system	Rat (male)	Inhalation	50 to 300 ppm	8 hrs/day, 5 days/weeks for 6 weeks	LOAEL = 12 ppm	Significant decreases in wakefulness	13	6.4	4.8	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; *Total UF=300*	Arito et al. (1994)
	Human (both sexes)	Inhalation	704 ppm × years of exposure (mean cumulative exposure)	Mean of 16 years	LOAEL = 14 ppm	Trigeminal nerve effects (increased latency in masseter reflex)	14	7.0	5.3	UF_S=1; UF_A= 1; UF_H=3; UF_L=3; *Total UF=10*	Ruijten et al. (1991)
	Rat (male)	Oral (drinking water)	24 to 47 mg/kg-bw/day	8 weeks	LOAEL = 47 mg/kg-bw/day	Cognitive effects (demyelination of hippocampus)	18	9.2	7.1	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Isaacson et al. (1990)
	Rat (male)	Oral (gavage)	1,000 mg/kg-bw/day	5 days/week for 6 weeks	LOAEL = 710 mg/kg-bw/day	Degeneration of dopamine-containing neurons in substantia nigra	126	62	47	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Gash et al. (2008)
	Rat (female)	Inhalation	300 ppm	24 hrs/day for 24 days	LOAEL = 300 ppm	Decreased regeneration of sciatic nerve	274	127	93	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kjellstrand et al. (1987)
	Mouse (male)	Inhalation	150 to 300 ppm	24 hrs/day for 24 days	LOAEL = 150 ppm		378	163	120	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-4 Immunotoxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Immune system	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decrease in thymus weight and thymus cellularity	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	1.4 to 14 ppm (0.35 to 3.5 mg/kg-bw/day)	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Autoimmunity (increased anti-dsDNA and ssDNA antibodies)	0.092	0.045	0.033	UF_S=1; UF_A= 3; UF_H=3; UF_L=3; *Total UF=30* [4]	Keil et al. (2009)
	Mouse (female)	Oral (drinking water)	18 to 660 mg/kg-bw/day	16 or 24 weeks (4 or 6 months)	LOAEL = 18 mg/kg-bw/day	Immuno-suppression	4.8	2.4	1.7	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Sanders et al. (1982)
	Rat (female)	Inhalation	100 to 1,000 ppm	6 hrs/day, 5 days/week for 4 weeks	$BMDL_{1SD}$= 24.9 ppm	Immuno-suppression	29	15	11	UF_S=10; UF_A= 3; UF_H=3; UF_L=1; *Total UF=100*	Woolhiser et al. (2006)
	Mouse (males; auto-immune prone strain)	Inhalation	500 to 2,000 ppm	4 hrs/day, 6 days/week for 8 weeks	LOAEL = 70 ppm	Autoimmunity (changes in immunoreactive organs)	97	48	37	UF_S=10; UF_A= 3; UF_H=1; UF_L=10; *Total UF=300*	Kaneko et al. (2000)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

[4] Two different effects were reported by Keil et al, (2009): decreased thymic weight and cellularity and autoimmunity. A total UF of 100 was used for the thymus toxicity, whereas a total UF of 30 was used for the autoimmune effects. The TCE IRIS assessment allocated different LOAEL-to-NOAEL uncertainty factors (UF_L) based on the severity of the effects, which resulted in different total UF (EPA, 2011e).

L-5 Reproductive Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Reproductive system	Human (male)	Inhalation	29.6 ppm (mean exposure)	Measured values after an 8-hr work shift; mean 5.1 years on the job	$BMDL_{10}$ = 1.4 ppm	Decreased normal sperm morphology and hyperzoospermia	1.4	0.7	0.5	UF_S=10; UF_A= 1; UF_H=3; UF_L=1; *Total UF=30*	Chia et al. (1996)
	Rat (male)	Oral (drinking water)	143 to 270 mg/kg-bw/day	14 days	LOAEL = 141 mg/kg-bw/day	Decreased *in vitro* fertilization	16	11	9.3	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	DuTeaux et al. (2004)
	Rat (male)	Inhalation	376 ppm	4 hrs/day, 5 days/week, 2-10 weeks exposed, 2-8 weeks unexposed	LOAEL = 45 ppm	Sperm effects and male reproductive tract effects	32	16	13	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Kumar et al., 2000 Kumar et al. (2000)
				4 hrs/day, 5 days/week for 12 or 24 weeks							Kumar et al. (2001)
	Rat (female damns)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	9 days (during gestational days 6 to 15)	LOAEL = 475 mg/kg-bw/day	Delayed parturition	98	48	37	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; *Total UF=100*	Narotsky et al. (1995)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 19 days over 4 weeks	LOAEL = 180 ppm	Effects on epididymis epithelium	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Forkert et al. (2002)
				6 hrs/day, 5 days/week for 1-4 weeks							Kan et al. (2007)
	Mouse (male)	Inhalation	1,000 ppm	6 hrs/day, 5 days/week for 6 weeks	LOAEL = 180 ppm	Sperm effects (decreased in vitro sperm-oocyte binding and *in vivo* fertilization)	190	91	67	UF_S=10; UF_A= 3; UF_H=3; UF_L=10; *Total UF=1000*	Xu et al. (2004)

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Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Reproductive system	Rat (male)	Oral (drinking water)	72 to 389 mg/kg-bw/day	Breeders exposed 1 week premating and then for 13 weeks/ Pregnant females exposed throughout gestation (i.e., 18 weeks total)	LOAEL = 389 mg/kg-bw/day	Decreased mating (both sexes exposed)	204	97	71	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; UF_D=1 *Total UF=100*	NTP (1986)

Notes:

[1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.

[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.

[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

L-6 Developmental Toxicity

Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentrations [1]	Duration	POD Type [2]	Effect	HEC_{50} (ppm)	HEC_{95} (ppm)	HEC_{99} (ppm)	Uncertainty Factors (UFs) [3]	Reference
Developmental effects	**PRE- AND POSTNATAL MORTALITY**										
	Rat (female)	Inhalation	**1.** ppm	4 hrs/day, gestational days 8 to 21	LOAEL =17 ppm	Increased resorptions	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	Rat (female)	Oral (gavage)	10.1 to 1,125 mg/kg-bw/day	Gestational days 6 to 15	$BMDL_{01}$= 32.2 mg/kg-bw/day	Increased resorptions	57	29	23	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Narotsky et al. (1995)
	PRE- AND POSTNATAL GROWTH										
	Rat (female)	Inhalation	100 ppm	4 hrs/day, gestational days 8 to 21	LOAEL = 17 ppm	Decreased fetal weight and skeletal effects	16	8	6.2	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Healy et al. (1982)
	CONGENITAL DEFECTS										
	Rat (female)	Oral (drinking water)	2.5 to 1,100 ppm (2.5 to 1,100 mg/kg-bw/day)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0051	0.0037	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	Johnson et al. (2003)
	DEVELOPMENTAL NEUROTOXICITY										
	Rat (male pups)	Oral (gavage)	50 to 290 mg/kg-bw/day	Postnatal days 10 to 16	LOAEL = 50 mg/kg-bw/day	Decreased rearing activity	8	4	3	UF_S=3; UF_A= 3; UF_H=3; UF_L=10; Total UF=300	Fredriksson et al. (1993)
	Rat (female)	Oral (drinking water)	45 to 140 mg/kg-bw/day	Dams and pups exposed from 14 days prior to mating until end of lactation	LOAEL = 45 mg/kg-bw/day	Increased exploratory behavior in male pups (offspring)	22	11	8.4	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	Taylor et al. (1985)

Notes: [1] Controls (or zero dose/concentration) are not presented to reflect the lowest and highest values tested in the studies.
[2] POD type can be NOAEL, LOAEL, or BMDL. The IRIS program adjusted all values to continuous exposure.
[3] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.

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Appendix M BENCHMARK DOSE ANALYSIS OF BLOSSOM ET AL. 2013

Male MRL +/+ mice were maternally exposed to vehicle control or TCE from birth through weaning via drinking water (0, 2, or 28 mg/kg/day). At postnatal day (PND) 21, the offspring were weaned and the male mice were exposed directly to vehicle control or TCE via drinking water until PND 42. The study reported alterations in brain neurotrophin expression, glutathione redox homeostasis, DNA hypomethylation and a number of behavioral parameters, such as increased motor activity, and novelty/exploratory behavior at the highest dose tested (28 mg/kg/day). The NOAEL for neurobehavioral impairments was 2 mg/kg/day (Blossom et al., 2013).

EPA conducted benchmark dose (BMD) analysis using the exploratory behavior data reported in Figure 7A and7B (Blossom et al., 2013). The data are described in Table M-1. The response (endpoint) is the number of times a test animal entered a central zone in 10 minutes with a novel object (Figure 7A) or a novel mouse (Figure 7B) at the center of a 1 m^2 arena.

Table M-1. Neurotoxicological Endpoints Selected for Dose-Response Modeling (Blossom et al., 2013)

TCE in drinking water		Sample size[1]	Figure 7A, novel object (inverted wire cup)		Figure 7B, novel mouse, placed under inverted wire cup	
mg/ml	mg/kg-day		Mean	SD	Mean	SD
0	0	9	5.27	5.78	5.32	3.96
0.01	2	8	4.36	5.16	7.85	6.88
0.1	28	8	10.54	4.30	10.19	7.46

Notes:
[1] Number of pups tested (one per dam with different pups tested for each endpoint)

The BMD analysis is summarized in Table M-2 and additional information is provided in the supplementary files: *1_Blossom_NObject_SD.xlsm* and *2_Blossom_NMouse_SD.xlsm*). The $BMDL_{1SD}$ ranged from 14-20 mg/kg/day depending upon the neurobehavioral endpoint (Endpoint A or Endpoint B).

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Table M-2. Summary of BMD modeling Results for Number of Entries into a Central Zone With a Novel Object (Endpoint A) or Novel Mouse (Endpoint B) (Blossom et al., 2013)					
Model	**Goodness of fit**		**BMD_{1SD}[a] (mg/kg-d)**	**$BMDL_{1SD}$[a] (mg/kg-d)**	**Basis for Model Selection**
	***p*-value**	**AIC**			
Endpoint A (novel object)					Only the linear model provided an adequate fit.
Linear [b]	0.577	110.05	23.7	14.3	
Endpoint B (novel mouse)					Only the linear model provided an adequate fit.
Linear [c]	0.428	119.67	41.9	19.8	

Notes:

[a] BMR is 1 SD change from the control mean

[b] Constant variance models were used (BMDS Test 2, p-value = 0.684), with the selected model in bold. Scaled residuals for selected model for doses 0, 2, and 28 mg/kg-d were 0.366, -0.418, and 0.0298, respectively.

[c] Constant variance models were used (BMDS Test 2, p-value = 0.176), with the selected model in bold. Scaled residuals for selected model for doses 0, 2, and 28 mg/kg-d were -0.519, 0.592, and -0.0423, respectively. The power model gave an identical fit to these data. Note that the BMD lies above the highest dose.

Figure M-1. Linear Dose-Response Model for Endpoint A: Number of Times Entered Central Zone With Novel Object

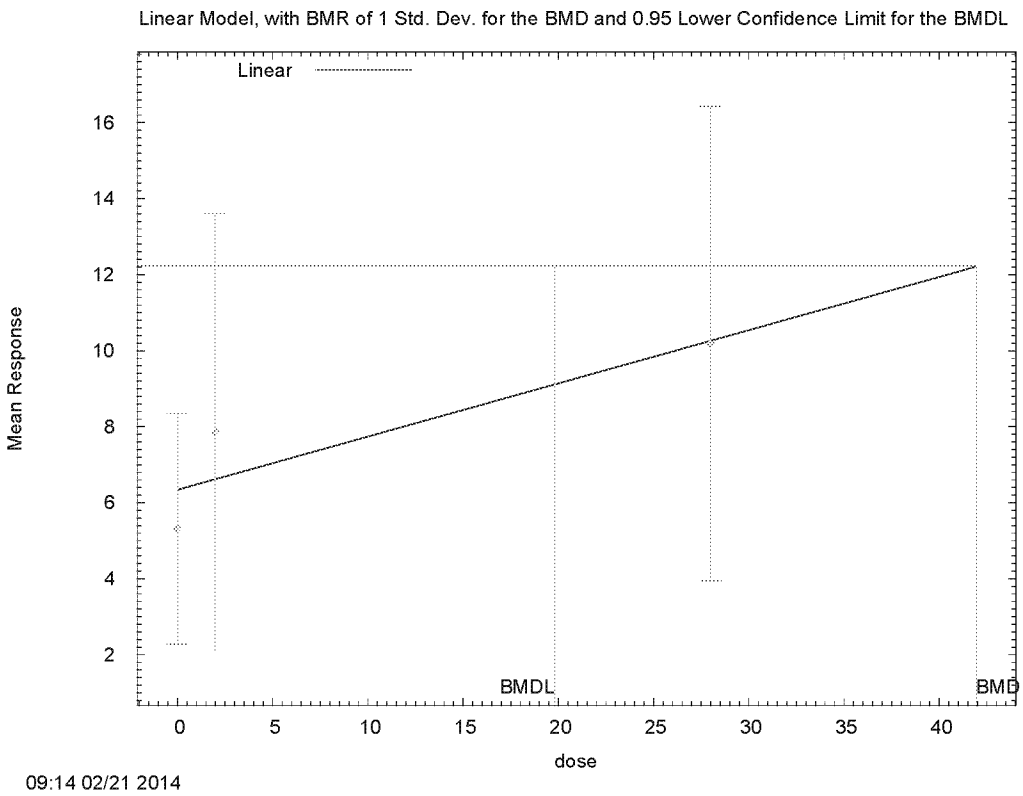
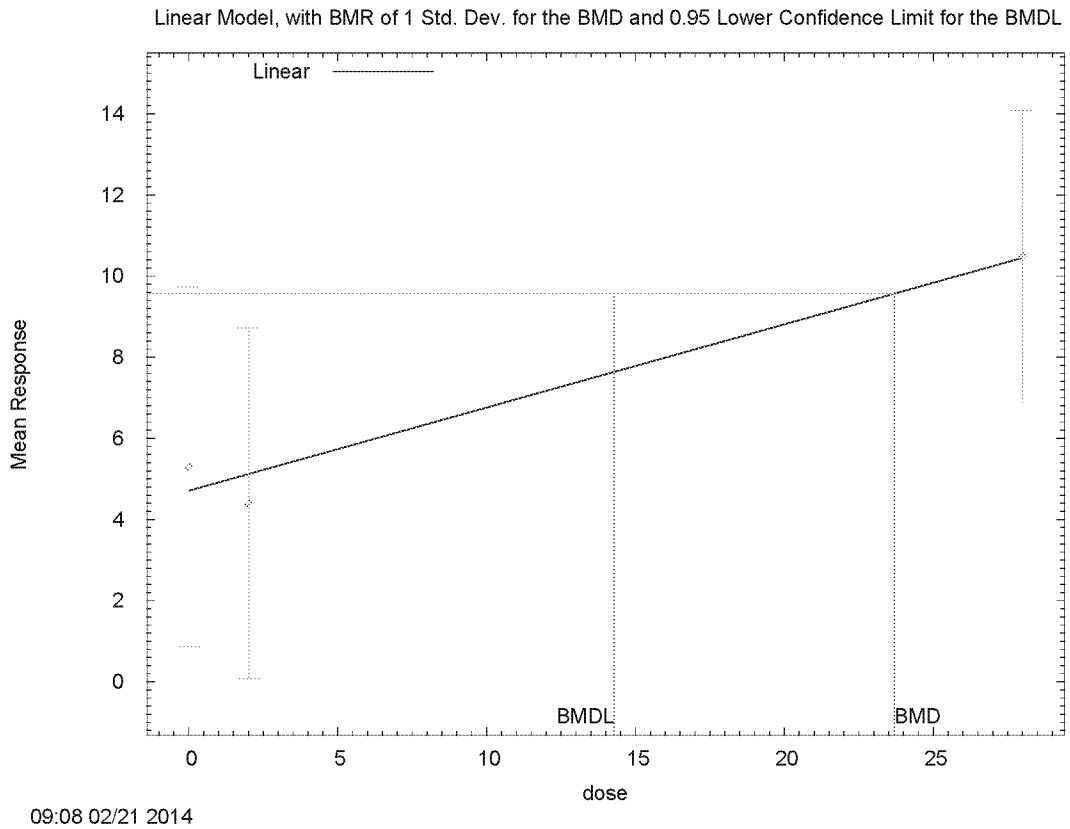


Figure M-2. Linear Dose-Response Model for Endpoint B: Number of Times Entered Central Zone with Novel Mouse



***Note that BMD lies above highest observed response.**

Appendix N Weight-of-Evidence Analysis for Fetal Cardiac Malformations Following TCE Exposure

Appendix N contains a weight-of-evidence analysis for the association between short-term exposure to TCE and fetal cardiac defects.

The analysis only addresses the fetal cardiac defects observed following gestational exposures to TCE and/or its oxidative metabolites dichloroacetic acid (DCA) and trichloroacetic acid (TCA), and includes updated information that was not part of the 2011 TCE IRIS assessment. This update includes 1) identification of any new literature, 2) a systematic evaluation of available data, 3) an evaluation of the weight of evidence for the association of TCE exposures with cardiac defects, and 4) a transparent presentation of the evaluation.

A systematic literature search was conducted to identify all studies published subsequent to the final literature search that had been conducted by EPA during completion of the 2011 TCE IRIS assessment (EPA, 2011e). A total of 1686 unique citations were initially identified from PubMed, Toxline, and Web of Science (WoS). These citations were screened using the title, abstract, and/or full text for pertinence to evaluation of the developmental toxicity of TCE, TCA, and DCA exposure. The literature search identified no new animal toxicology studies of fetal cardiac defects, one new epidemiology study that assessed the association of TCE or chlorinated solvent exposures with cardiac defects, and two studies that provided mechanistic information relevant to alterations of cardiac development following TCE (or metabolite) exposures.

The analysis does not provide an update on other developmental effects of TCE exposure, i.e., ocular malformations, developmental neurotoxicity, and developmental immunotoxicity.

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Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
Temporality	Timing of exposures and response	Tox	Studies in various species in which TCE (or metabolites DCA or TCA) were administered during a sensitive period of in utero cardiac development resulted in morphological and/or functional alterations. • Drinking water administration of TCE to rats on GD 1-22 resulted in a statistically significant treatment-related increase in the incidence of cardiac defects (Dawson et al., 1993; Johnson et al., 2003). • Drinking water administration of TCA (the TCE oxidative metabolite) to rats on GD 1-22 resulted in a statistically significant treatment-related increase in the incidence of cardiac defects (Johnson et al., 1998a). Gavage administration of TCE metabolites (DCA and TCA) on GD 6-15 (Smith et al., 1989, 1992) or of DCA during discrete windows of time within GD 6-15 (Epstein et al., 1992) resulted in treatment-related increases in the incidences of cardiac defects. • Avian in ovo studies that administered TCE or TCA during the period of valvuloseptal morphogenesis (e.g., HH 15-20) resulted in altered cardiac morphology and/or function (Drake, V. et al., 2006; Drake, V. J. et al., 2006; Loeber et al., 1988; Rufer et al., 2010). • A study of DCA exposure to zebra fish (Hassoun et al., 2005) demonstrated	Some in vivo or in vitro studies rodent studies in which TCE (or metabolites DCA or TCA) was administered during a sensitive period of in utero cardiac development resulted in no morphological alterations. • Gavage administration of TCE or metabolites (DCA and TCA) to rats on GD 6-15 did not result in treatment-related cardiac defects (Fisher et al., 2001). • Inhalation exposures of TCE to rats on GD 6-20 (Carney et al., 2006) or to rats and mice on GD 6-15 (Schwetz et al., 1975) did not result in treatment-related cardiac defects.	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			evidence of a disruption in cardiac development (pericardial edema and altered heart rate). • Mouse whole embryo culture studies of DCA and TCA administered at the period of 3-6 somites detected cardiac defects (Hunter et al., 1996); a chicken whole embryo culture study of TCE administered at HH 13-14 detected alterations in AV cushion (Mishima et al., 2006). • Avian atrioventricular canal cell culture (HH 16) study found evidence of inhibited endothelial cell separation and early events of mesenchymal cell formation in the heart following TCE exposures (Boyer et al., 2000).		
	Exposure occurs before outcomes onset	Epi	• Four cohort or case-control studies consider temporality (Forand et al., 2012; Goldberg et al., 1990; Ruckart et al., 2013; Yauck et al., 2004). Three studies observe an association between the TCE exposure surrogate and major cardiac defects (Forand et al., 2012; Goldberg et al., 1990; Yauck et al., 2004). An association with conotruncal defects, specifically, observed in Forand et al. (2012).	• Temporality was not considered in Bove (1996); Bove et al. (1995); Goldberg et al. (1990); and Lagakos et al. (1986)	• The small numbers of conotruncal heart defects in Ruckart et al. (2013) precluded any analysis of this endpoint and TCE exposure.
Strength of association	Study quality, including study strengths and limitations	Tox	• For Dawson et al. (1993); Johnson et al. (1998a); and Johnson et al. (2003), all of which detected cardiac malformations, study quality strengths include randomized assignment to test group, detailed description of	• For Johnson et al. (2003) major study quality limitations include the use of data pooled from separate study cohorts conducted over an approximately 6-year period, the use of tap water as the vehicle for some of	• Some studies that reported no cardiac defects following TCE gestational exposures (Hardin et al., 1981; Healy et al., 1982; Narotsky et al., 1995;

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			fetal cardiac dissection and evaluation procedures, evaluation of fetal hearts without knowledge of treatment group, and confirmation of all cardiac defects by consensus of 3 experts. Statistical analysis of data from this study was appropriately conducted by EPA statisticians using individual fetal and litter data that were provided by the study author. • The power of detection in the Johnson et al. (2003) study was enhanced by the use of historical controls that did not demonstrate a temporal shift in cardiac defects. A significant dose related trend in cardiac defects was observed even without large group sizes. • A strong association of exposure to response was observed at high dose levels in multiple studies that identified cardiac defects. In Johnson et al. (2003) there was a highly significant positive trend for cardiac defects. • Potential confounding factors exist in studies that did not identify cardiac defects (e.g., different routes of exposure, the use of different rodent strains or suppliers across studies, and the use of soybean oil as a vehicle in (Fisher et al., 2001).	control and treated groups (as reported by Dawson et al. (1993) with no characterization of possible contaminants and incomplete reporting of study methods and results. • While Dawson et al. (1993) indicated that levels of TCE in dose formulations were tested by gas chromatography, the analytical findings were not reported. Johnson et al. (2003) did not report whether dose formulations were analyzed. Further, levels of TCE were not assessed in the vehicle control water; therefore, it is plausible that TCE contaminated the water and that doses were actually higher than measured. • The Dawson et al. (1993) and Johnson et al. (2003) studies estimated doses based on the average water consumption. This method does not provide precise information to calculate TCE dose because variability in drinking water consumption among dams is not characterized. • The dose selection for Johnson et al. (2003) resulted in a NOAEL that is approximately 700-fold lower than the next highest dose. • Some studies that did not identify treatment-related cardiac defects following developmental exposures to TCE (e.g.,Carney et al., 2006; Fisher et	Narotsky and Kavlock, 1995) or avian in ovo studies (Bross et al., 1983; Elovaara et al., 1979) did not indicate that detailed evaluation of fetal hearts was conducted. • A rat whole embryo culture study of TCE administered at the period of 4-7 somites detected no cardiac defects in a study by Saillenfait et al. (1995); however, the study methods indicate that there was no evaluation of the embryonic heart.

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
				al., 2001; Schwetz et al., 1975) were well-conducted and adequately-reported GLP and/or guideline studies with no substantive limitations identified. • One study (Fisher et al., 2001) attempted to replicate the methods used in the Johnson et al. (2003) study, utilizing the same fetal cardiac dissection and evaluation techniques, and including one of Johnson et al. (2003) study authors in the assessment team, yet found no treatment-related cardiac defects.	
	Magnitude of the effect measure	Epi	• Increased risk estimates between all or major cardiac defects ranged from 1.24 (95% CI: 0.75, 1.94) to 2.40 (95% CI: 1.27, 3.62) observed in 3 studies (Bove, 1996; Bove et al., 1995; Forand et al., 2012; Goldberg et al., 1990). Stronger associations, observed with the TCE exposure surrogate for conotruncal defects and ventricular septal defects than for major cardiac defects, a broader category (Bove, 1996; Bove et al., 1995; Forand et al., 2012). A fourth study observed an increased risk estimate of 6.2 (95% CI: 2.6, 14.5) for cardiac defects in infants of mothers aged >38 years and maternal residence within 1.32 miles from at least one TCE emissions source (Yauck et al., 2004).	• No association in Yauck et al. (2004) in mothers <38 years of age and maternal residence within 1.32 miles from at least one TCE emissions source nor in Lagakos et al. (1986), which does not observe an association with cardiac defects. Alternative reasons such as lower statistical power may explain these observations.	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
Variability analysis	Sources of within- and cross-study variability that contribute to uncertainty	Tox	• Johnson et al. (2003) test subject source, husbandry, and randomization procedures were consistent across all cohorts, i.e., including Dawson et al. (1993) and metabolite studies Johnson et al. (2003). Fetal cardiac evaluation methodology, which included evaluation without knowledge of treatment group and confirmation of all cardiac anomalies by 3 expert scientists, was also consistently applied across cohorts and studies from the UAZ laboratory. This had the result of reducing intra- and inter-study variability in the assessment. • Johnson et al. (2003) reported that cardiac defect incidences were consistent across all control cohorts (55 litters over approximately 6 years). An EPA review of the available control data did not observe unusual heterogeneity in prevalence of malformations. • Studies that reported cardiac defects following administration of metabolites (DCA and TCA) used randomized assignment of maternal animals to test group, thus reducing intra-study variability. • Although Dawson et al. (1993) and Johnson et al. (2003) identified cardiac defects following exposures to TCE during development, (Carney et al., 2006; Fisher et al., 2001; Schwetz et	• The Johnson et al. (2003) study reported data from several cohorts of animals, which were on study over a period of approximately 6 years. The data included control cohorts, some of which were concurrent and some that were non-concurrent to the TCE-treated groups (Johnson et al., 2005; Johnson, 2014). Data that definitively link the individual control litter response data with each particular cohort are no longer available for independent examination. • Different study outcomes were observed in studies that had many similarities in study design and conduct, i.e., Dawson et al. (1993) and Johnson et al. (2003) identified exposure related cardiac defects while Fisher et al. (2001) did not. In the Fisher et al. (2001) study, care was taken to ensure that the same cardiac evaluation methods were used as in the Dawson et al. (1993) and Johnson et al. (2003) studies, including fetal evaluation with knowledge of treatment group, and one of the study authors of Johnson et al. (2003) participated in the fetal examination. • The use of soy bean oil in the Fisher et al. (2001) study vs. water vehicle and control for Johnson et al. (2003) and Dawson et al. (1993) studies. • The Johnson et al. (2003) and Dawson	• Based upon the toxicokinetic profile of TCE (EPA, 2011e), it is considered unlikely that toxicokinetic factors contributed significantly to differences in response across study protocols.

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			al., 1975) did not find treatment-related cardiac abnormalities. This may be the result of differences in the study design and assessment methods. This includes such aspects as animal strain, age, source, exposure route and vehicle, duration of exposure, and cardiac evaluation methods.	et al. (1993) studies did not calculate variability in TCE dose by measuring individual dam water consumption.	
	Sources of within- and cross-study variability that contribute to uncertainty	Epi	• NE (not considered in Hill analysis)	• NE (not considered in Hill analysis)	• Studies examined different populations, exposure levels, gradients, and media. Additionally, different sets of strengths and uncertainties in this set of studies would contribute to observed cross-study variability.
Uncertainty analysis	Missing information or data gaps, within and across studies	Tox	• For the studies conducted by the UAZ laboratory that identified cardiac defects following exposures to TCE, DCA, or TCA (Dawson et al., 1993; Johnson et al., 1998a; Johnson et al., 2003), detailed descriptions of evaluation methods for assessment of cardiovascular effects were provided. • Individual fetal and litter cardiac findings data, as well as detailed information on study conduct and fetal evaluation methods, were provided to the EPA for Dawson et al. (1993) and Johnson et al. (2003).	• The publications for studies conducted by the UAZ laboratory that identified cardiac defects following exposures to TCE, DCA, or TCA (Dawson et al., 1993; Johnson et al., 1998a; Johnson et al., 2003) did not report essential study details, and generally did not include summaries of maternal data or fetal data for endpoints other than cardiac defects. • For well-conducted studies that did not detect cardiac defects following developmental exposures to TCE or metabolites (Carney et al., 2006; Fisher et al., 2001) adequate descriptions of study methodology and summary data	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
				for maternal and fetal findings were reported. • Mechanistic data for alterations in cardiac development are limited and do not identify initiating events for the putative AOP.	
	Missing information or data gaps, within and across studies	Epi	• NE (not considered in Hill analysis)	• NE (not considered in Hill analysis)	
Qualitative dose-response	Association between exposure/dose and degree of effect	Tox	• Alterations in cardiac development were observed in multiple studies at high dose levels following TCE, DCA, or TCA exposures (Dawson et al., 1993; Johnson et al., 1998a; Johnson et al., 2003; Smith et al., 1989, 1992). • The incidence of cardiovascular effects increased as a function of dose in Johnson et al. (2003). • An association between exposure to TCE (or DCA or TCA) and alterations in cardiac development was reported in various animal models, i.e., LE and SD rats, CD-1 mice, chicken embryos, and zebra fish (Dawson et al., 1993; Drake, V. et al., 2006; Drake, V. J. et al., 2006; Hassoun et al., 2005; Johnson et al., 2003; Smith et al., 1989, 1992; Williams et al., 2006). • A BMDL for Johnson et al. (2003) was derived by EPA statisticians from individual cardiac defect data provided to EPA. Litter contribution to the	• The dose response for cardiac defects identified by Johnson et al. (2003) could only be fit to a model with elimination of the high dose data from the analysis. The lowest dose tested had a zero response for cardiac defects, below the historical control incidence. The doses tested were spaced over several orders of magnitude, with wide gaps. • Carney et al. (2006) was the only other study in the database that evaluated developmental effects of TCE over multiple dose levels. In that study, no fetal toxicity and minimal maternal toxicity was reported.	• TCE doses tested in Dawson et al. (1993) and Johnson et al. (2003) (drinking water): 2.5 ppb, 250 ppb, 1.5 ppm, or 1100 ppm (0, 0.00045, 0.048, 0.218, or 129 mg/kg-day) • TCE doses tested Fisher et al. (2001) (gavage): 500 mg/kg-day • TCE doses tested in Carney et al. (2006) (inhalation): 50, 150, or 600 ppm (268.5, 805.5, or 3222 mg/m^3)

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Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			outcome of interest was incorporated in the analysis. A significant dose-response trend was identified, whether or not the high dose value was included in the analysis.		
	Exposure-response gradient: Association between exposure/dose and degree of effect	Epi	• NE	• Goldberg et al. (1990) and Lagakos et al. (1986) examined exposure-response; none observed.	
Experimental evidence	Hypothesis testing: manipulation of exposure scenario with resulting alterations in response	Tox	• A study by Epstein et al. (1992) administered the metabolite DCA to rats on varied days of gestation and identified critical windows of exposure for eliciting cardiac developmental defects. • No statistically significant increases in congenital heart defects were observed in groups of rats that were exposed to TCE prior to pregnancy only Dawson et al. (1993). • Drake, V. J. et al. (2006) demonstrated that cardiac defects did not occur in chick embryos exposed to TCE and TCA during the period of cardiac specification (approximately GD 6 in rats) rather than the period of valvuloseptal morphogenesis.	• Studies in rodents that administered TCE via drinking water detected an increase in fetuses with cardiac defects (Dawson et al., 1993; Johnson et al., 2003); studies that administered TCE via other routes (gavage and inhalation) were negative for this response (Carney et al., 2006; Fisher et al., 2001; Schwetz et al., 1975). • In a whole embryo culture (WEC) study of DCA and TCA (Hunter et al., 1996), that identified cardiac defects, the acid nature of DCA and TCA may have impacted dysmorphogenesis.	• Studies that manipulated the gestational exposure period were not conducted with TCE.

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
	Association not observed once exposure ceases	Epi	• NE	• No differences between observed and expected numbers of cardiac defect cases once wells were closed in contaminated area (Goldberg et al., 1990).	
Reproducibility [Consistency]	Reproducibility: Corroboration across studies, labs, routes of exposure, species, etc.	Tox	• Studies that administered TCE in drinking water to rats on GD 1-22 were conducted over a period of approximately 6 years by researchers at the same academic facility (UAZ, Tucson) used the same cardiac evaluation methods and identified treatment and dose-related cardiac malformations (Dawson et al., 1993; Johnson et al., 1998a; Johnson et al., 2003). A preliminary screening study that utilized intrauterine administration of TCE also detected cardiac defects (Dawson et al., 1990). The types of cardiac malformations observed were similar across study cohorts and treatment groups throughout the duration of the research program. • Studies on TCE metabolites (TCA and TCA) conducted in other laboratories (Epstein et al., 1992; Smith et al., 1989, 1992) identified cardiac defects similar to those observed in the UAZ studies. • Cardiac septal anomalies were observed in avian in ovo studies (Drake, V. et al., 2006; Rufer et al., 2010), and in WEC assays (Hunter et	• Studies conducted in other laboratories than UAZ and that administered TCE by gavage or inhalation (Carney et al., 2006; Fisher et al., 2001; Schwetz et al., 1975) did not identify statistically significant increases in cardiac defects. Fisher et al. (2001) used the same cardiac evaluation methods as the UAZ lab.	• Studies that did not identify cardiac defects with TCE and/or metabolite exposures (Carney et al., 2006; Fisher et al., 2001; Schwetz et al., 1975) did not replicate all aspects of the Johnson et al. (2003) study, even though Fisher et al. (2001) used the same cardiac evaluation techniques as Johnson et al. (2003) andDawson et al. (1993), and therefore provide only limited evidence of lack of reproducibility.

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			al., 1996; Mishima et al., 2006) with TCE and/or metabolite exposures. Zebrafish studies also demonstrated evidence of alterations in cardiac development (Hassoun et al., 2005; Williams et al., 2006).		
	Consistency: Association observed in different populations, places, time and circumstances.	Epi	• Association between cardiac defects and TCE exposure surrogate observed in four studies. These studies were of different populations living in different state (NY, NJ) and covered slightly different time period (1983-2000, 1985-1988) (Bove, 1996; Bove et al., 1995; Forand et al., 2012). Two other studies of weaker designs were of different populations and carried out in two different locations in the United States, and provide supporting evidence (Goldberg et al., 1990; Yauck et al., 2004).	• Lagakos et al. (1986) compared a pregnancy receiving contaminated residential well water to a pregnancy not receiving residential water from contaminated wells and does not observed an association between cardiac defects and contaminated drinking water.	
Biological plausibility	Observed outcome can be attributed to toxic insult given the known science	Tox	• Avian in ovo studies and atrioventricular cell culture studies support the biological plausibility of effects of TCE on cardiac development, given that early chick heart development is similar to mammalian (including human), particularly regarding the role of the cardiac cushion in septation (NRC, 2006; Richards and Garg, 2010). • Preliminary exploration of a possible adverse outcome pathway (AOP) has resulted in a reasonable conceptual	• A definitive AOP for TCE-induced cardiac defects, including a putative initiating event, has not yet been characterized. Additional mechanistic data are needed to support the hypothesized AOP. • There are insufficient mechanistic data to characterize additional potential MOAs other than that hypothesized in the AOP.	• It is possible that multiple modes of action are involved in alterations to cardiac development.

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			model for TCE-induced congenital heart defects. In this construct, the vulnerable period is defined by endocardial morphogenesis. Endothelial–mesenchyme transition is disrupted in the area of the atrioventricular canal, leading to septal defects. Possible genetic contributions to abnormal cardiac development include disruption of TGF-beta pathway, endrin pathway, Notch pathway, VEGF pathway, and RXR signaling. At a cellular level, epithelial-mesenchymal transition may be affected in the endocardium, at the tissue level, there is altered cellularity of the endocardial cushion, and secondary effects such as dysregulation of cellular Ca^{2+} fluxes may result in additional impacts on the developing heart.		
	Observed association plausible given the known science	Epi	• NE	• NE	• In vitro and in vivo animal studies report cardiac defects with TCE and TCE-metabolite exposure.
Alternative or multiple explanations	Other possible explanations for observed outcome after the exposure of interest	Tox	• Given the presumed contribution of both environmental exposures and genetic predisposition in human congenital heart disease (Richards and Garg, 2010), it is possible that the test subjects used in the Johnson et al. (2003) study and others conducted in that laboratory may have been	• There is a possibility that cardiac defects detected in the Dawson et al. (1993) study were associated in part with the use of tap water as a control vehicle (i.e., possible presence of contaminants).	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
			particularly susceptible to alterations in cardiac development. • Other contributing factors or confounding factors were not specifically identified in the evaluated in-vivo studies. • It is possible that the absence of treatment-related cardiac defects in well-conducted TCE studies (Carney et al., 2006; Fisher et al., 2001) or metabolite studies (Fisher et al., 2001) was due to confounding variables such as differences in strain/source of animal model, route of exposure, toxicokinetics, vehicle [e.g., soybean oil in Fisher et al. (2001)], or differences in cardiac evaluation methods. • It is unlikely that the cardiac defects observed by Johnson et al. (2003) were an artifact of the evaluation procedures used, since a study by Fisher et al. (2001), using the same fetal cardiac evaluation procedures, did not identify an association between TCE exposure and the incidence of cardiac defects.		
	Other possible explanations for observed outcome after the exposure of interest (not considered in	Epi	• Potential maternal risk factors were adjusted in statistical analysis in Forand et al. (2012) and Yauck et al. (2004) or were not found in statistical analyses to influence observed association by +15% (Bove, 1996; Bove et al., 1995).	• Potential for confounding from another exposure given the poor exposure definition in Yauck et al. (2004). The positive association in Goldberg et al. (1990) may result from likely selection biases in controls.	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
	Hill analysis)				
Specificity	Single cause and effect relationship resulting from exposure to test substance	Tox	• Cardiac defects in rats appear to be attributable to direct chemical exposure to TCE or metabolites (DCA or TCA) and are unlikely to be the result of secondary effect of maternal toxicity. Johnson et al. (2003) reported that TCE exposure via drinking water to pregnant rats did not result in maternal toxicity. Carney et al. (2006) reported minimal decreases in body weight gain in dams, with no adverse fetal outcomes. In fetuses, there was no indication of TCE-related fetal weight deficits, external or skeletal anomalies, or of soft tissue alterations other than cardiac defects in Johnson et al. (2003) nor in any other study. • The majority of the cardiac malformations following TCE exposures to rats (Dawson et al., 1993; Johnson et al., 2003) or chicks (Drake, V. et al., 2006; Rufer et al., 2010) during sensitive periods of cardiac development were ventricular septal defects, valve defects, or outflow tract abnormalities. Mechanistic data suggest a common etiology (disruption of the cardiac cushion formation) for the observed cardiac defects Boyer et al. (2000).	• Studies conducted in other laboratories than UAZ and that administered TCE by gavage or inhalation (Carney et al., 2006; Fisher et al., 2001; Schwetz et al., 1975) did not identify cardiac defects. Fisher et al. (2001) used the same cardiac evaluation methods as the UAZ lab. • The cardiac defects detected in the Dawson et al. (1993) study may have been related to the use of tap water as a vehicle (i.e., possible contaminants).	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
	Single cause and effect relationship resulting from exposure to test substance	Epi	• NE	• Specificity not a critical compared to other Hill aspects since outcomes may have several risk factors. Maternal risk factors, specifically chemical risk factors, associated with cardiac defects in infants have not been well studied.	
Coherence	Summary: Extent to which data are similar in outcome and exposure across database	Tox	• Multiple studies were conducted at UAZ (Dawson et al., 1993; Johnson et al., 1998a; Johnson et al., 2003), in which rats were administered TCE or metabolites DCA or TCA in drinking water on GD 1-22 and for which study design and cardiac evaluation methodologies were consistent. The outcomes of these studies (detection of cardiac defects, particularly septal defects, valve abnormalities, and outflow tract anomalies) are consistent across these studies. Additionally, these outcomes are supported by the results of avian in ovo and in vitro studies, studies with TCE metabolites (DCA and TCA) in rodents, in vitro whole embryo culture studies, and mechanistic data.	• Developmental toxicity studies with TCE that were conducted in other laboratories (Carney et al., 2006; Fisher et al., 2001; Schwetz et al., 1975) administered TCE to rats of other strains or sources, using different routes of exposure (inhalation or gavage), administered on different days of gestation (i.e., not including GD 1-6) than the UAZ studies and did not identify cardiac defects. No other study in the TCE database reported cardiac defects at the low dose levels reported by Johnson et al. (2003).	
	Cause and effect interpretation should not conflict with the generally known facts of the natural	Epi	• Associations in epidemiologic studies of cardiac defects and maternal occupational exposure to degreasing solvents or to organic solvents (Gilboa et al., 2012; Loffredo et al., 1991; Tikkanen and Heinonen, 1988, 1991).	• NE	

Key Factor [a,b]	Type of evidence to consider	Data	Evidence for stronger weight of association	Evidence for weaker weight of association	Comments or Null Evidence
	history and biology of the disease				

NE = No relevant evidence.
HH = Hamburger-Hamilton stages of chick development (Hamburger and Hamilton, 1951).
Tox = Animal toxicology studies; Epi = Epidemiological studies
Key Factor references:
a EPA (2006b)
b Hill (1965)