Trichloroethylene (TCE) Inhalation Immediate Action Levels and Response Guidance for Indoor Air Protective of Cardiac Developmental Defects

NC Department of Environmental Quality Report

to the

Secretaries' Science Advisory Board

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Executive Summary

Trichloroethylene is one of the most common groundwater contaminants in North Carolina. In 2011, the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) released an update of their toxicological review for trichloroethylene ("TCE"). In that update IRIS published their initial oral reference dose (RfD) and inhalation reference concentration (RfC) for TCE. The IRIS toxicological review identifies a development effect observed in rat studies, fetal cardiac malformations, as one of two non-cancer critical health effects used for the calculation of the inhalation toxicity value. After the IRIS review was released, EPA and others realized that TCE may pose an immediate potential hazard and adverse developmental outcomes could potentially result from short-term or peak TCE inhalation exposures during pregnancy. Because cardiac development begins during the earliest stages of embryonic development, at a time before a woman may realize she is pregnant, TCE exposures during the first trimester of a pregnancy is of particular concern. The EPA identifies that a single exposure to a developmental toxicant during critical windows of embryonic or fetal development may be sufficient to produce an adverse developmental effect. The current science for TCE, including studies published after the IRIS review, indicates that permanent adverse effects to cardiac function may occur as a result of short-term maternal inhalation exposures during this period of extreme vulnerability.

The current North Carolina Department of Environmental Quality Division of Waste Management *Supplemental Vapor Intrusion Guidance - Trichloroethylene (TCE) Indoor Air Inhalation Immediate Action Levels and Response* guidance was developed to be protective of the potential for cardiac developmental defects resulting from low-level TCE exposures to women that may be in their first trimester of pregnancy. The protection relies on an immediate response action initiated at the earliest indications of potential TCE exposure at or above the short-term inhalation action levels to remove or reduce exposures to women that may be in the first trimester of pregnancy. The TCE short-term inhalation action levels are calculated from the IRIS candidate reference concentration (RfC) of 2.0 $\mu g/m^3$ for cardiac developmental defects using EPA's default exposure parameters for residential and occupational receptors.

The objective of this document is to present to the Secretaries' Science Advisory Board for their review and recommendations a summary of the science and policies supporting the TCE short-term inhalation action levels and rapid response guidance for residential and occupational receptors developed by the Department of Environmental Quality in concert with the U.S. Environmental Protection Agency Region 4 and the North Carolina Department of Health and Human Services.

Introduction

In September 2011 the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System[1] (IRIS) issued the *Toxicological Review of Trichloroethylene* (CAS No. 79-01-6)[2]. This assessment established trichloroethylene[3] (TCE) non-cancer and cancer toxicity values for oral and inhalation exposures. This report will focus on the IRIS TCE toxicity values for the inhalation exposure route and indoor air action levels for short-term exposures with cardiac developmental defect[4] implications and rapid response guidance to protect against the developmental endpoint developed by the North Carolina Department of Environmental Quality (DEQ) Division of Waste Management (DWM). The cardiac developmental defect endpoint was identified as one of two principal studies that served as the basis of the IRIS TCE non-cancer inhalation reference value. DWM's TCE guidance was developed in concert with input from the U.S. Environmental Protection Agency (EPA) Region 4 Science Support Staff and the N.C. Department of Health and Human Services (DHHS) Division of Public Health (DPH). The goal of the DEQ short-term TCE exposure guidance is to protect women that may be in their first trimester of pregnancy from short-term inhalation exposures above levels identified by IRIS as protective for cardiac developmental defects. A potential pathway of inhalation exposure to TCE is by the vapor intrusion mechanism in which TCE subsurface contamination present may migrate to the indoor air environment of residential and commercial buildings.

The DEQ's Charge to the Secretaries' Science Advisory Board

DEQ's charge to the Secretaries' Science Advisory Board for the TCE vapor intrusion issue is: *TCE is a common groundwater and soil contaminant that can migrate to the indoor air environment by the vapor intrusion pathway, presenting a potential inhalation exposure in the indoor air environment. The 2011 TCE IRIS assessment provided a RfC for a cardiac developmental defect as a critical effect and the U.S. EPA has identified the first trimester as the critical window of exposure. In response to the cardiac*

[1] Available at: http://www.epa.gov/iris
[2] Available at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199
[3] Trichloroethylene, CAS number 79-01-6, synonyms: trichloroethene, TCE
[4] A developmental defect is a structural or functional anomaly that results from an alteration in normal development originating in the embryo or fetus (Smart and Hodgson, 2018)

developmental defect concern, U.S. EPA Region 4, DHHS and DEQ developed TCE residential and occupational inhalation exposure action levels and a guidance protocol to respond to sites where TCE may be an inhalation hazard to women of child-bearing age. ***DHHS and DEQ are requesting the SAB review the public health aspects of the DEQ implementation guidance for TCE to determine if it is protective and appropriate and provide recommendations to DEQ and DHHS on the action levels and implementation of the proposed guidance*****.**

What is Vapor Intrusion?

Vapor intrusion is the general term given to the migration of contaminant vapors from a subsurface contaminant source, such as contaminated soil or groundwater, through subsurface soils and into the indoor air spaces of overlying buildings. Vapor intrusion can occur in a broad range of land use settings, including residential, commercial, and industrial, and affect buildings with virtually any foundation type (e.g., basement, crawl space(s), or slab on grade). Vapor intrusion is widely recognized as a potentially significant cause of human exposure to "volatile" (i.e., vapor-forming) hazardous chemicals in indoor spaces. When vapor intrusion is significant, concentrations of toxic vapors can accumulate indoors to a point where the health of the occupants (e.g., residents, workers, etc.) in those buildings could be at risk (EPA VI). Elevated indoor air levels of TCE can result from vapor intrusion (ATSDR 2014A). The vapor intrusion conceptual model in Figure 1 illustrates sub-surface vapor migration pathways to indoor air environments.

Fate of Trichloroethylene in the Sub-Surface Environment

Trichloroethylene (TCE) is one of the most common groundwater contaminants (EPA 2011b). TCE is volatile, moderately water soluble and readily migrates in the sub-surface. TCE is a dense non-aqueous phase liquid (DNAPL) that can move through the unsaturated zone into the saturated zone[5] where it displaces soil water. TCE volatilizes rapidly from water and its volatility increases with increasing temperature, with water movement and with air movement. Volatilization of TCE from soil is slower than from water, but is more rapid than that of many other volatile organic compounds. The calculated

[5] The unsaturated zone is the portion of the subsurface above the groundwater table. Source: https://water.usgs.gov/ogw/. The saturated zone is the area in an aquifer, below the water table, in which relatively all pores and fractures are saturated with water. Also called the phreatic zone. Source: Wikipedia, https://en.wikipedia.org

K_{OC}[6] values for TCE are indicative of medium to high soil mobility and soil type appears to have little effect on volatilization rates. The solid/vapor partition coefficient of TCE decreases substantially with increasing soil moisture content due to polar water molecules competing with nonpolar TCE for the polar sorption sites (ATSDR 2014A). The physical and chemical properties of TCE are summarized in Table 1. The chemical structure of TCE is provided in Figure 2.

In the subsurface the dominant TCE fate mechanism is volatilization rather than degradation. Chemical degradation and biodegradation rates of TCE in the soil and groundwater are slow with a biodegradation half-life of months to years (ATSDR 2014A). The dominant microbial degradation pathway of TCE (C_2HCl_3) in groundwater and soil is the anaerobic process of reductive dehalogenation. TCE anaerobic degradation products include dichloroethylene ($C_2H_4Cl_2$), vinyl chloride (C_2H_3Cl) and ethylene (C_2H_2). Biodegradation rates vary with soil type, with rates increasing with increasing soil organic matter, temperature and TCE concentration. Aerobic biodegradation of TCE is a cometabolic[7] process requiring an organic substrate. It is reported that TCE may be toxic to indigenous microbial populations, resulting in inhibition of biodegradative pathways (ATSDR 2014A).

Absorption, Distribution, Metabolism and Elimination Characteristics of Trichloroethylene Relevant to Short-term Inhalation Exposures in Humans

Both animal and human studies indicate that TCE is widely distributed to all tissue of the body following absorption (IRIS 2011b). TCE is rapidly adsorbed following inhalation exposures ATSDR (2014a), crosses biological membranes following exposure by all routes and is rapidly systemically distributed to tissues (IRIS 2011b). Human data show wide systemic distribution across all tested tissues, including the heart, muscle, lung, liver, brain, kidney, and adipose tissues.

TCE was historically used as an anesthetic and has a blood/gas partition coefficient comparable to other anesthetic gases such as chloroform. TCE has an increased lipophilicity relative to other anesthetic gases

[6] K_{oc} is the soil organic carbon/water partition coefficient. $K_{OC} = C_{organic\ carbon}/C_{water}$ in units of L/kg

[7] Cometabolism is the biological degradation from which bacteria do not derive any energy. Bacteria secrete metabolic enzymes that break down complex organic matter around them for easier digestion. These enzymes are often nonspecific and can operate on many different substrate molecules, including those that the bacteria itself cannot use for energy. Source: EPA 2013.

resulting in a higher absorption rate, which ATSDR describes by as “quite high” (ATSDR 2014a). Most systemic absorption occurs in the lung alveoli. Inhalation absorption of TCE is proportional to the air concentration, duration of exposure, ventilation rate and cardiac output, with studies indicating 37-64% absorption from the lungs (ATSDR 2014a, IRIS 2011b). Human inhalation experiments indicate peak blood levels reaching steady-state after 1 to 2 hours (ATSDR 2014a). Animal studies support the rapid absorption of inhaled TCE from the lungs and into the circulation, with absorption reported as exceeding 90% in the first 5 minutes (ATSDR 2014A). In a rat tissue distribution study TCE tissue concentrations reached near-maximal values 2 hours after initiation of repeated daily inhalation exposure (IRIS 2011b). An accidental exposure of three men to unspecified TCE levels in air resulted in acute symptoms requiring hospitalization after less than 30 minutes exposure (ATSDR 2014A).

Organ-specific distribution may vary by gender and is dependent on organ blood flow, and the water and lipid content of the organ, with adipose tissue potentially serving as a TCE storage compartment. In human subject studies higher concentrations of TCE in expired breath post-exposure were found in the subjects with the greatest amount of adipose tissue. Another study reported higher TCE distribution to adipose tissue in women compared to men and led to greater blood concentrations in the women 16 hours after exposure (IRIS 2011b). During pregnancy TCE is distributed to the placenta in both animals and humans (IRIS 2011b, Laham, 1970) and fetal transfer from an exposed mother has been demonstrated in humans (IRIS 2011b, Laham, 1970). The small molecular size and lipid solubility lead to the easy placental transfer (Johnson et al., 2003; Laham, 1970). The ratio of TCE in fetal:maternal blood found in human newborns at childbirth ranged from 0.5 to 2 (Laham 1970). TCE mother to fetal transfer has also been reported in rat and rabbit studies, with TCE also detected in various organs following gestational exposures including the liver, kidneys and heart. TCE’s ability to cross the blood-brain barrier is indicated by reports of detectable levels in the prenatal brain following gestational exposures. In rat studies, approximately two-thirds of the maternal TCE and trichloroacetic acid (TCA, a toxic metabolite of TCE) exposure reached the fetus by all exposure routes (IRIS 2011b). Detections of TCE in the post-natal brain indicate the capacity to permeate the blood-brain barrier continues and may occur to a greater extent in younger children (IRIS 2011b). Studies in mice report the cycling of TCE to the fetus into the amniotic fluid and back to the fetus. Human and animal studies report lower blood:air partition coefficients in infants compared to adults, suggesting longer residence times (IRIS 2011b).

Humans extensively metabolize single or repeated exposures of inhaled TCE (40-75% metabolized) with an indication of metabolic saturation only at extreme exposure levels (≥2000 ppm) (ATSDR 2014A). At low exposure concentrations TCE is completely removed from circulation in a single pass through the liver. TCE metabolism occurs predominantly through the Phase I cytochrome P-450 mixed-function oxidase system, with lesser subsequent metabolism by the Phase II glutathione (GSH)-dependent conjugation pathway. The majority of the toxic effects associated with TCE exposure is considered to be associated with bioactivated metabolites, with certain metabolites thought to cause some of the same non-cancer toxicities and cancer effects as the parent compound (IRIS 2011b, ATSDR 2014A). Both Phase I and II pathways produce reactive metabolites more toxic than the parent TCE (ATSDR 2014a), with the GSH conjugate pathway considered responsible for the production of more cytotoxic and carcinogenic TCE metabolites than the CYP-P450 pathway (IRIS 2011b). Bioactivated metabolites include dichloroacetic acid (DCA) and trichloroacetic acid (TCA) generated by the cytochrome P-450 pathway, which are associated with hepatotoxicity and liver cancer. The GSH conjugation pathway bioactivated metabolites include S-(1,2-dichlrovinyl)-*L*-cysteine (DCVC) which is associated with nephrotoxicity and kidney cancer (Barton, 2014). The IRIS review noted that while TCE oxidation is likely greater quantitatively than the GSH conjugation metabolic pathway in rodents and humans, the GSH flux is anticipated to be much more significant that is indicated by urinary biomarker studies (IRIS 2011b). The major metabolites of the two pathways are illustrated in Figure 3.

The expression of cytochrome P-450 and GSH enzymes is known to change during fetal development and postnatally, with the potential to alter susceptibility to TCE and other xenobiotics (IRIS 2011b). In humans, the expression of CYP2E1, the main TCE metabolic enzyme, has been detected in the prenatal brain beginning at gestational week 8, with increasing concentrations thereafter. Fetal liver levels of CYP2E1 are very low during the second and third trimesters (found in 37% and 80% of samples, respectively), and surges immediately after birth and reportedly reaches adult levels at 3 months (IRIS 2011b). Fetal levels of the Phase II conjugating enzyme glutathione S-transferases (GST) protein isoforms are also believed to change during fetal development.

The Makawana et al. (2013) study demonstrated that the earliest embryonic expression of phase I detoxification enzymes is in the developing heart and their expression is relevant to the unique susceptibility of the embryonic heart at the earliest stages of development to environmental teratogens,

including TCE. Developing chick embryos were dosed with TCE at 8 and 800 ppb, followed by examination of genetic material-associated effects in cardiac and other tissues. The authors reported TCE-induced adverse effects to cardiovascular development prior to development of the liver systems able to mediate xenobiotic insults. Increased expression of early embryo cardiac tissue-specific cytochrome P450 metabolizing enzyme genetic material (mRNA and cytochrome precursor proteins) were observed, with no detectable response in extra-cardiac tissue. The dose-response in the cardiac tissue was non-monotonic (the response was greater at 8 ppb TCE than at 800 ppb TCE), supporting observations in prior studies. The known cytochrome P-450 oxidative metabolite of TCE, trichloroacetic acid (TCA), which has been shown to elicit greater cardiac toxicity than TCE, was detected. The authors suggested a possible pathway of non-monotonic dose-response in early stages of embryonic TCE exposures associated with the cardiac-specific enzyme system metabolizes TCE producing toxic metabolites that act in concert with the TCE to induce adverse cardiac effects. As exposure concentrations increase, response systems may be quickly overwhelmed until additional metabolizing systems are developed in the liver and other tissues, producing toxic metabolites that increase the level of adverse effects.

Following development of the liver, it is the primary site of oxidative metabolism of TCE regardless of exposure route. The stable toxic metabolite trichloroacetic acid (TCA) is a major product of oxidative TCE metabolism by cytochrome P-450 oxidation pathways (ATSDR 2014A, IRIS 2011b). The primary CYP-450 isozyme responsible for TCE oxidation is CYP2E1, with human studies reporting a 10-fold variability in metabolism by the cytochrome P-450 pathway among individuals (ASDTR 2018). The presence of multiple P450 isoforms with variable affinities for TCE, with variable metabolic capacities and variations in the enzyme concentrations suggested as an explanation for the variation in individuals' ability to metabolize TCE (IRIS 2011b). In animal experiments pregnancy decreased CYP2E1 induction, CYP2E1 levels were lower in mature relative to immature rats, and at puberty CYP2E1 was higher in female than male rats (ATSDR 2108). This has implications for the relative toxicity and vulnerability of prenatal receptors, with the increased maternal metabolism resulting in increased production of metabolites with greater toxicity than that of the parent compound available to cross the placenta.

The major route of elimination of un-metabolized TCE following inhalation is through pulmonary elimination and the urine for TCE metabolites (ATSDR 2014A, IRIS 2011b). Pulmonary elimination is

related to the solubility of TCE in the blood and tissues, the ventilation rate and cardiac output (IRIS 2011b). High absorption of TCE into adipose tissue and subsequent slow desorption is reported and is suggested as the explanation for finding TCE in exhaled air 18 hours after inhalation exposure ended. A human TCE half-life of 14-23 hours was reported following 6-hour inhalation exposures (ATSDR 2014A, IRIS 2011b). It is not known if there are age-related differences in the excretion of TCE (IRIS 2011b). In some human experimental exposures women have been found to excrete higher levels of TCE and TCE metabolites compared to men (IRIS 2011b).

Contaminant Co-Exposures Commonly Associated with TCE

Co-exposures to other volatile compounds that are mobile in the subsurface may occur with TCE exposures and have implications for exposure concerns. These include materials that contain industrial use mixtures that contain TCE, chemicals that degrade to TCE or its degradation products, or chemicals or mixtures that produce metabolites similar to TCE or its degradation products (such as tetrachloroethylene) (IRIS 2011b). These occurrences may induce or saturate toxicokinetic pathways, altering how TCE is metabolized or eliminated, or may contribute to additive exposures. Co-occurrence with tetrachloroethylene ("PERC", C_2Cl_4, CASN 127-18-4) is common, particularly at sites associated with past dry-cleaner operations. Under anaerobic conditions tetrachloroethylene degrades to TCE (EAWAG 2018). Tetrachloroethylene is metabolized by the same Phase I cytochrome P-450 primary isozyme CYP2E1 as is TCE, generating some of the same metabolites. Tetrachloroethylene is also metabolized by the same Phase II GST glutathione conjugation pathway as is TCE, again also generating some of the same bioactivated metabolites (ATSDR 2014).

The IRIS 2011 Review of Trichloroethylene and the Fetal Cardiac Malformation Endpoint

In September 2011, the U.S. Environmental Protection Agency (EPA) published an update of their toxicological assessment for TCE (IRIS 2011b). Based on a weight-of-evidence evaluation of the available information including human epidemiologic studies, animal dosing studies, and experimental mechanistic studies, the assessment concluded that TCE poses a potential human health hazard for non-cancer toxicity to the central nervous system, kidney, liver, immune system, male reproductive system, and the developing fetus, and is "carcinogenic to humans" by all routes of exposure (EPA 2014). The IRIS assessment derived a chronic inhalation reference concentration (RfC) of 2 $\mu g/m^3$ for non-cancer effects.

The chronic RfC is based in part on a developmental toxicity endpoint of increased incidence of fetal cardiac malformations identified in a rat reproductive study. The IRIS TCE summary document (IRIS 2011a) is included in Appendix A. The full TCE IRIS review and the supporting documents are available at https://www.epa.gov/iris/supporting-documents-trichloroethylene.

IRIS (2011a, 2011b) cited two rodent drinking water exposure studies as the principal studies selected as the basis of the TCE chronic RfC. One of the principal studies was a 30-week drinking water exposure reporting an immunotoxic critical effect as decreased thymus weight in female mice (Keil et al., 2009). The second RfC principal study was a rat developmental/reproduction study with drinking water exposures on gestational days (GD) 1 to 22 that reported the critical effect of increased incidence of fetal cardiac malformations (Johnson et al., 2003). The candidate RfCs for the two studies were 1.9 $\mu g/m^3$ for the immunotoxic endpoint and 2.1 $\mu g/m^3$ for the developmental endpoint, with the TCE final chronic RfC set at 2 $\mu g/m^3$ (0.4 ppbv). The candidate RfC for the cardiac developmental endpoint is the basis of the short-term inhalation action levels protective of the cardiac developmental defect.

The point of departures (POD) for both critical studies were converted to human equivalent concentrations (HECs) using physiologically based pharmacokinetic (PBPK) models for route-to-route and interspecies dose extrapolation. Figure 4 is a flow-chart outlining the IRIS dose-response analyses of the rodent non-cancer effects. IRIS used benchmark dose (BMD) modeling to extrapolate the Johnson et al. study (2003) fetal cardiac malformation effect to a 99^{th} percentile HEC (1% extra effect, $BMDL_{01}$). This level of effect ($HEC_{99,BMDL01}$) was chosen because of the uncertainty of the rat to human internal dose toxicokinetics, potential human inter-species variability, and the potential severity of the developmental cardiac defects which may be fatal (IRIS 2011b). A composite uncertainty factor of 10 (∑UF 10) was applied to the developmental endpoint candidate RfC calculation. The composite UF included a factor of 3 (UF_A) to account for toxicodynamic uncertainty associated with PBPK models to extrapolate from a rat internal dose to humans and the concern that the PBPK model does not account for the possibility that humans may be more sensitive to TCE than are rats due to toxicodynamic differences. The composite UF also included a factor of 3 (UF_H) to account for possible toxicodynamic differences in sensitive humans since the probabilistic human PBPK model does not account for humans who may be sensitive due to toxicodynamic factors. An UF was not applied for a LOAEL to NOAEL extrapolation (UF_L = 1) since the POD was benchmark dose modeled, nor was an UF adjustment applied for the sub-chronic POD since

the exposure window covered the relevant window of exposure for the critical effect (UF_S = 1). A summary of the study parameters and RfC calculation for the Johnson et al (2003) study and the fetal cardiac endpoint are included in Table 2.

In their discussion of the critical studies and RfC development, IRIS noted the confidence in the overall chronic RfC was high and the confidence in the candidate RfC for the cardiac developmental defect was moderate-to-high (IRIS 2011a, IRIS 2011b), noting the sensitive developmental effects were similar to or, in most cases, lower than the PODs for the most sensitive reproductive effects, suggesting the developmental effects are not a result of parental toxicity (IRIS 2011b). IRIS further noted that while the Johnson et al. (2003) study had important limitations, the overall weight-of-evidence supports the TCE effect on cardiac development and greater confidence in the selected dose metric with the data suitability for BMD and PBPK modeling. IRIS also noted that the multiple candidate RfCs fell within a narrow range, providing robust support for the final RfC, that cardiac birth defects have been observed following TCE exposure to humans, rodents and chicks, and that several studies have reported induction of heart malformations following prenatal exposures to the TCE oxidative metabolites TCA and DCA (IRIS 2011b).

The EPA identifies that a single exposure at any of several developmental stages may be sufficient to produce an adverse developmental effect (EPA 1991). The increased susceptibility to toxic insult during development is associated with the processes of rapid cell division, migration and differentiation common to all mammals during developmental stages (Johnson et al., 2003). In mammals, cellular specification of the fertilized embryo begins at the 8-cell stage. In humans the onset of embryonic cellular differentiation begins at day 21 post fertilization, with organogenesis (the process of organ development) continuing through approximately days 56-60, with the fetal period marked by cell-proliferation-driven growth that sculpts organ details and fine-tunes organ function (Smart and Hodgson, 2018). In humans the cardiac system is the second to develop following fertilization, with cardiac development beginning at approximately 3 weeks following implantation. Substantial cardiac system development continues through 8 to 9 weeks post implantation, with the most sensitive period of cardiac development occurring weeks 3 to 6 (Smart and Hodgson, 2018). The period of TCE exposure in the Johnson et al. (2003) rat study was daily on rat GDs 1 to 22.

DWM's Supplemental Vapor Intrusion Guidance for Short-Term TCE Exposures

The current DEQ vapor intrusion screening levels for TCE reflect the revised 2011 IRIS values. IRIS toxicity values represent the EPA's official scientific position regarding the toxicity of chemicals based on the data available at the time of the review and is the EPA's preferred source of human health toxicity values (EPA 1991b). In their discussions of TCE indoor air action levels, the EPA states "*Existing guidance provides that responders should consider early or interim action(s) where appropriate to eliminate, reduce, or control the hazards posed by a site. In doing so, IRIS generally provides the best available toxicological information in support of early or interim action for buildings where investigations of indoor air contamination identify site-related concentrations of TCE*" (EPA 1991b).

IRIS is also DEQ's primary source of human health toxicity values to establish regulatory levels, guidance levels and toxicity values that serve as the DEQ's basis develop human health risk estimates. In addition to the vapor intrusion screening levels that are used as indicators of the need for further investigations of potential human exposure concerns, DEQ has established indoor air inhalation exposure immediate action levels (Table 3) for TCE to protect sensitive populations (groups of people most likely to suffer adverse health effects) from short-term TCE exposures that may result in long-term effects.

Following the publication of the 2011 IRIS review the TCE toxicity reference values were incorporated into EPA's Regional Screening Level (RSL) tables (RSL 2018) referenced by DEQ for toxicity values and screening levels for human health risk assessment. The RSLs use IRIS as their initial source of reference concentrations (RfCs) for inhalation exposures, reference doses (RfDs) for oral exposures, and cancer potency factors for oral (SFO, Slope Factor Oral) and inhalation exposures (IUR, Inhalation Unit Risk). The RSLs also incorporate screening levels for residential and occupational receptors calculated using EPA's default exposure parameters. The TCE vapor intrusion action levels protective of cardiac developmental defects are calculated using IRIS RfC[8] value and the EPA default inhalation exposure parameters for residential and occupational receptors (Table 4). The TCE short-term action levels reflect inhalation concentrations equivalent to a TCE inhalation Hazard Quotient of 1.0.

[8] The U.S. EPA defines a reference concentration (RfC) as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of a chemical to the human population through inhalation (including sensitive subpopulations), that is likely to be without an appreciable risk of deleterious effects during a lifetime. Generally used in EPA's non-cancer health assessments. Source: IRIS Glossary, available at:

$$HQ_{inhalation} = \frac{Air\ Concetration}{Action\ Level}$$

In the consideration of non-cancer health effects, the EPA Office of Solid Waste and Emergency Response has stated that "*unacceptable risk occurs when exposures exceed concentrations to which the human population, including sensitive subgroups, may be exposed without adverse effect during a lifetime or part of a lifetime, as appropriate to address teratogenic and developmental effects"* (EPA 2014, EPA 1991b).

DEQ specifies that concentrations of TCE exceeding the receptor-scenario specific action levels may pose an unacceptable level of risk to the children of women exposed in their first trimester of pregnancy after short-term inhalation exposures. The TCE action level guidance requires immediate action after identification of TCE air concentrations greater than the receptor-scenario specific action levels (>1.0 HQ) to: (1) identify if the receptor-scenario specific female population is present at the location of concern and may be exposed to the TCE; (2) notify DWM within 1 business day of the TCE action level exceedance; (3) if the receptor-scenario specific female population is present at the location of concern work with DWM to provide risk communication to the involved persons, and (4) implement immediate measures to eliminate the TCE exposure, or to reduce TCE exposure levels to concentration below the action level. Every effort is to be made with the expectation exposure mitigation will be completed within 72-hours after awareness of TCE concentrations above the action level. During risk communication activities DEQ also cautions exposures to women that may plan to become pregnant within 2-4 weeks to allow adequate time for elimination of TCE from the body after removal or reduction of the exposure concentration.

The rationale for the 72-hour time-frame to identify and reduce/eliminate the TCE exposure to the sensitive population lies in rapid absorption and distribution characteristics of TCE, the potential for TCE and TCE metabolites to cross the placenta and reach the developing childe, the critical window of exposure defined by the susceptibility of the embryo/fetus during developmental stages, the unique sensitivity to low-level short-term TCE exposure impacts during cardiac organogenesis, and the potential

severity of these exposures to elicit chronic effects. In responding to incidents with known TCE exposures to the sensitive population DEQ routinely works in concert with public health staff from both DHHS and local health departments to provide coordinated risk communication and health consultation efforts. Additionally, EPA Region 4 often assists with mitigation efforts to affect rapid exposures reductions.

DEQ has prepared guidance documents and risk communication materials for property owners, property developers, environmental consultants and potentially exposed populations (Appendix B). In addition, DWM staff have done numerous presentations to stakeholders to review the response guidance and the underlying science. One such presentation is included in Appendix C.

STAKEHOLDER COMMENTS FOLLOWING RELEASE OF TCE RfC for the DEVELOPMENTAL ENDPOINT

As regulatory agencies implemented response activities referenced to the TCE short-term action levels some stakeholders questioned the reliability of the toxicological science identified as the critical study, the Johnson et al. (2003) study, that served as the basis of the cardiac developmental reference value. In response to these concerns, DEQ staff in 2016 performed a literature review to identify peer-reviewed science and epidemiological studies that would fill mechanistic and epidemiological data gaps relevant to the cardiac developmental effect. Additionally, the Massachusetts Department of Environmental Protection and a group of U.S. EPA scientists also published comprehensive reviews of the state-of-the-science in 2014 and 2016, respectively. These reviews discussed the science presented in the IRIS 2011 document, as well as studies published subsequent to the IRIS review efforts. These reviews have been made available to the SAB and are discussed briefly here.

As summarized by the Massachusetts Department of Environmental Protection in their 2014 (MADEP 2014) publication reviewing the state-of-the science for the developmental cardiac endpoint and the candidate RfC, issues raised by those questioning the endpoint and the RfC included: (1) the apparent lack of a clearly defined dose-response relationship in the critical study, (2) the use of historical control values versus concurrent control values in the study, and (3) and the lack of strong supporting scientific evidence for TCE-induced congenital cardiac defects. Stakeholder groups identified specific concerns with the Johnson et al. (2003) principal study included the authors' combining data from multiple

treatment groups studied in 1989-1992 by Dawson et al. (1993) with their data studies ins in 1994-1995. In the Johnson et al. (2003) study cardiac malformation incidence data were compared between treated groups and combined control data from cohorts studied concurrent to treated groups over the course of the 6-year research program, including controls from studies of TCE metabolites (Makris et al., 2016).

In 2014 MADEP published their reassessment of the available data presented in the IRIS 2011 review and other relevant literature on TCE-induced fetal cardiac toxicity aimed at determining if the TCE RfC based on congenital cardiac defects (CCD) as an endpoint are appropriate and can possibly be useful for short-term exposure duration risk assessment. In summarizing the findings of their review, MADEP stated:

> *"Although the critical study reporting CCDs [congenital cardiac defects] has limitations, multiple studies in mammalian and avian models suggest that TCE or one or more of its metabolites (trichloroacetic acid and dichloroacetic acid) can cause cardiac teratogenesis. The avian studies are the most convincing, while oral and inhalation rodent studies have had mixed results suggesting either methodological (route of exposure, duration of exposure, analytical techniques), or strain differences. A two-to three-fold increase in risk of congenital heart defects was found in multiple animal studies, and the most frequently found defects in the animal studies have also been reported in human populations exposed to TCE and other solvents (defects of the interventricular septae and the valves). In addition, mechanistic support is provided by studies in avian and mammalian cells demonstrating altered processes that are critical to normal valve and septum formation. The NAS TCE review document stated that the combined animal and human evidence generates the greatest level of plausibility for TCE-induced congenital cardiac defects compared to many observed developmental adverse outcomes in other studies. However, the NAS recommended further low dose studies to replicate the effects observed in the critical study. Until such studies are conducted, ORS concurs with US EPA that the current available weight of the scientific evidence on TCE-induced congenital cardiac toxicity is sufficient to warrant concern and the critical study is a reasonable basis for developing toxicity numbers."*

In 2016 DWM toxicologists performed a literature review to address data gaps in the TCE science related to the developmental cardiac effect. Those efforts are summarized in the *Time Line of Trichloroethylene (TCE) Inhalation Action Level Toxicity References and Discussion Documents, N.C. Department of Environmental Quality, January 2017*. Among summary discussions of the MADEP (2014) and Makris et al. (2016) studies are mechanistic and epidemiological studies adding to the WOE for TCE developmental cardiac defects. A mechanistic study using the common cardiac zebrafish model by Wirbisky et al. (2016) reports cardiac vasculature and musculature network defects, and alterations to more than 70 genes known associated with associated with cardiovascular disease, organ morphology and function, and

skeletal and muscular disorders at environmentally relevant TCE concentrations. Epidemiological evidence for cardiac defects included a 2014 study of the Texas Birth Defects Registry evaluating birth records from 1996 through 2008 (Brender et al., 2014). They identified a significant correlation of obstructive heart defect incidence in offspring of mothers 35 years or older with maternal residential proximity to industrial releases of chlorinated solvents (odds ratio 1.43, 95% CI 1.08, 1.88; the odds ratio represents the odds of an exposed person developing the disease relative to a non-exposed person developing the disease).

DWM's review also identified two epidemiological studies reviewed by ATSDR (ATSDR, 2014). One reported significantly elevated risk (2.5-fold) of cardiac defects at birth in children of parents exposed to TCE in drinking water during the month before conception and the 1st trimester of pregnancy for a population in Endicott, NY. The other epidemiological study reported significant (3-fold) increased risk of congenital heart defects in children born to women living within 1.3-miles of a TCE-emitting site in Milwaukee, WI. In their discussion of the implications for TCE-induced cardiac developmental effects ATSDR stated reports of TCE-induced cardiac malformations in rat fetuses is valid and relevant to humans, and despite the limitations of the Johnson et al study, there was insufficient evidence to dismiss it, particularly considering the epidemiological, animal and mechanistic evidence.

Later in 2016, a group of U.S. EPA scientists published a review of the TCE state-of-the-science (Makris, et al., 2016). They also performed an updated literature search of TCE-related developmental cardiac defects, performed a weight-of-evidence (WOE) analysis of epidemiological, toxicological, *in vitro*, *in ovo* and mechanistic data, and developed a putative adverse outcome pathway (AOP) to explore key events for common cardiac defects. The EPA group reviewed and summarized the limitations and strengths of the toxicological studies and noted these limitations were evaluated and considered in the 2011 IRIS assessment and subsequent peer-reviewed publications. They also noted the corresponding author provided clarification on a number of questions and provided a detailed discussion of study methods. The reviewers noted the Johnson et al. (2003) study authors provided additional detail aimed at specific concerns related to study animal husbandry and provided adequate clarification that concurrent controls were used for each treatment group, that fetal randomization and blinded cardiac evaluation procedures were adequate for confidence in the reported study findings (Makris et al., 2016). The EPA review confirmed the Johnson et al. (2003) and Dawson et al. (1993) studies observed fetal cardiac

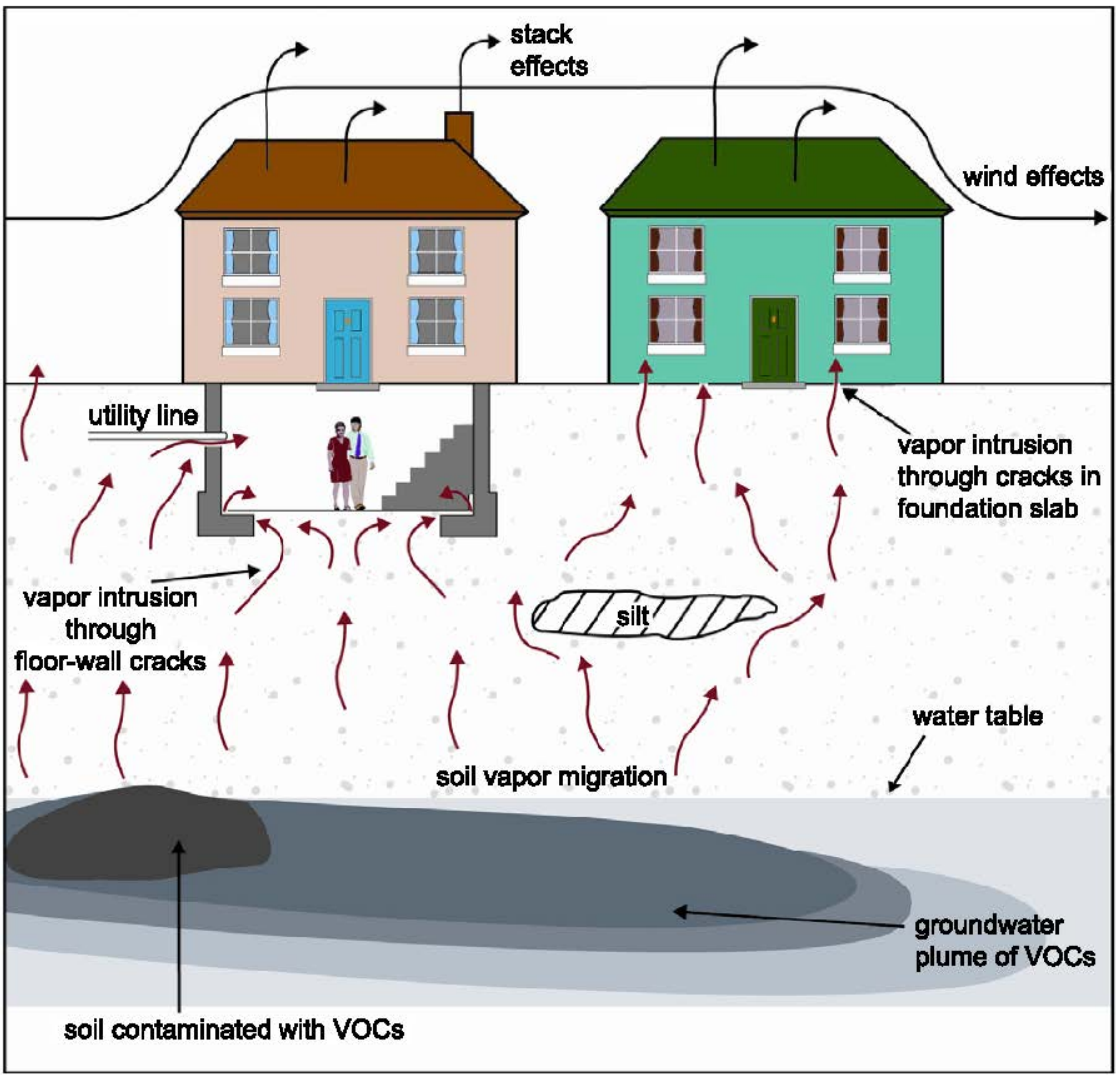
defects following gestational drinking water exposures in rats that were not confirmed in other studies, but noted none of the other studies had similar design (route of exposure, vehicle, source or strain of animals) and these factors as well as other unknown factors may contribute to the differences in detection of cardiac malformations. The EPA group concluded that TCE has the potential to cause cardiac defects in humans when exposures occur at sufficient doses during a sensitive window of fetal development. They acknowledged the limitations in the Johnson et al. (2003) study, but affirmed it was suitable for hazard characterization and reference value derivation. Additionally, the EPA reviewers noted a number of environmental exposures and genetic factors likely contribute to the commonality of human cardiovascular malformation birth defects.

Additional discussion of related peer-reviewed articles and state-of-the-science reviews are included in the document *Time Line of Trichloroethylene (TCE) Inhalation Action Level Toxicity References and Discussion Documents, N.C. Department of Environmental Quality, January 2017*, included in Appendix D.

SUMMARY

The DWM TCE Vapor Intrusion action levels for residential and occupational exposures were developed from the best available science and following current human health risk assessment protocols established by IRIS and the U.S. EPA. The appropriateness of the residential and occupational inhalation exposure TCE short-term action levels developed by the EPA to protective of fetal cardiac effects were confirmed by DWM, NC DHHS and the ATSDR. The TCE short-term inhalation action levels are responsive to the documented human health exposure characteristics of TCE, including rapid absorption, distribution, metabolism producing toxic metabolites and the capacity to cross the placenta. The TCE action levels and the response time-frame is intended to be protective of the potential for developmental effects that may result from short-term exposures to a woman that is in the first trimester of pregnancy, at a time that she may not yet know that she is pregnant. Short-term TCE exposures at this stage of development have the potential to cause chronic (life-long) effects to the cardiac development of her unborn child. The current science on TCE confirms the rapid absorption and distribution of TCE in humans, its ability to cross the placenta to the developing fetus, the unique sensitivity of the cardiac development to TCE insult during the earliest stages of fetal and embryonic cardiogenesis. Epidemiological studies support the implications of maternal exposures to impact fetal

cardiac development. The TCE action levels focus on the population of concern, women in their first trimester of pregnancy and the sensitive population, the unborn child at a period of extreme vulnerability. In their response efforts, DEQ goes to great lengths to assist both residents and commercial operations to minimize disruptions of day-to-day activities and operations, and to facilitate a coordinated response to identify effective, efficient mitigation efforts and to provide risk communication and health consultation for potentially impacted populations.



This figure depicts the migration of volatile chemicals from contaminated soil and groundwater plumes into buildings. Volatile chemicals are shown to enter buildings through cracks in the foundation and openings for utility lines. Atmospheric conditions and building ventilation are shown to influence vapor intrusion.

(Source: The 2008 Brownfields Technology Primer: Vapor Intrusion Considerations for Redevelopment, EPA 542-R-08-001)

Figure 1. Vapor intrusion conceptual model.

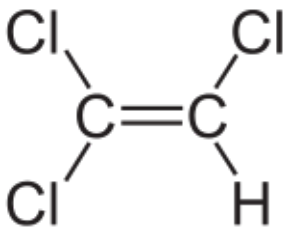


Figure 2. Chemical Structure of Trichloroethylene. Source: Wikipedia, https://en.wikipedia.org/wiki/Trichloroethylene

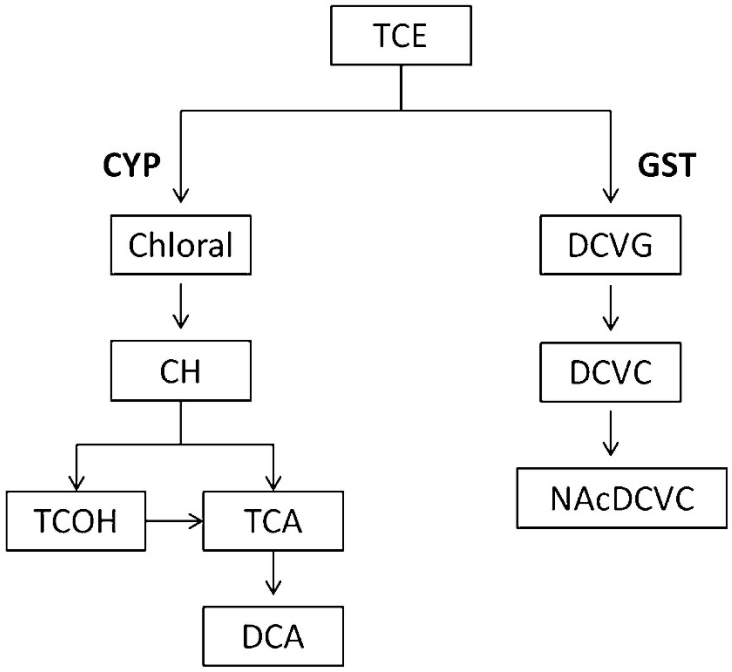


Figure 3. Major metabolites of the TCE metabolic pathways. **CYP**, Cytochrome P450; CH, chloral hydrate; DCA, dichloroacetic acid; DCVC, S-dichlorovinyl-L-cysteine; DCVG, S-dichlorovinyl-L-glutathione; **GST**, glutathione-S-transferase; TCA trichloroacetic acid; TCOH, trichloroethanol. Source: Jiang et al., 2017.

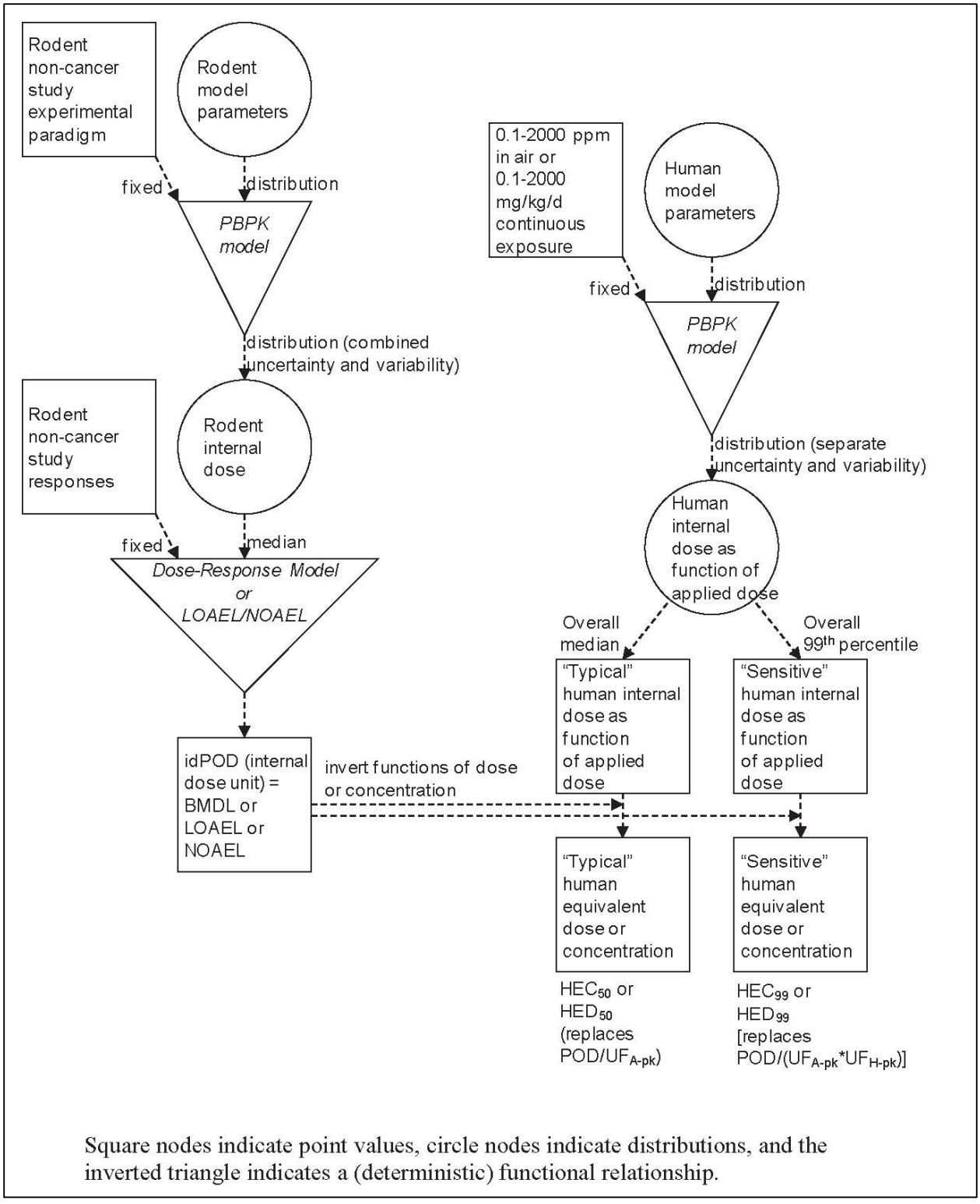


Figure 4. Flow chart for dose-response analyses of rodent non-cancer effects using PBPK model-based dose-metrics. Source: IRIS 2011b

Table 1. Physicochemical Properties of Trichloroethylene (TCE). Source: ChemID*plus,* Wikipedia, ATSDR 2014a

Physical Property	**Value**
Synonyms	Trichloroethylene, Trichloroethene, TCE
Chemical formula	C_2HCl_3
Molecular weight	131.4 g/mole
Boling Point	-84.7 °C
Log K_{ow}	2.42
K_{OC}	49 to 460
Water Solubility	1280 mg/L
Vapor Pressure	69 mm Hg
Henry's Law Constant	0.00985 atm-m^3/mole

Table 2. Johnson et al. 2003 principal study parameters and fetal cardiac endpoint dose-response data selected for RfC calculation components (IRIS 2011b).

Test Species	Rats, Sprague-Dawley, Pregnant females 9-13 per treatment 55 in control group
Exposure concentrations (Exposure dose concentrations)	0, 2.5, 250, 1500, 1.1E06 µg/L (4.5E-04, 4.8E-02, 2.18E-01, 1.29E02 mg/kg-day)
TCE exposure medium	Drinking water
Exposure period	Gestational days 1 to 22 (encompassing entire pregnancy)
Critical effect	Developmental, significant increase of fetal cardiac malformations
Effect level, drinking water	NOAEL 2.5 µg/L LOAEL 250 µg/L
Internal dose POD[a]	0.139 mg TCE metabolized/$kg^{3/4}$/day (PBPK predicted internal dose)
Critical effect level, BMD modeling	BMR = 1% extra risk of effect to pups, due to severity of effects
Exposure extrapolation	Rodent PBPK model – oral to internal dose Human PBPK model – rodent to human internal dose
POD_{human}	21 µg/m^3 TCE as $HEC_{99,BMDL01}$ (3.7 ppbv TCE)
Uncertainty Factors	Composite UF = 10 = (3 UF_A x 3 UF_H)
Calculated Chronic RfC_{Human}	2.1 µg/m^3 TCE (0.037 ppbv TCE)
Confidence in the candidate RfC	Medium

a. The total amount of oxidative metabolism of TCE scaled by the ¾ power of body weight (TotOxmetabNW34[mg/$kg^{3/4}$/week]) was used as the primary dose-metric to include possible contributions of reactive metabolites to overall toxicity

UF_A = interspecies uncertainty factor

UF_H = human variability (intraspecies) uncertainty factor

BMR = Benchmark dose modeling response factor

Table 3. Division of Waste Management (DWM) Immediate Action Levels for Trichloroethylene (TCE) Inhalation Exposures

Exposure Scenario	TCE Action Level - Inhalation	Required Action by the State-Lead Contractor, Consultant or Remediation Party [1]
Residential	2.1 µg/m^3 (0.39 ppbv)	1. Notify DWM within 1 business day 2. Immediately provide fact sheets to potentially affected individuals and involve DWM 3. Initiate measures to reduce exposure below the action level immediately.
Non-residential	8.8 µg/m^3 (1.6 ppbv)	
TCE sensitive populations are defined as: Women of child-bearing age (15 to 50 years of age) [2]		

[1] The required action time frame begins when the remediating party, DWM State-Lead Program or Brownfields Program applicants receives the validated laboratory data

[2] A site-specific evaluation of the appropriate age range for women of child-bearing age should be made in consultation with the exposed women and DWM

TCE = trichloroethylene (trichloroethene, CASN 79-01-6)

Table 4. Residential and occupational receptor inhalation exposure parameters included in the trichloroethylene vapor intrusion action levels. Screening levels are for short-term exposures protective of fetal cardiac effects. Exposure parameters are EPA default human health risk values. (Source: USEPA RSLs)

Exposure Parameter	Residential Receptor	Occupational Receptor [a]
RfC, µg/m^3	2.0	2.0
Exposure frequency, days per year	350	250
Exposure time, hours per day	24	8
Exposure duration, years	26	25
Acceptable Risk Level	HQ = 1.0	HQ = 1.0
Developmental Defect Short-term Exposure Action Level, µg/m^3	2.1	8.8
Population of concern	Women in the 1st trimester of pregnancy, or women that may wish to become pregnant in the next 2-4 weeks	

a. The DWM occupational receptor is identified in the EPA RSLs as the "composite worker" receptor

RSL = USEPA Superfund Program Regional Screening Levels, accessed at: https://www.epa.gov/risk/regional-screening-levels-rsls

HQ = Hazard Quotient = (exposure concentration/screening level)

RfC = Reference concentration

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Appendix A

USEPA IRIS Summary for TCE

September 2011

Trichloroethylene; CASRN 79-01-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR TRICHLOROETHYLENE

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/28/2011
Inhalation RfC (I.B.)	yes	09/28/2011
Carcinogenicity Assessment (II.)	yes	09/28/2011

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name —Trichloroethylene
CASRN — 79-01-6
Section I.A. Last Revised — 09/28/2011

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is

essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous RfD for trichloroethylene (TCE) on the IRIS database.

I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD**
Multiple	**Multiple**	**Multiple**	**0.0005 mg/kg/day**
Decreased thymus weight in female B6C3F_1 mice 30-week drinking water study Keil et al. (2009)	$HED_{99,LOAEL}$: 0.048 mg/kg/day	100	candidate RfD = 0.00048 mg/kg/day
Decreased plaque-forming cell (PFC) response, increased delayed-type hypersensitivity in B6C3F_1 mice Drinking water exposure from gestation day (GD) 0 to 3 or 8 weeks of age Peden-Adams et al. (2006)	LOAEL: 0.37 mg/kg/day	1,000	candidate RfD = 0.00037 mg/kg/day
Increased fetal cardiac malformations in Sprague-Dawley rats Drinking water exposure from GD 1 to 22 Johnson et al. (2003)	$HED_{99,BMDL01}$***: 0.0051 mg/kg/day	10	candidate RfD = 0.00051 mg/kg/day

*Conversion Factors and Assumptions – For Keil et al. (2009), the $HED_{99,LOAEL}$ is the 99^{th} percentile (due to human toxicokinetic uncertainty and variability) human equivalent dose (HED) to the mouse lowest-observed-adverse-effect level (LOAEL) of 0.35 mg/kg/day, using

the internal dose metric of TCE metabolized/kg^{¾}/day. For Peden-Adams et al. (2006), there were no conversion factors. For Johnson et al. (2003), the $HED_{99,BMDL01}$ is the 99th percentile (due to human toxicokinetic uncertainty and variability) HED to the rat internal dose $BMDL_{01}$ of 0.0142 mg TCE oxidized/kg^{¾}/day. Details of the methods used are presented in Section 5.1.3 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011).

**As a whole, the estimates support an RfD of 0.0005 mg/kg/day. This RfD reflects the midpoint among the similar candidate RfDs for the critical effects—0.0004 mg/kg/day for developmental immunotoxicity (decreased PFC and increased delayed-type hypersensitivity) in mice and 0.0005 mg/kg/day for both heart malformations in rats and decreased thymus weights in mice—rounded to one significant figure, and is within 25% of each candidate RfD.

***BMDL associated with a 1% extra risk on a pup basis.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

The *Toxicological Review of Trichloroethylene* reviews and summarizes the available data on noncancer effects caused by TCE (for summary of the noncancer effects, see U.S. EPA (2011), Section 4.11.1). Adverse noncancer effects associated with oral TCE exposure include decreased body weight, liver and kidney effects, and neurological, immunological, reproductive, and developmental effects. As recommended by *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002), the RfD was developed based on consideration of all relevant and appropriate endpoints carried through to the derivation of "candidate" RfDs. Candidate RfDs were developed for all endpoints on the basis of applied dose (U.S. EPA (2011), Section 5.1.2), and for the more sensitive endpoints within each type of toxicity (e.g., neurotoxicity, immunotoxicity, etc.), on the basis of physiologically based pharmacokinetic (PBPK) model-derived internal dose (U.S. EPA (2011), Sections 3.5 and 5.1.3). Candidate RfDs were developed from oral studies as well as from inhalation studies via route-to-route extrapolation using the PBPK model. Because the same internal dose metric is used for each type of toxicity, based on data informing the role of parent compound or different metabolites or metabolic pathways, applying the PBPK modeling only for the more sensitive endpoints for each type of toxicity is adequate to identify the more sensitive endpoints overall. The most sensitive observed adverse effects, which were used as the primary basis for the RfD, were those affecting the immune system and the developing fetus, and were all based on oral studies. Additional support for the RfD was based on adverse effects in the kidney.

Multiple candidate RfDs for the principal and supporting effects from oral studies are in the relatively narrow range of 0.0003−0.0008 mg/kg/day, at the low end of the overall range of candidate RfDs for all adverse effects. Given the somewhat imprecise nature of the individual

candidate RfDs, and the fact that multiple effects/studies lead to similar candidate RfDs, the approach taken in this assessment is to select an RfD supported by multiple effects/studies. The advantages of this approach are that it leads to a more robust RfD (less sensitive to limitations of individual studies) and that it provides the important characterization that the RfD exposure level is similar for multiple noncancer effects rather than being based on a sole explicit critical effect.

Three principal (Keil et al., 2009; Peden-Adams et al., 2006; Johnson et al., 2003) and two supporting (Woolhiser et al., 2006; NTP, 1988) studies/effects have been chosen as the basis of the RfD for TCE noncancer effects (see the table below). Two of the lowest candidate RfDs for the primary dose metrics—0.0008 mg/kg/day for increased kidney weight in rats and 0.0005 mg/kg/day for both heart malformations in rats and decreased thymus weights in mice—are derived using the PBPK model for inter- and intraspecies extrapolation, and a third—0.0003 mg/kg/day for increased toxic nephropathy in rats—is derived using the PBPK model for inter- and intraspecies extrapolation as well as route-to-route extrapolation from an inhalation study. The other of these lowest values—0.0004 mg/kg/day for developmental immunotoxicity (decreased PFC response and increased delayed-type hypersensitivity) in mice—is based on applied dose.

There is medium confidence in the candidate RfDs for decreased thymus weights (U.S. EPA (2011), Section 5.1.2.5), heart malformations (U.S. EPA (2011), Section 5.1.2.8), and developmental immunological effects (U.S. EPA (2011), Section 5.1.2.8), and these effects are considered the critical effects used for deriving the RfD. For heart malformations, although the available study has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. For adult and developmental immunological effects, there is high confidence in the evidence for an immunotoxic hazard from TCE. However, the available dose-response data for immunological effects preclude application of benchmark dose (BMD) modeling.

For kidney effects (U.S. EPA (2011), Section 5.1.2.2), there is high confidence in the evidence for a nephrotoxic hazard from TCE. Moreover, the two lowest candidate RfDs for kidney effects (toxic nephropathy and increased kidney weight) are both based on BMD modeling and one is derived from a chronic study. However, as discussed in U.S. EPA (2011), Section 3.3.3.3, there remains substantial uncertainty in the PBPK model-based extrapolation of glutathione (GSH) conjugation from rodents to humans due to limitations in the available data. In addition, the candidate RfD for toxic nephropathy had greater dose-response uncertainty since the estimation of its point of departure (POD) involved extrapolation from high response rates (>60%). Therefore, kidney effects are considered supportive but are not used as a primary basis for the RfD.

As a whole, the estimates support an RfD of 0.0005 mg/kg/day. This RfD reflects the midpoint among the similar candidate RfDs—0.0004 mg/kg/day for developmental immunotoxicity (decreased PFC and increased delayed-type hypersensitivity) in mice and 0.0005 mg/kg/day for both heart malformations in rats and decreased thymus weights in mice—rounded to one significant figure, and is within 25% of each candidate RfD. This estimate is also within approximately a factor of 2 of the supporting effect estimates of 0.0003 mg/kg/day for toxic nephropathy in rats and 0.0008 mg/kg/day for increased kidney weight in rats. Thus, there is strong, robust support for an RfD of 0.0005 mg/kg/day provided by the concordance of estimates derived from multiple effects from multiple studies. The estimates for kidney effects, thymus effects, and developmental heart malformations are based on PBPK model-based estimates of internal dose for interspecies and intraspecies extrapolation, and there is sufficient confidence in the PBPK model and support from mechanistic data for one of the dose metrics (total oxidative metabolism for the heart malformations). There is high confidence that the amount of bioactivated S-dichlorovinyl-L-cysteine (DCVC) would be an appropriate dose metric to use for kidney effects, but there is substantial quantitative uncertainty in the PBPK model predictions for this dose metric in humans (U.S. EPA (2011), Section 5.1.3.1). Note that there is some human evidence of developmental heart defects from TCE exposure in community studies (U.S. EPA (2011), Section 4.8.3.1.1) and of kidney toxicity in TCE-exposed workers (U.S. EPA (2011), Section 4.4.1).

In summary, the RfD is **0.0005 mg/kg/day** based on the critical effects of heart malformations (rats), adult immunological effects (mice), and developmental immunotoxicity (mice), all from oral studies. This RfD is further supported by results from an oral study for the effect of toxic nephropathy (rats) and route-to-route extrapolated results from an inhalation study for the effect of increased kidney weight (rats).

Summary of principal studies, effects, PODs, and uncertainty factors (UFs) used to derive the RfD

Keil et al. (2009)—Decreased thymus weight in female B6C3F$_1$ mice exposed for 30 weeks by drinking water.

- Internal dose POD = 0.139 mg TCE metabolized/kg^{¾}/day, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/day (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape) (U.S. EPA (2011), Appendix F, Section F.6.3).
- $HED_{99,LOAEL}$ = 0.048 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 100.
- Primary candidate RfD = $HED_{99,LOAEL}$/UF = 0.048/100 = 0.00048 mg/kg/day.

Peden-Adams et al. (2006)—Decreased PFC response (3 and 8 weeks), and increased delayed-type hypersensitivity (8 weeks) in pups exposed from GD 0 until 3 or 8 weeks of age through drinking water (placental and lactational transfer, and pup ingestion).

- POD = 0.37 mg/kg/day is the applied dose LOAEL (estimated daily dam dose) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape). No PBPK modeling was attempted due to lack of appropriate models/parameters to account for complicated fetal/pup exposure pattern (U.S. EPA (2011), Appendix F, Section F.6.5).
- Composite UF = 1,000.
- Primary candidate RfD = LOAEL/UF = 0.37/1,000 = 0.00037 mg/kg/day.

Johnson et al. (2003)—Fetal heart malformations in Sprague-Dawley rats exposed on GDs 1–22 by drinking water.

- Internal dose POD = 0.0142 mg TCE metabolized by oxidation/kg^{¾}/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest dose group (1,000-fold higher than next highest dose group) dropped, pup as unit of analysis, benchmark response (BMR) = 1% extra risk (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation (U.S. EPA (2011), Appendix F, Section F.6.4).
- $HED_{99,BMDL01}$ = 0.0051 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.

- Composite UF = 10
- Primary candidate RfD = $HED_{99,BMDL01}$/UF = 0.0051/10 = 0.00051 mg/kg/day.

Summary of supporting studies, effects, PODs, and UFs for the RfD

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Internal dose POD = 0.0132 mg DCVC bioactivated/$kg^{¾}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 5% extra risk (clearly toxic effect), and Log-logistic model (U.S. EPA (2011), Appendix F, Section F.6.1).
- $HED_{99,BMDL05}$ = 0.0034 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 10.
- Supporting candidate RfD = $HED_{99,BMDL05}$/UF = 0.0034/10 = 0.00034 mg/kg/day.

Woolhiser et al. (2006)—Increased kidney weight in female Sprague-Dawley rats exposed for 4 weeks by inhalation (6 hours/day, 5 days/week).

- Internal dose POD = 0.0309 mg DCVC bioactivated/$kg^{¾}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 10% increase in relative weight, and Hill model with constant variance (U.S. EPA (2011), Appendix F, Section F.6.2).
- $HED_{99,BMDL10}$ = 0.0079 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 10.
- **Supporting candidate RfD = $HED_{99,BMDL10}$/UF = 0.0079/10 = 0.00079 mg/kg/day.**

I.A.3. UNCERTAINTY FACTORS

Specific UFs that were applied in deriving the candidate RfDs are summarized in the following tables. The specific factors are intended to account for (1) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (abbreviated UF_L); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty, abbreviated UF_A); (3) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability, abbreviated UF_H); (4) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to

chronic exposure, abbreviated UF_S); and (5) uncertainty associated with extrapolation when the database is incomplete (abbreviated UF_D). In consideration of database uncertainties, UF_D = 1 because there is minimal potential for deriving an underprotective toxicity value as a result of an incomplete characterization of TCE toxicity. (Note that UF values of "3" actually represent $10^{0.5}$, and, when two such values are multiplied together, the result is 10 rather than 9.)

Principal studies — Summary of UFs applied to derive the candidate RfDs

Keil et al. (2009)—Decreased thymus weight in female $B6C3F_1$ mice exposed for 30 weeks by drinking water.

- Composite UF = 100.
- UF_L = 10 was applied because the POD is a LOAEL for an adverse effect.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from mice to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than mice to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

Peden-Adams et al. (2006)—Decreased PFC response (3 and 8 weeks) and increased delayed-type hypersensitivity (8 weeks) in pups exposed from GD 0 until 3 or 8 weeks of age through drinking water (placental and lactational transfer, and pup ingestion).

- Composite UF = 1,000.
- UF_L = 10 was applied because the POD is a LOAEL for multiple adverse effects.
- UF_A = 10 was applied to account for toxicokinetic and toxicodynamics differences between mice and humans on the basis of applied dose.
- UF_H = 10 was applied to account for human variability in toxicokinetics and toxicodynamics.
- UF_S = 1 was applied because the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect.

Johnson et al. (2003)—Fetal heart malformations in Sprague-Dawley rats exposed on GDs 1–22 by drinking water.

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{01}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect.

Supporting studies — Summary of UFs applied to derive the candidate RfDs

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{05}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

Woolhiser et al. (2006)—Increased kidney weight in female Sprague-Dawley rats exposed for

4 weeks by inhalation (6 hours/day, 5 days/week).

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a BMDL for a 10% increase in relative weight.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because Kjellstrand et al. (1983) reported that in mice, kidney effects after exposure for 120 days was no more severe than those after 30 days of exposure.

I.A.4. ADDITIONAL STUDIES/COMMENTS

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.10 (PDF).

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study – High-medium/medium/low-medium (for each endpoint individually, as described below)
Data Base – High
RfD – High

For adult and developmental immunological effects, there is high confidence in the evidence of immunotoxic hazard from TCE. However, the available dose-response data for the most sensitive immunological effects (Keil et al., 2009; Peden-Adams et al., 2006) precluded application of BMD modeling. There are inadequate data on the active moiety for TCE-induced immunological effects, so PBPK modeling applied to Keil et al. (2009) used a generic dose metric. The PBPK model could not be applied to Peden-Adams et al. (2006) due to a lack of data on gestational and lactational transfer. Thus, due to the high confidence in the immunotoxic hazard coupled with the quantitative uncertainties in the dose-response

assessment, the confidence in candidate RfDs derived from these studies is characterized as medium-to-high.

For developmental cardiac effects, although the available study (Johnson et al., 2003) has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. Both BMD and PBPK modeling could be applied to these data. With respect to PBPK modeling, data suggest that oxidative metabolites are involved in TCE-induced cardiac malformations, lending greater confidence in the appropriateness of the selected dose metric. Thus, due to the important limitations of the available study coupled with the higher confidence in the dose-response analysis, the confidence in the candidate RfD derived from this study is characterized as medium.

For kidney effects, there is high confidence in the evidence of nephrotoxic hazard from TCE. Both BMD and PBPK modeling could be applied to the most sensitive studies for this endpoint (Woolhiser et al., 2006; NTP, 1988), and one of these studies is of chronic duration (NTP, 1988). However, although there is high confidence in the conclusion that GSH conjugation metabolites are involved in TCE nephrotoxicity, there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, BMD modeling of the NTP (1988) data involved extrapolation from response rates much higher than the chosen BMR. Therefore, due to the high qualitative confidence coupled with the low quantitative confidence, the overall confidence in candidate RfDs derived from these studies is characterized as low-to-medium.

The RfD is supported by three principal studies (whose candidate RfDs are characterized as being of medium-to-high/medium confidence) and two supporting studies (whose candidate RfDs are characterized as being of low-to-medium confidence). Moreover, the multiple candidate RfDs from these studies fall within a narrow range, providing robust support for the final RfD. In addition, numerous studies were available for other potential candidate critical effects, which were also considered. Thus, overall, confidence in both the database and the RfD is characterized as high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document -- U.S. EPA (2011)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists

external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix I, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 09/28/2011

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Trichloroethylene
CASRN – 79-01-6
Section I.B. Last Revised – 09/28/2011

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers both toxic effects of the respiratory system (portal-of-entry) and effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous RfC for TCE on the IRIS database.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC**
Multiple	**Multiple**	**Multiple**	**0.002 mg/m^3 (0.0004 ppm)**
Decreased thymus weight in female B6C3F$_1$ mice 30-Week drinking water study Route-to-route extrapolation using PBPK model Keil et al. (2009)	HEC$_{99,LOAEL}$: 0.19 mg/m^3 (0.033 ppm)	100	candidate RfC = 0.0019 mg/m^3 [0.00033 ppm]
Increased fetal cardiac malformations in Sprague-Dawley rats Drinking water exposure from GD 1 to 22 Route-to-route extrapolation using PBPK model Johnson et al. (2003)	HEC$_{99,BMDL01}$***: 0.021 mg/m^3 (0.0037 ppm)	10	candidate RfC = 0.0021 mg/m^3 [0.00037 ppm]

*Conversion Factors and Assumptions—For Keil et al. (2009), the HEC$_{99,LOAEL}$ is the route-to-route extrapolated 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent concentration (HEC) to the mouse LOAEL of 0.35 mg/kg/day, using the internal dose metric of TCE metabolized/kg^{¾}/day. For Johnson et al. (2003), the HEC$_{99,BMDL01}$ is the route-to-route extrapolated 99th percentile (due to human toxicokinetic uncertainty and variability) HEC to the rat internal dose BMDL$_{01}$ of 0.0142 mg TCE oxidized/kg^{¾}/day. Details of the methods used, including PBPK model-based route-to-route extrapolation, are presented in Section 5.1.3 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011).

**As a whole, the estimates support an RfC of 0.0004 ppm (0.4 ppb or 2 µg/m^3). This RfC

reflects the midpoint between the candidate RfC estimates for the two critical effects (0.00033 ppm for decreased thymus weight in mice and 0.00037 ppm for heart malformations in rats), rounded to one significant figure, and is within 25% of either candidate RfC.

***BMDL associated with a 1% extra risk on a pup basis.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

The *Toxicological Review of Trichloroethylene* reviews and summarizes the available data on noncancer effects caused by TCE (for summary of noncancer effects, see U.S. EPA (2011), Section 4.11.1). Adverse noncancer effects associated with TCE exposure by inhalation include hepatic, renal, neurological, immunological, reproductive, and developmental effects. As recommended by *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002), the RfC was developed based on consideration of all relevant and appropriate endpoints carried through to the derivation of "candidate" RfCs. In particular, candidate RfCs were developed for all endpoints on the basis of applied dose (U.S. EPA (2011), Section 5.1.2) and, for the more sensitive endpoints within each type of toxicity (e.g., neurotoxicity, immunotoxicity, etc.), on the basis of PBPK model-derived internal dose (U.S. EPA (2011), Sections 3.5 and 5.1.3). Candidate RfCs were developed from inhalation studies as well as from oral studies via route-to-route extrapolation using the PBPK model. Because the same internal dose metric is used for each type of toxicity, based on data informing the role of parent compound or different metabolites or metabolic pathways, applying the PBPK modeling only for the more sensitive endpoints for each type of toxicity is adequate to identify the more sensitive endpoints overall. The most sensitive observed adverse effects, which were used as the primary basis for the RfC, were those affecting the immune system and the developing fetus, and were all based on route-to-route extrapolation from oral studies. Additional support for the RfC was based on adverse effects in the kidney.

In particular, multiple candidate RfCs for the principal and supporting effects are in the relatively narrow range of 0.0003−0.0006 ppm, at the low end of the overall range of candidate RfCs for all adverse effects. Given the somewhat imprecise nature of the individual candidate RfCs, and the fact that multiple effects/studies lead to similar candidate RfCs, the approach taken in this assessment is to select an RfC supported by multiple effects/studies. The advantages of this approach are that it leads to a more robust RfC (less sensitive to limitations of individual studies) and that it provides the important characterization that the RfC exposure level is similar for multiple noncancer effects rather than being based on a sole explicit critical effect.

Two principal (Keil et al., 2009; Johnson et al., 2003) and one supporting (NTP, 1988) studies/effects have been chosen as the basis of the RfC for TCE noncancer effects (see the

table below). Each of these lowest candidate RfCs, ranging from 0.0003 to 0.0006 ppm, for developmental, immunologic, and kidney effects, are values derived from route-to-route extrapolation using the PBPK model. The lowest candidate RfC estimate (for a primary dose metric) from an inhalation study is 0.001 ppm for kidney effects, which is higher than the route-to-route extrapolated candidate RfC estimate from the most sensitive oral study. For each of the candidate RfCs, the PBPK model was used for inter- and intraspecies extrapolation, based on the preferred dose metric for each endpoint.

There is medium confidence in the lowest candidate RfC for developmental effects (heart malformations) (U.S. EPA (2011), Section 5.1.2.8) and the lowest candidate RfC estimate for immunological effects (U.S. EPA (2011), Section 5.1.2.5), and these are considered the critical effects used for deriving the RfC. For developmental effects, although the available study has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. For immunological effects, there is high confidence in the evidence for an immunotoxic hazard from TCE, but the available dose-response data preclude application of BMD modeling.

For kidney effects (U.S. EPA (2011), Section 5.1.2.2), there is high confidence in the evidence for a nephrotoxic hazard from TCE. Moreover, the lowest candidate RfC for kidney effects (toxic nephropathy) is derived from a chronic study and is based on BMD modeling. However, as discussed in U.S. EPA (2011, Section 3.3.3.3), there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, the candidate RfC based on PBPK modeling for toxic nephropathy had greater dose-response uncertainty since the estimation of its POD involved extrapolation from high response rates (>60%). Therefore, toxic nephropathy is considered supportive but is not used as a principal basis for the RfC. The other sensitive candidate RfCs for kidney effects were all within a factor of 5 of that for toxic nephropathy; however, these values similarly relied on the uncertain inter-species extrapolation of GSH conjugation.

As a whole, the estimates support an RfC of 0.0004 ppm (0.4 ppb or 2 $\mu g/m^3$). This RfC reflects the midpoint between the similar candidate RfC estimates for the two critical effects (0.00033 ppm for decreased thymus weight in mice and 0.00037 ppm for heart malformations in rats), rounded to one significant figure, and is within 25% of either candidate RfC. This estimate is also within a factor of 2 of the candidate RfC estimate of 0.00006 ppm for the supporting effect of toxic nephropathy in rats. Thus, there is robust support for an RfC of 0.0004 ppm provided by estimates for multiple effects from multiple studies. The estimates are based on PBPK model-based estimates of internal dose for interspecies, intraspecies, and route-to-route extrapolation, and there is sufficient confidence in the PBPK model and support from mechanistic data for one of the dose metrics (total oxidative metabolism for the heart

malformations). There is high confidence that the amount of DCVC bioactivated and the amount of GSH conjugation metabolism would be appropriate dose metrics for kidney effects, but there is substantial uncertainty in the PBPK model predictions for these dose metrics in humans (U.S. EPA (2011), Section 5.1.3.1). Note that there is some human evidence of developmental heart defects from TCE exposure in community studies (U.S. EPA (2011), Section 4.8.3.1.1) and of kidney toxicity in TCE-exposed workers (U.S. EPA (2011), Section 4.4.1).

In summary, the RfC is **0.0004 ppm** (0.4 ppb or 2 µg/m^3) based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations (rats) and immunotoxicity (mice). This RfC is further supported by route-to-route extrapolated results from an oral study of toxic nephropathy (rats). In all cases, route-to-route extrapolation was performed using a PBPK model.

Summary of principal studies, effects, PODs, and UFs used to derive the RfC

Keil et al. (2009)—Decreased thymus weight in female B6C3F$_1$ mice exposed for 30 weeks by drinking water.

- Internal dose POD = 0.139 mg TCE metabolized/kg^{¾}/day, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/day (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape) (U.S. EPA (2011), Appendix F, Section F.6.3).
- $HEC_{99,LOAEL}$ = 0.033 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- Composite UF = 100.
- Principal candidate RfC = $HEC_{99,LOAEL}$/UF = 0.033/100 = 0.00033 ppm (2 µg/m^3).

Johnson et al. (2003)—Fetal heart malformations in S-D rats exposed on GDs 1–22 by drinking water.

- Internal dose POD = 0.0142 mg TCE metabolized by oxidation/kg^{¾}/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest dose group (1,000-fold higher than next highest dose group) dropped, pup as unit of analysis, BMR = 1% extra risk (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation (U.S. EPA (2011), Appendix F, Section F.6.4).
- $HEC_{99,BMDL01}$ = 0.0037 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- Composite UF = 10.

- Principal candidate RfC = $HEC_{99,BMDL01}$/UF = 0.0037/10 = 0.00037 ppm (2 µg/m^3).

Summary of supporting study, effect, POD, and UFs for the RfC

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Internal dose POD = 0.0132 mg DCVC bioactivated/$kg^{¾}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 5% extra risk (clearly toxic effect), and log-logistic model (U.S. EPA (2011), Appendix F, Section F.6.1).
- $HEC_{99,BMDL05}$ = 0.0056 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- Composite UF = 10.
- Supporting candidate RfC = $HEC_{99,BMDL05}$/UF = 0.0056/10 = 0.00056 ppm (3 µg/m^3).

I.B.3. UNCERTAINTY FACTORS

Specific UFs that were applied in deriving the candidate RfCs are summarized in the following tables. The specific factors are intended to account for (1) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (abbreviated UF_L); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty, abbreviated UF_A); (3) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability, abbreviated UF_H); (4) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, abbreviated UF_S); and (5) uncertainty associated with extrapolation when the database is incomplete (abbreviated UF_D). In consideration of database uncertainties, UF_D = 1 because there is minimal potential for deriving an underprotective toxicity value as a result of an incomplete characterization of TCE toxicity. (Note that UF values of "3" actually represent $10^{0.5}$, and, when two such values are multiplied together, the result is 10 rather than 9.)

Principal studies — Summary of UFs applied to derive the candidate RfCs

Keil et al. (2009)—Decreased thymus weight in female B6C3F$_1$ mice exposed for 30 weeks by drinking water.

- Composite UF = 100.
- UF_L = 10 was applied because POD is a LOAEL for an adverse effect.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from mice to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than mice to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

Johnson et al. (2003)—Fetal heart malformations in S-D rats exposed on GDs 1–22 by drinking water.

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{01}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect.

Supporting study — Summary of UFs applied to derive the candidate RfC

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{05}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

I.B.4. ADDITIONAL STUDIES/COMMENTS

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.10 (PDF).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study – High-medium/medium/low-medium (for each endpoint individually, as described below)
Data Base – High
RfC – High

For adult immunological effects, there is high confidence in the evidence of immunotoxic hazard from TCE. However, the available dose-response data for the most sensitive immunological effects (Keil et al., 2009) precluded application of BMD modeling. There are inadequate data on the active moiety for TCE-induced immunological effects, so PBPK modeling applied to Keil et al. (2009) used a generic dose metric. Thus, due to the high confidence in the immunotoxic hazard coupled with the quantitative uncertainties in the dose-response assessment, the confidence in the candidate RfC derived from this study is characterized as medium-to-high.

For developmental cardiac effects, although the available study (Johnson et al., 2003) has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. Both BMD and PBPK modeling could be applied to these data. With respect to PBPK modeling, data suggest that oxidative metabolites are involved in TCE-induced cardiac malformations, lending greater confidence in the appropriateness of the selected dose metric. Thus, due to the important limitations of the available study coupled with the higher confidence in the dose-response analysis, the confidence in the candidate RfC derived from this study is characterized as medium.

For kidney effects, there is high confidence in the evidence of nephrotoxic hazard from TCE. Both BMD and PBPK modeling could be applied to the most sensitive study for this endpoint (NTP, 1988), which is of chronic duration. However, although there is high confidence in the conclusion that GSH conjugation metabolites are involved in TCE nephrotoxicity, there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, BMD modeling of the NTP (1988) data involved extrapolation from response rates much higher than the chosen BMR. Therefore, due to the high qualitative confidence coupled with the low quantitative confidence, the overall confidence in the candidate RfCs derived from these studies is characterized as low-to-medium.

The RfC is supported by two principal studies (whose candidate RfCs are characterized as being of medium-to-high/medium confidence) and one supporting study (whose candidate RfC is characterized as being of low-to-medium confidence). Moreover, the multiple candidate RfCs from these studies fall within a narrow range, providing robust support for the final RfC. In addition, numerous studies were available for other potential candidate critical effects, which were also considered. Thus, overall, confidence in both the database and the RfC is characterized as high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – U.S. EPA (2011)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I of the

Toxicological Review of Trichloroethylene (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix I, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 09/28/2011

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Trichloroethylene
CASRN – 79-01-6
Section II. Last Revised – 09/28/2011

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b, a). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, per $\mu g/m^3$ air breathed (see Section II.C.1).

A previous cancer assessment for TCE is not available on the IRIS database.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Following U.S. EPA (2005b) *Guidelines for Carcinogen Risk Assessment*, TCE is characterized as "carcinogenic to humans" by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The kidney cancer association cannot be reasonably attributed to chance, bias, or confounding. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for non-Hodgkin lymphoma (NHL), but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer. In addition to the body of evidence pertaining to kidney cancer, NHL, and liver cancer, the available epidemiologic studies also provide more limited evidence of an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia. Differences between these sets of data and the data for kidney cancer, NHL, and liver cancer are observations from fewer numbers of studies, a mixed pattern of observed risk estimates, and the general absence of exposure-response data from the studies using a quantitative TCE-specific exposure measure.

There are several lines of supporting evidence for TCE carcinogenicity in humans. First, TCE induces multiple types of cancer in rodents given TCE by gavage and inhalation, including cancers in the same target tissues identified in the epidemiologic studies – kidney, liver, and lymphoid tissues. Second, toxicokinetic data indicate that TCE absorption, distribution, metabolism, and excretion are qualitatively similar in humans and rodents. Finally, there is sufficient weight of evidence to conclude that a mutagenic mode of action is operative for TCE-induced kidney tumors, and this mode of action is clearly relevant to humans. Modes of action have not been established for other TCE-induced cancers in rodents, and no mechanistic data indicate that any hypothesized key events are biologically precluded in humans.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.10 (PDF).

II.A.2. HUMAN CARCINOGENICITY DATA

The available epidemiologic studies provide convincing evidence of a causal association between TCE exposure and cancer. The strongest epidemiologic evidence consists of reported increased risks of kidney cancer, with more limited evidence for NHL and liver cancer, in several well-designed cohort and case-control studies (discussed below). The summary evaluation below of the evidence for causality is based on guidelines adapted from Hill (1965)

by U.S. EPA (2005b), and focuses on evidence related to kidney cancer, NHL, and liver cancer.

(a) Consistency of observed association. Elevated risks for kidney cancer have been observed across many independent studies. Twenty-four studies in which there was a high likelihood of TCE exposure in individual study subjects (e.g., based on job-exposure matrices or biomarker monitoring) and which were judged to have met, to a sufficient degree, the standards of epidemiologic design and analysis were identified in a systematic review of the epidemiologic literature. Of the 15 of these 24 studies reporting risks of kidney cancer (Moore et al., 2010; Radican et al., 2008; Charbotel et al., 2006; Zhao et al., 2005; Brüning et al., 2003; Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Pesch et al., 2000; Boice et al., 1999; Dosemeci et al., 1999; Morgan et al., 1998; Anttila et al., 1995; Axelson et al., 1994; Greenland et al., 1994; Siemiatycki, 1991), most estimated relative risks (RRs) between 1.1 and 1.9 for overall exposure to TCE (U.S. EPA, 2011, Sections 4.1 and 4.4.2). Six of these 15 studies reported statistically significant increased risks either for overall exposure to TCE (Moore et al., 2010; Brüning et al., 2003; Raaschou-Nielsen et al., 2003; Dosemeci et al., 1999) or for one of the highest TCE exposure groups (Moore et al., 2010; Charbotel et al., 2006; Zhao et al., 2005; Raaschou-Nielsen et al., 2003). Thirteen other cohort, case-control, and geographic based studies were given less weight because of their lesser likelihood of TCE exposure and other study design limitations that would decrease statistical power and study sensitivity (U.S. EPA, 2011, Sections 4.1. and 4.4.2).

The consistency of the association between TCE exposure and kidney cancer is further supported by the results of the meta-analyses of the 15 cohort and case-control studies of sufficient quality and with high probability of TCE exposure to individual subjects. These analyses observed a statistically significant increased summary RR estimate for kidney cancer of 1.27 (95% confidence interval [CI]: 1.13, 1.43) for overall TCE exposure. The summary RR estimates were robust and did not change appreciably with the removal of any individual study or with the use of alternate RR estimates from individual studies. In addition, there was no evidence for heterogeneity or publication bias.

The consistency of increased kidney cancer RR estimates across a large number of independent studies of different designs and populations from different countries and industries argues against chance, bias, or confounding as the basis for observed associations. This consistency thus provides substantial support for a causal effect between kidney cancer and TCE exposure.

Some evidence of consistency is found between TCE exposure and NHL and liver cancer. In a weight-of-evidence review of the NHL studies, 17 studies in which there was a high likelihood of TCE exposure in individual study subjects (e.g., based on job-exposure matrices

or biomarker monitoring) and which met, to a sufficient degree, the standards of epidemiologic design and analysis were identified. These studies generally reported excess RR estimates for NHL between 0.8 and 3.1 for overall TCE exposure (U.S. EPA (2011),Sections 4.1 and 4.6.1.2). Statistically significant elevated RR estimates for overall exposure were observed in two cohort studies (Raaschou-Nielsen et al., 2003; Hansen et al., 2001) and one case-control study (Hardell et al., 1994). The other 14 identified studies reported elevated RR estimates with overall TCE exposure that were not statistically significant (Purdue et al., 2011; Cocco et al., 2010; Wang et al., 2009; Radican et al., 2008; Miligi et al., 2006; Zhao et al., 2005; Boice et al., 1999; Persson and Fredrikson, 1999; Morgan et al., 1998; Nordström et al., 1998; Anttila et al., 1995; Axelson et al., 1994; Greenland et al., 1994; Siemiatycki, 1991). Fifteen additional studies were given less weight because of their lesser likelihood of TCE exposure and other design limitations that would decrease study power and sensitivity (U.S. EPA (2011), Sections 4.1 and 4.6.1.2). The observed lack of association with NHL in these studies likely reflects study design and exposure assessment limitations and is not considered inconsistent with the overall evidence on TCE and NHL.

Consistency of the association between TCE exposure and NHL is further supported by the results of meta-analyses. These meta-analyses found a statistically significant increased summary RR estimate for NHL of 1.23 (95% CI: 1.07, 1.42) for overall TCE exposure. This result and its statistical significance were not overly influenced by most individual studies. Some heterogeneity was observed across the 17 studies of overall exposure, although it was not statistically significant ($p = 0.16$). Analyzing the cohort and case-control studies separately resolved most of the heterogeneity, but the result for the summary case-control studies was only about a 7% increased RR estimate and was not statistically significant. The sources of heterogeneity are uncertain but may be the result of some bias associated with exposure assessment and/or disease classification, or from differences between cohort and case-control studies in average TCE exposure. In addition, there is some evidence of potential publication bias in this data set; however, it is uncertain that this is actually publication bias rather than an association between standard error and effect size resulting for some other reason (e.g., a difference in study populations or protocols in the smaller studies). Furthermore, if there is publication bias in this data set, it does not appear to account completely for the finding of an increased NHL risk.

There are fewer studies on liver cancer than for kidney cancer and NHL. Of nine studies, all of them cohort studies, in which there was a high likelihood of TCE exposure in individual study subjects (e.g., based on job-exposure matrices or biomarker monitoring) and which met, to a sufficient degree, the standards of epidemiologic design and analysis in a systematic review (Radican et al., 2008; Boice et al., 2006; Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Boice et al., 1999; Morgan et al., 1998; Anttila et al., 1995; Axelson et al., 1994;

Greenland et al., 1994), most reported RR estimates for liver and gallbladder cancer between 0.5 and 2.0 for overall exposure to TCE (U.S. EPA (2011), Sections 4.1 and 4.5.2). Relative risk estimates were generally based on small numbers of cases or deaths, with the result of wide CIs on the estimates, except for one study (Raaschou-Nielsen et al., 2003). This study reported almost 6 times more cancer cases than the next largest study and observed a statistically significant elevated liver and gallbladder cancer risk with overall TCE exposure (RR = 1.35 [95% CI: 1.03, 1.77]). Ten additional studies were given less weight because of their lesser likelihood of TCE exposure and other design limitations that would decrease statistical power and study sensitivity (U.S. EPA (2011), Sections 4.1 and 4.5.2).

Consistency of the association between TCE exposure and liver cancer is further supported by the results of meta-analyses. These meta-analyses found a statistically significant increased summary RR estimate for liver and biliary tract cancer of 1.29 (95% CI: 1.07, 1. 56) with overall TCE exposure. Although there was no evidence of heterogeneity or publication bias and the summary estimate was fairly insensitive to the use of alternative RR estimates, the statistical significance of the summary estimate depends heavily on the one large study by Raaschou-Nielsen et al. (2003). However, there were fewer adequate studies available for meta-analysis of liver cancer (9 versus 17 for NHL and 15 for kidney), leading to lower statistical power, even with pooling. Moreover, liver cancer is comparatively rarer, with age-adjusted incidences roughly half or less those for kidney cancer or NHL; thus, fewer liver cancer cases are generally observed in individual cohort studies.

(b) Strength of the observed association. In general, the observed associations between TCE exposure and cancer are modest, with RRs or odds ratios (ORs) for overall TCE exposure generally <2.0 and higher RRs or ORs for high exposure categories. Among the highest statistically significant RRs were those reported for kidney cancer in the studies by Henschler et al. (1995) (7.97 [95% CI: 2.59, 8.59]) and Vamvakas et al. (1998) (10.80 [95% CI: 3.36, 34.75]). As discussed in U.S. EPA (2011), Section 4.5.3, risk magnitude in both studies is highly uncertain due, in part, to possible selection biases, and neither was included in the meta-analyses. However, the findings of these studies were corroborated, though with lower reported RRs, by later studies, which overcame many of their deficiencies, such as Brüning et al. (2003) (2.47 [95% CI: 1.36, 4.49]), Charbotel et al. (2006) (2.16 [95% CI: 1.02, 4.60] for the high cumulative exposure group), and Moore et al. (2010) (2.05 [95% CI: 1.13, 3.73] for high confidence assessment of TCE). In addition, the very high apparent exposure in the subjects of Henschler et al. (1995) and Vamvakas et al. (1998) may have contributed to their reported RRs being higher than those in other studies. Exposures in most population case-control studies are of lower overall TCE intensity compared to exposures in Brüning et al. (2003) and Charbotel et al. (2006), and, as would be expected, observed RR estimates are lower: 1.24 (95% CI: 1.03, 1.49) (Pesch et al., 2000) and 1.30 (95% CI: 0.9, 1.9) (Dosemeci et al., 1999). A few high-quality cohort and case-control studies reported statistically significant

RRs of approximately 2.0 with highest exposure, including Zhao et al. (2005) (4.9 [95% CI: 1.23, 19.6] for high TCE score), Raaschou-Nielsen et al. (2003) (1.7 [95% CI: 1.1, 2.4] for ≥5-year exposure duration, subcohort with higher exposure]), Charbotel et al. (2006) (2.16 [95% CI: 1.02, 4.60] for high cumulative exposure and 2.73 [95% CI: 1.06, 7.07] for high cumulative exposure plus peaks) and Moore et al. (2010) (2.23 [95% CI: 1.07, 4.64] for high cumulative exposure and 2.41 [95% CI: 1.05, 5.56] for high average intensity TCE exposure).

Among the highest statistically significant RRs reported for NHL were those of Hansen et al. (2001) (3.1 [95% CI: 1.3, 6.1]) and Hardell et al. (1994) (7.2 [95% CI: 1.3, 42]), the latter a case-control study whose magnitude of risk is uncertain because of self-reported occupational TCE exposure. A similar magnitude of risk was reported in Purdue et al. (2011) for highest exposure (3.3 [95% CI: 1.1, 10.1], >234,000 ppm-hour, and 7.9 [95% CI: 1.8, 34.3], >360 ppm-hour/week). Observed RR estimates for liver cancer and overall TCE exposure are generally more modest.

The strength of association between TCE exposure and cancer is modest with overall TCE exposure. Large RR estimates are considered strong evidence of causality; however, a modest risk does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level (U.S. EPA, 2005b). Modest RR estimates have been observed with several well-established human carcinogens such as benzene and secondhand smoke. Chance cannot explain the observed association between TCE and cancer; statistically significant associations were found in a number of the studies that contribute greater weight to the overall evidence, given their design and statistical analysis approaches. In addition, other known or suspected risk factors cannot fully explain the observed elevations in kidney cancer RRs. All kidney cancer case-control studies except Moore et al. (2010), discussed below, included adjustment for possible confounding effects of smoking, and some studies included body mass index (BMI), hypertension, and co-exposure to other occupational agents such as cutting or petroleum oils. Cutting and petroleum oils, known as metalworking fluids, have not been associated with kidney cancer (Mirer, 2010; NIOSH, 1998), and potential confounding by this occupational co-exposure is unable to explain the observed association with TCE. Additionally, the associations between kidney cancer and TCE exposure remained in these studies after statistical adjustment for possible known and suspected confounders. Charbotel et al. (2005) observed a nonstatistically significantly kidney cancer risk with exposure to TCE adjusted for cutting or petroleum oil exposures (1.96 [95% CI: 71, 5.37] for the high-cumulative exposure group and 2.63 [95% CI: 0.79, 8,83] for high-exposure group with peaks).

All kidney cancer case-control studies adjusted for smoking except the Moore et al. (2010) study. However, Moore et al. (2010) reported that smoking did not significantly change the overall association with TCE exposure. Although direct examination of smoking and other

suspected kidney cancer risk factors is usually not possible in cohort studies, confounding is less likely in Zhao et al. (2005), given their use of an internal referent group and adjustment for socioeconomic status, an indirect surrogate for smoking, and other occupational exposures. In addition, the magnitude of the lung cancer risk in Raaschou-Nielsen et al. (2003) suggests that a high smoking rate is unlikely and cannot explain their finding on kidney cancer. Last, a meta-analysis of the nine cohort studies that reported kidney cancer risks found a summary RR estimate for lung cancer of 0.96 (95% CI: 0.76, 1.21) for overall TCE exposure and 0.96 (95% CI: 0.72, 1.27) for the highest exposure group. These observations suggest that confounding by smoking is not an alternative explanation for the kidney cancer meta-analysis results.

Few risk factors are recognized for NHL, with the exception of viruses and suspected factors such as immunosuppression or smoking, which are associated with specific NHL subtypes. Associations between NHL and TCE exposure are based on groupings of several NHL subtypes. Three of the seven NHL case-control studies adjusted for age, sex, and smoking in statistical analyses (Wang et al., 2009; Miligi et al., 2006), two others adjusted for age, sex, and education (Purdue et al., 2011; Cocco et al., 2010), and the other three case-control studies adjusted for age only or age and sex (Persson and Fredrikson, 1999; Nordström et al., 1998; Hardell et al., 1994). Like for kidney cancer, direct examination of possible confounding in cohort studies is not possible. The use of internal controls in some of the higher quality cohort studies is intended to reduce possible confounding related to lifestyle differences, including smoking habits, between exposed and referent subjects.

Heavy alcohol use and viral hepatitis are established risk factors for liver cancer, with severe obesity and diabetes characterized as a metabolic syndrome associated with liver cancer. Only cohort studies for liver cancer are available, and they were not able to consider these possible risk factors.

(c) Specificity of the observed association. Specificity is generally not as relevant as other aspects for judging causality. As stated in the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b), based on our current understanding that many agents cause cancer at multiple sites and that cancers have multiple causes, the absence of specificity does not detract from evidence for a causal effect. Evidence for specificity could be provided by a biological marker in cancers that was specific to TCE exposure. There is some evidence suggesting that particular von Hippel-Lindau (VHL) mutations in kidney tumors may be caused by TCE, but uncertainties in these data preclude a definitive conclusion.

(d) Temporal relationship of the observed association. Each cohort study was evaluated for the adequacy of the follow-up period to account for the latency of cancer development. The studies with the greatest weight based on study design characteristics (e.g., those used in the

meta-analysis) all had adequate follow-up to assess associations between TCE exposure and cancer. Therefore, the findings of those studies are consistent with a temporal relationship.

(e) Biological gradient (exposure-response relationship). Exposure-response relationships are examined in the TCE epidemiologic studies only to a limited extent. Many studies examined only overall "exposed" versus "unexposed" groups and did not provide exposure information by level of exposure. Others do not have adequate exposure assessments to confidently distinguish between levels of exposure. For example, many studies used duration of employment as an exposure surrogate; however, this is a poor exposure metric given subjects may have differing exposure intensity with similar exposure duration (NRC, 2006).

Three studies of kidney cancer reported a statistically significant trend of increasing risk with increasing TCE exposure, Zhao et al. (2005) (p = 0.023 for trend with TCE score), Charbotel et al. (2006) (p = 0.04 for trend with cumulative TCE exposure), and Moore et al. (2010) (p = 0.02 for trend with cumulative TCE exposure). Charbotel et al. (2006) was specifically designed to examine TCE exposure and had a high-quality exposure assessment, and the Moore et al. (2010) exposure assessment considered detailed information on jobs using solvents. Zhao et al. (2005) also had a relatively well-designed exposure assessment. A positive trend was also observed in one other study (Raaschou-Nielsen et al., 2003) with employment duration).

Biological gradient is further supported by meta-analyses for kidney cancer using only the highest exposure groups and accounting for possible reporting bias, which yielded a higher summary RR estimate (1.58 [95% CI: 1.28, 1.96]) than for overall TCE exposure (1.27 [95% CI: 1.13, 1.43]). Although this analysis uses a subset of studies in the overall TCE exposure analysis, the finding of higher risk in the highest exposure groups, where such groups were available, is consistent with a trend of increased risk with increased exposure.

The NHL case-control study of Purdue et al. (2011) reported a statistically significant trend with TCE exposure (p = 0.02 for trend with average-weekly TCE exposure), and NHL risk in Boice et al. (1999) appeared to increase with increasing exposure duration (p = 0.20 for routine-intermittent exposed subjects). The borderline trend with TCE intensity in the case-control studies of Wang et al. (2009) (p = 0.06) and Purdue et al. (2011) (p = 0.08 for trend with cumulative TCE exposure) is consistent with their findings for average weekly TCE exposure. As with kidney cancer, further support was provided by meta-analyses using only the highest exposure groups, which yielded a higher summary RR estimate (1.43 [95% CI: 1.13, 1.82]) than for overall TCE exposure (1.23 [95% CI: 1.07, 1.42]). For liver cancer, the meta-analyses using only the highest exposure groups yielded a lower, and nonstatistically significant, summary estimate (1.28 [95% CI: 0.93, 1.77]) than for overall TCE exposure (1.29 [95% CI: 1.07, 1.56]). There were no case-control studies on liver cancer and TCE, and the

cohort studies generally had few liver cancer cases, making it more difficult to assess exposure-response relationships. The one large study (Raaschou-Nielsen et al., 2003) used only duration of employment, which is an inferior exposure metric.

(f) Biological plausibility. TCE metabolism is similar in humans, rats, and mice and results in reactive metabolites. TCE is metabolized in multiple organs and metabolites are systemically distributed. Several oxidative metabolites produced primarily in the liver, including chloral hydrate (CH), trichloroacetic acid (TCA), and dichloroacetic acid (DCA), are rodent hepatocarcinogens. Two other metabolites, DCVC and S-dichlorovinyl-L-glutathione (DCVG), which can be produced and cleared by the kidney, have shown genotoxic activity, suggesting the potential for carcinogenicity. Kidney cancer, NHL, and liver cancer have all been observed in rodent bioassays (see below). The laboratory animal data for liver and kidney cancer are the most robust and are corroborated in multiple studies, sexes, and strains, although each has only been reported in a single species and the incidences of kidney cancer are quite low. Lymphomas were only reported to be statistically significantly elevated in a single study in mice, but one additional mouse study reported elevated lymphoma incidence and one rat study reported elevated leukemia incidence. In addition, there is some evidence both in humans and laboratory animals for kidney, liver, and immune system noncancer toxicity from TCE exposure. Several hypothesized modes of action have been presented for the rodent cancer findings, and the available evidence does not preclude the relevance of the hypothesized modes of action to humans.

(g) Coherence. Coherence is defined as consistency with the known biology. As discussed under biological plausibility, the observance of kidney and liver cancer and NHL in humans is consistent with the biological processing and toxicity of TCE.

(h) Experimental evidence (from human populations). Few experimental data from human populations are available on the relationship between TCE exposure and cancer. The only study of a "natural experiment" (i.e., observations of a temporal change in cancer incidence in relation to a specific event) notes that childhood leukemia cases appeared to be more evenly distributed throughout Woburn, Massachusetts, after closure of the two wells contaminated with TCE and other organic solvents (MDPH, 1997).

(i) Analogy. Exposure to structurally related chlorinated solvents such as tetrachloroethylene and dichloromethane have also been associated with kidney, lymphoid, and liver tumors in humans, although the evidence for TCE is considered stronger.

Conclusion. In conclusion, based on the weight-of-evidence analysis for kidney cancer and in accordance with U.S. EPA guidelines, TCE is characterized as "carcinogenic to humans." This hazard descriptor is used when there is convincing epidemiologic evidence of

a causal association between human exposure and cancer. Convincing evidence is found in the consistency of the kidney cancer findings. The consistency of increased kidney cancer RR estimates across a large number of independent studies of different designs and populations from different countries and industries provides compelling evidence given the difficulty, a priori, in detecting effects in epidemiologic studies when the RRs are modest and the cancers are relatively rare, and, therefore, individual studies have limited statistical power. This strong consistency argues against chance, bias, and confounding as explanations for the elevated kidney cancer risks. In addition, statistically significant exposure-response trends are observed in high-quality studies. These studies were designed to examine kidney cancer in populations with high TCE exposure intensity. These studies addressed important potential confounders and biases, further supporting the observed associations with kidney cancer as causal. In a meta-analysis of the 15 studies that met the inclusion criteria, a statistically significant summary RR estimate was observed for overall TCE exposure (summary RR: 1.27 [95% CI: 1.13, 1.43]). The summary RR estimate was greater for the highest TCE exposure groups (summary RR: 1.58 [95% CI: 1.28, 1.96]; n = 13 studies). Meta-analyses investigating the influence of individual studies and the sensitivity of the results to alternate RR estimate selections found the summary RR estimates to be highly robust. Furthermore, there was no indication of publication bias or significant heterogeneity. It would require a substantial amount of negative data from informative studies (i.e., studies having a high likelihood of TCE exposure in individual study subjects and which meet, to a sufficient degree, the standards of epidemiologic design and analysis in a systematic review) to contradict this observed association.

The evidence is strong but less convincing for NHL, where issues of (nonstatistically significant) study heterogeneity, potential publication bias, and weaker exposure-response results contribute greater uncertainty. The evidence is more limited for liver cancer mainly because only cohort studies are available and most of these studies have small numbers of cases. In addition to the body of evidence described above pertaining to kidney cancer, NHL, and liver cancer, the available epidemiologic studies also provide suggestive evidence of an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia. Differences between these sets of data and the data for kidney cancer, NHL, and liver cancer are fewer studies, a mixed pattern of observed risk estimates, and the general absence of exposure-response data from the studies using a quantitative TCE-specific cumulative exposure measure.

II.A.3. ANIMAL CARCINOGENICITY DATA

Additional evidence of TCE carcinogenicity consists of increased incidences of cancers reported in multiple chronic bioassays in rats and mice. In total, this database identifies some

of the same target tissues of TCE carcinogenicity also seen in epidemiological studies, including the kidney, liver, and lymphoid tissues.

Of particular note is the site-concordant finding of TCE-induced kidney cancer in rats. In particular, low, but biologically and sometimes statistically significant, increases in the incidence of kidney tumors were observed in multiple strains of rats treated with TCE by either inhalation or corn oil gavage (NTP, 1990b, 1988; Maltoni et al., 1986). For instance, Maltoni et al. (1986) reported that although only 4/130 renal adenocarcinomas were noted in rats in the highest dose group, these tumors had never been observed in over 50,000 Sprague-Dawley rats (untreated, vehicle-treated, or treated with different chemicals) examined in previous experiments in the same laboratory In addition, the gavage study by NCI (1976) and two inhalation studies by Henschler et al. (1980), and Fukuda et al. (1983) each observed one renal adenoma or adenocarcinoma in some dose groups and none in controls. The largest (but still small) incidences were observed in treated male rats, only in the highest dose groups. However, given the small numbers, an effect in females cannot be ruled out. Several studies in rats were limited by excessive toxicity, accidental deaths, or deficiencies in reporting (NTP, 1990b, 1988; NCI, 1976). Individually, therefore, these studies provide only suggestive evidence of renal carcinogenicity. Overall, given the rarity of these types of tumors in the rat strains tested and the repeated similar results across experiments and strains, these studies taken together support the conclusion that TCE is a kidney carcinogen in rats, with males being more sensitive than females. No other tested laboratory species (i.e., mice and hamsters) have exhibited increased kidney tumors, although high incidences of kidney toxicity have been reported in mice (NTP, 1990b; Maltoni et al., 1986; NCI, 1976). The GSH-conjugation-derived metabolites suspected of mediating TCE-induced kidney carcinogenesis have not been tested in a standard 2-year bioassay, so their role cannot be confirmed definitively. However, it is clear that GSH conjugation of TCE occurs in humans and that the human kidney contains the appropriate enzymes for bioactivation of GSH conjugates. Therefore, the production of the active metabolites thought to be responsible for kidney tumor induction in rats likely occurs in humans.

Statistically significant increases in TCE-induced liver tumors have been reported in multiple inhalation and gavage studies with male Swiss mice and B6C3F$_1$ mice of both sexes (Bull et al., 2002; Anna et al., 1994; NTP, 1990b; Herren-Freund et al., 1987; Maltoni et al., 1986; NCI, 1976). On the other hand, in female Swiss mice, Fukuda et al. ((1983) (in CD-1 [ICR, Swiss-derived] mice) and Maltoni et al. (1986) both reported small, nonsignificant increases at the highest dose by inhalation. Henschler et al. (1984; 1980) reported no increases in either sex of Han:NMRI (also Swiss-derived) mice exposed by inhalation and ICR/HA (Swiss) mice exposed by gavage. However, the inhalation study (Henschler et al., 1980) had only 30 mice per dose group and the gavage study (Henschler et al., 1984) had dosing interrupted due to toxicity. Studies in rats (NTP, 1990b, 1988; Maltoni et al., 1986; Henschler et al., 1980; NCI,

1976) and hamsters (Henschler et al., 1980) did not report statistically significant increases in liver tumor induction with TCE treatment. However, several studies in rats were limited by excessive toxicity or accidental deaths (NTP, 1990b, 1988; NCI, 1976), and the study in hamsters only had 30 animals per dose group. These data are inadequate for concluding that TCE lacks hepatocarcinogenicity in rats and hamsters, but are indicative of a lower potency in these species. Moreover, it is notable that a few studies in rats reported low incidences (too few for statistical significance) of very rare biliary- or endothelial-derived tumors in the livers of some treated animals (Maltoni et al., 1986; Fukuda et al., 1983; Henschler et al., 1980). Further evidence for the hepatocarcinogenicity of TCE is derived from chronic bioassays of the TCE oxidative metabolites CH, TCA, and DCA in mice (e.g., DeAngelo et al., 2008; Leakey et al., 2003; George et al., 2000; DeAngelo et al., 1999; DeAngelo et al., 1996; Bull et al., 1990), all of which reported hepatocarcinogenicity. Very limited testing of these TCE metabolites has been done in rats, with a single experiment reported in both Richmond et al. (1995) and DeAngelo et al. (1996) finding statistically significant DCA-induced hepatocarcinogenicity. With respect to TCA, DeAngelo et al. (1997), often cited as demonstrating lack of hepatocarcinogenicity in rats, actually reported elevated adenoma multiplicity and carcinoma incidence from TCA treatment. However, statistically, the role of chance could not be confidently excluded because of the low number of animals per dose group (20–24 per treatment group at final sacrifice). Overall, TCE and its oxidative metabolites are clearly carcinogenic in mice, with males more sensitive than females and the $B6C3F_1$ strain appearing to be more sensitive than the Swiss strain. Such strain and sex differences are not unexpected, as they appear to parallel, qualitatively, differences in background tumor incidence. 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 these compounds in rats or hamsters. However, to the extent that there is hepatocarcinogenic potential in rats, TCE is clearly less potent in the strains tested in this species than in $B6C3F_1$ and Swiss mice.

Additionally, there is more limited evidence for TCE-induced lymphohematopoietic cancers in rats and mice, lung tumors in mice, and testicular tumors in rats. With respect to lymphomas, Henschler et al. (1980) reported statistically significant increases in lymphomas in female Han:NMRI mice treated via inhalation. While Henschler et al. (1980) suggested that these lymphomas were of viral origin specific to this strain, subsequent studies reported increased lymphomas in female $B6C3F_1$ mice treated via corn oil gavage (NTP, 1990b) and leukemias in male Sprague-Dawley and female August rats (NTP, 1988; Maltoni et al., 1986). However, these cancers had relatively modest increases in incidence with treatment, and were not reported to be increased in other studies. With respect to lung tumors, rodent bioassays have demonstrated a statistically significant increase in pulmonary tumors in mice following chronic inhalation exposure to TCE (Maltoni et al., 1988; Maltoni et al., 1986; Fukuda et al., 1983). Pulmonary tumors were not reported in other species tested (i.e., rats and hamsters)

(Maltoni et al., 1988; Maltoni et al., 1986; Fukuda et al., 1983; Henschler et al., 1980). Chronic oral exposure to TCE led to a nonstatistically significant increase in pulmonary tumors in mice but, again, not in rats or hamsters (NTP, 1990b, 1988; Maltoni et al., 1986; Henschler et al., 1984; Van Duuren et al., 1979; NCI, 1976). A lower response via oral exposure would be consistent with a role of respiratory metabolism in pulmonary carcinogenicity. Finally, increased testicular (interstitial cell and Leydig cell) tumors have been observed in rats exposed by inhalation and gavage (NTP, 1990a, 1988; Maltoni et al., 1986). Statistically significant increases were reported in Sprague-Dawley rats exposed via inhalation (Maltoni et al., 1986) and Marshall rats exposed via gavage (NTP, 1988). In three rat strains, ACI, August, and F344/N, a high (>75%) control rate of testicular tumors was observed, limiting the ability to detect a treatment effect (NTP, 1990b, 1988).

In summary, there is clear evidence for TCE carcinogenicity in rats and mice, with multiple studies showing TCE to cause multiple kinds of cancers. The apparent lack of site concordance across laboratory animal species may be due to limitations in design or conduct in a number of rat bioassays and/or genuine interspecies differences in sensitivity. Nonetheless, these studies have shown carcinogenic effects across different strains, sexes, and routes of exposure, and site-concordance is not necessarily expected for carcinogens. Of greater import is the finding that there is support in experimental animal studies for the main cancers observed in TCE-exposed humans—in particular, cancers of the kidney, liver, and lymphoid tissues.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Additional evidence from toxicokinetic, toxicity, and mechanistic studies supports the biological plausibility of TCE carcinogenicity in humans.

Toxicokinetic data indicate that TCE is well absorbed by all routes of exposure, and that TCE absorption, distribution, metabolism, and excretion are qualitatively similar in humans and rodents. There is evidence that TCE is systemically available, distributes to organs and tissues, and undergoes systemic metabolism from all routes of exposure. Therefore, although the strongest evidence from epidemiologic studies largely involves inhalation exposures, the evidence supports TCE carcinogenicity being applicable to all routes of exposure. In addition, there is no evidence of major qualitative differences across species in TCE absorption, distribution, metabolism, and excretion. Extensive in vivo and in vitro data show that mice, rats, and humans all metabolize TCE via two primary pathways: oxidation by cytochrome P450s (CYPs) and conjugation with glutathione via glutathione-S-transferases (GSTs). Several metabolites and excretion products from both pathways have been detected in blood and urine from exposed humans as well as from at least one rodent species. In addition, the subsequent distribution, metabolism, and excretion of TCE metabolites are

qualitatively similar among species. Therefore, humans possess the metabolic pathways that produce the TCE metabolites thought to be involved in the induction of rat kidney and mouse liver tumors, and internal target tissues of both humans and rodents experience a similar mix of TCE and metabolites. (See U.S. EPA (2011), Sections 3.1–3.4 for additional discussion of TCE toxicokinetics.) Quantitative interspecies differences in toxicokinetics do exist, and are addressed through PBPK modeling (U.S. EPA (2011), Section 3.5 and Appendix A). Importantly, these quantitative differences affect only interspecies extrapolations of carcinogenic potency, and do not affect inferences as to the carcinogenic hazard for TCE.

Available mechanistic data do not suggest a lack of human carcinogenic hazard from TCE exposure. In particular, these data do not suggest qualitative differences between humans and test animals that would preclude any of the hypothesized key events in the carcinogenic mode of action in rodents from occurring in humans. For the kidney, the predominance of positive genotoxicity data in the database of available studies of TCE metabolites derived from GSH conjugation (in particular DCVC), together with toxicokinetic data consistent with their systemic delivery to, and in situ formation in, the kidney, supports the conclusion that a mutagenic mode of action is operative in TCE-induced kidney tumors. While supporting the biological plausibility of this hypothesized mode of action, available data on the VHL gene in humans or transgenic animals do not conclusively elucidate the role of VHL mutation in TCE-induced renal carcinogenesis. Cytotoxicity and compensatory cell proliferation, similarly presumed to be mediated through metabolites formed after GSH-conjugation of TCE, have also been suggested to play a role in the mode of action for renal carcinogenesis, as high incidences of nephrotoxicity have been observed in animals at doses that induce kidney tumors. Human studies have reported markers for nephrotoxicity at current occupational exposures, although data are lacking at lower exposures. Nephrotoxicity is observed in both mice and rats, in some cases with nearly 100% incidence in all dose groups, but kidney tumors are only observed at low incidences in rats at the highest tested doses. Therefore, nephrotoxicity alone appears to be insufficient, or at least not rate-limiting, for rodent renal carcinogenesis, since maximal levels of toxicity are reached before the onset of tumors. In addition, nephrotoxicity has not been shown to be necessary for kidney tumor induction by TCE in rodents. In particular, there is a lack of experimental support for causal links, such as compensatory cellular proliferation or clonal expansion of initiated cells, between nephrotoxicity and kidney tumors induced by TCE. Furthermore, it is not clear if nephrotoxicity is one of several key events in a mode of action, if it is a marker for an "upstream" key event (such as oxidative stress) that may contribute independently to both nephrotoxicity and renal carcinogenesis, or if it is incidental to kidney tumor induction. Therefore, although the data are consistent with the hypothesis that cytotoxicity and regenerative proliferation contribute to TCE-induced kidney tumors, the weight of evidence is not as strong as the support for a mutagenic mode of action. Moreover, while

toxicokinetic differences in the GSH conjugation pathway along with their uncertainty are addressed through PBPK modeling, no data suggest that any of the proposed key events for TCE-induced kidney tumors in rats are precluded in humans. (See U.S. EPA (2011), Section 4.4.7 for additional discussion of the mode of action for TCE-induced kidney tumors.) Therefore, TCE-induced rat kidney tumors provide additional support for the convincing human evidence of TCE-induced kidney cancer, with mechanistic data supportive of a mutagenic mode of action.

With respect to other cancers, data are insufficient to conclude that any of the other hypothesized modes of action are operant. In the liver, a mutagenic mode of action mediated by CH, which has evidence for genotoxic effects, or some other oxidative metabolite of TCE cannot be ruled out, but data are insufficient to conclude it is operant. A second mode-of-action hypothesis for TCE-induced liver tumors involves activation of the peroxisome proliferator activated receptor alpha (PPARα) receptor. Clearly, in vivo administration of TCE leads to activation of PPARα in rodents and likely does so in humans as well. However, the evidence as a whole does not support the view that PPARα is the sole operant mode of action mediating TCE hepatocarcinogenesis. Rather, there is evidential support for multiple TCE metabolites and multiple toxicity pathways contributing to TCE-induced liver tumors. Furthermore, recent experiments have demonstrated that PPARα activation and the sequence of key events in the hypothesized mode of action are not sufficient to induce hepatocarcinogenesis (Yang et al., 2007). Moreover, the demonstration that the PPARα agonist di(2-ethylhexyl) phthalate induces tumors in PPARα-null mice supports the view that the events comprising the hypothesized PPARα activation mode of action are not necessary for liver tumor induction in mice by this PPARα agonist (Ito et al., 2007). (See U.S. EPA (2011), Section 4.5.7 for additional discussion of the mode of action for TCE-induced liver tumors.) For mouse lung tumors, as with the liver, a mutagenic mode of action involving CH has also been hypothesized, but there are insufficient data to conclude that it is operant. A second mode-of-action hypothesis for mouse lung tumors has been posited involving other effects of oxidative metabolites including cytotoxicity and regenerative cell proliferation, but experimental support remains limited, with no data on proposed key events in experiments ≥2 weeks in duration. (See U.S. EPA (2011), Section 4.7.4 for additional discussion of the mode of action for TCE-induced lung tumors.) A mode of action subsequent to *in situ* oxidative metabolism, whether involving mutagenicity, cytotoxicity, or other key events, may also be relevant to other tissues where TCE would undergo CYP metabolism. For instance, CYP2E1, oxidative metabolites, and protein adducts have been reported in the testes of rats exposed to TCE, and, in some rat bioassays, TCE exposure increased the incidence of rat testicular tumors. However, inadequate data exist to adequately define a mode of action hypothesis for this tumor site (see U.S. EPA (2011), Section 4.8.2.3 for additional discussion of the mode of action for TCE-induced testicular tumors).

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. Oral Slope Factor –

The oral slope factor, calculated from adult exposure, is equivalent to the risk (as a fraction, i.e., 0.01 here) divided by the LED_{01}, the 95% lower bound on the exposure associated with an 1% extra cancer risk, and represents an upper bound risk estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to TCE's mutagenic mode of action for kidney tumors. A 1% extra risk level is used for the determination of the POD for low-exposure extrapolation because the exposure-response analysis is based on epidemiologic data, which normally demonstrate lower cancer response rates than rodent bioassays; an LED_{10} is not calculated because it would involve an upward extrapolation for these data.

> Adult-based oral slope factor - 4.6×10^{-2} per mg/kg/day (rounded to one significant figure = 5×10^{-2} per mg/kg/day)
>
> Adult-based LED_{01}, lower 95% bound on exposure at 1% extra risk – 0.21 mg/kg/day*
> Adult-based ED_{01}, central estimate of exposure at 1% extra risk – 0.46 mg/kg/day**
>
> The slope of the linear extrapolation from the central estimate ED_{01} is 0.01/(0.46 mg/kg/day) = 0.022 per mg/kg/day.
>
> The slope factor for TCE should not be used with exposures exceeding 10 mg/kg/day, because above this level, the route-to-route extrapolation relationship is no longer linear. Additionally, it is recommended that the application of ADAFs to (the kidney cancer component of) this slope factor be considered when assessing cancer risks to individuals exposed in early life (i.e., <16 years old), as discussed below (U.S. EPA (2011), Section 5.2.3.3.2).

*The oral slope factor estimate for TCE is actually calculated from route-to-route extrapolation of the inhalation unit risk estimate for kidney cancer with a factor of 5 applied to include NHL and liver cancer risks (Section II.B.1.3, below; U.S. EPA (2011), Section 5.2.2.3). The LED_{01} can be back-calculated, in abbreviated form, as follows: total cancer LED_{01} = kidney cancer LEC_{01} in ppm / 1.70 ppm/(mg/kg/day) / 5 = 1.82 ppm / 1.70 ppm/(mg/kg/day) / 5 = 0.21 mg/kg/day.

** The ED_{01} can be back-calculated as in the above footnote but using the kidney cancer EC_{01} in place of the LEC_{01}; thus, ED_{01} = 3.87 ppm / 1.70 ppm/(mg/kg/day) / 5 = 0.46 mg/kg/day.

EPA has concluded, by a weight-of-evidence evaluation, that TCE is carcinogenic by a mutagenic mode of action for induction of kidney tumors. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (*Supplemental Guidance*) (U.S. EPA, 2005a), those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for TCE are not sufficient to develop separate risk estimates for childhood exposure. The oral slope factor of 4.6×10^{-2} per mg/kg/day, calculated from data from adult exposure, does not reflect presumed increased early-life susceptibility to kidney tumors for this chemical. Generally, the application of ADAFs is recommended when assessing cancer risks for a carcinogen with a mutagenic mode of action. However, as illustrated in the detailed example calculation for oral drinking water exposures to TCE in Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011) (see related Excel spreadsheet), because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2–<16 years, and 1 for ≥16 years (U.S. EPA, 2005a). The 10- and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating kidney cancer risks from early life (<16 years age) exposure to TCE. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for TCE, age-specific values for cancer potency for kidney tumors are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, including adjusted kidney cancer potency values and unadjusted potency values for liver cancer and NHL, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance* and Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene*). A full lifetime oral potency value is not presented here because it is dependent on age-specific drinking water consumption rates; see the example calculation in 5.2.3.3.2 (U.S. EPA, 2011) and related Excel spreadsheet for the derivation of a lifetime potency estimate based on some standard assumptions about drinking water consumption.

II.B.1.2. Drinking Water Concentrations at Specified Risk Levels

Since TCE is carcinogenic by a mutagenic mode of action for kidney tumors and increased susceptibility to kidney tumors is assumed for early-life exposures (<16 years of age), the unit risk and concentrations at specified risk levels will change based on the age of the individuals in the exposed group. A detailed example application of ADAFs for oral drinking water exposures is provided in Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011) and related Excel spreadsheet. The results of that example for a lifetime exposure (ages 0-70) are as follows:

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	50 µg/L
E-5 (1 in 100,000)	5 µg/L
E-6 (1 in 1,000,000)	0.5 µg/L

* Assumes exposure from age 0-70 years with age-specific 90th percentile water consumption rates, rounded to one significant figure (for details, see Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene*(U.S. EPA, 2011) and related Excel spreadsheet.

However, as a general matter, risk assessors should use the oral slope factor and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.B.1.3. Modeling Approach and Extrapolation Method

The oral slope factor for TCE cancer risk, without consideration of increased early-life susceptibility due to TCE's mutagenic mode of action for kidney tumors, is derived from route-to-route extrapolation of the inhalation unit risk for TCE, using a PBPK model. As discussed in more detail below (Sections II.C.2 and II.C.3), the inhalation unit risk for TCE is based on three separate target tissue sites—kidney, lymphoid tissue, and liver. A linear low-dose extrapolation approach was used to estimate human carcinogenic risk from TCE exposure for kidney cancer due to the mutagenic mode of carcinogenic action. In the absence of a mode of action for the lymphoid and liver cancers associated with exposure to TCE, a

linear low-dose extrapolation approach was used to estimate human carcinogenic risk for these target sites. Because different internal dose metrics are preferred for each target tissue site, a separate route-to-route extrapolation was performed for each site-specific unit risk estimate, as shown in the Table below. The approach taken is to apply the human PBPK model in the low-dose range, where external and internal doses are linearly related, to derive a conversion that is the ratio of internal dose per mg/kg/day to internal dose per ppm. The expected value of the population mean for this conversion factor (in ppm per mg/kg/day) was used to extrapolate each inhalation unit risk in units of risk per ppm to an oral slope factor in units of risk per mg/kg/day.

Route-to-route extrapolation of site-specific inhalation unit risks to oral slope factors

	Kidney	NHL	Liver
Inhalation unit risk (risk per ppm)	5.49×10^{-3}	1.10×10^{-2}	5.49×10^{-3}
Dose-metric	ABioactDCVCBW34	TotMetabBW34	AMetLiv1BW34
ppm per mg/kg/day	1.70	1.97	2.82
Oral slope factor (risk per mg/kg/day)	9.33×10^{-3}	2.16×10^{-2}	1.55×10^{-2}

When one sums the oral slope factor estimates for the three individual cancer types, the resulting total cancer oral slope factor estimate is 4.64×10^{-2} per mg/kg/day. In the case of the oral route extrapolated results, the ratio of the risk estimate for the three cancer types combined to the risk estimate for kidney cancer alone is 5. This value differs from the factor of 4 used for the total cancer inhalation unit risk estimate (see II.C.2, below) because of differences in the relative values of the dose-metrics used for the different cancer types when the route-to-route extrapolation is performed.

II.B.2. DOSE-RESPONSE DATA

See Section II.C.2, below.

II.B.3. ADDITIONAL COMMENTS

As discussed above, the weight of evidence supports a mutagenic mode of action for TCE kidney carcinogenicity. Generally, in the absence of chemical-specific data to evaluate differences in susceptibility, increased early-life susceptibility is assumed for carcinogens with a mutagenic mode of action and application of the ADAFs to the adult-based unit risk estimate, in accordance with the *Supplemental Guidance* (U.S. EPA, 2005a), is recommended. However, as illustrated in the example calculation in Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011), because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases. Please consult the example in Section 5.2.3.3.2 (U.S. EPA, 2011) when applying the ADAFs for oral TCE exposures.

The adult-based oral slope factor estimate presented in II.B.1.1 (4.6×10^{-2} per mg/kg/day) is for total cancer incidence, reflecting the incidence risks for kidney cancer (renal cell carcinoma), NHL, and liver cancer. The adult-based oral slope factor estimates for the separate cancer types were 9×10^{-3} per mg/kg/day for renal cell carcinoma, 2×10^{-2} per mg/kg/day for NHL, and 2×10^{-2} per mg/kg/day for liver cancer.

II.B.4. DISCUSSION OF CONFIDENCE

The oral slope factor estimate is based on good-quality human data, thus avoiding uncertainties inherent in interspecies extrapolation. Uncertainties with respect to the inhalation unit risk, from which the oral slope factor was derived via route-to-route extrapolation, are discussed in Section II.C.4, below. In general, uncertainty in PBPK model-based route-to-route extrapolation is relatively low (Chiu, 2006; Chiu and White, 2006). In this particular case, extrapolation using different dose metrics yielded expected population mean risks within about a twofold range, and, for any particular dose metric, the 95% CI for the extrapolated population mean risks for each site spanned a range of no more than about threefold.

This oral slope factor estimate is further supported by estimates from multiple rodent bioassays, the most sensitive of which range from 3×10^{-2} to 3×10^{-1} per mg/kg/day. From the oral bioassays selected for analysis (**U.S. EPA, 2011**, Section 5.2.1.1), and using the preferred PBPK model-based dose metrics, the oral unit risk estimate for the most sensitive sex/species is 3×10^{-1} per mg/kg/day, based on kidney tumors in male Osborne-Mendel rats

(**NTP, 1988**). The oral unit risk estimate for testicular tumors in male Marshall rats (**NTP, 1988**) is somewhat lower at 7×10^{-2} per mg/kg/day. The next most sensitive sex/species result from the oral studies is for male mouse liver tumors (**NCI, 1976**), with an oral unit risk estimate of 3×10^{-2} per mg/kg/day. In addition, the 90% CIs for male Osborne-Mendel rat kidney tumors (**NTP, 1988**), male F344 rat kidney tumors (**NTP, 1990b**), and male Marshall rat testicular tumors (**NTP, 1988**), derived from the quantitative analysis of PBPK model uncertainty, all included the estimate based on human data of 5×10^{-2} per mg/kg/day, while the upper 95% confidence bound for male mouse liver tumors from NCI (**1976**) was slightly below this value at 4×10^{-2} per mg/kg/day. Furthermore, PBPK model-based route-to-route extrapolation of the most sensitive endpoint from the inhalation bioassays, male rat kidney tumors from Maltoni et al. (**1986**), leads to an oral unit risk estimate of 1×10^{-1} per mg/kg/day, with the preferred estimate based on human data falling within the route-to-route extrapolation of the 90% CI. Finally, for all of these estimates, the ratios of BMDs to the BMDLs did not exceed a value of 3, indicating that the uncertainties in the dose-response modeling for determining the POD in the observable range are small.

Therefore, although there are uncertainties in these various estimates [U.S. EPA (2011), Sections 5.2.1.4, 5.2.2.1.3, 5.2.2.2, and 5.2.2.3], confidence in the oral slope factor estimate of 5×10^{-2} per mg/kg/day, resulting from PBPK model-based route-to-route extrapolation of the inhalation unit risk estimate based on the human kidney cancer risks reported in Charbotel et al. (2006) and adjusted for potential risk for cancers at multiple sites (U.S. EPA, 2011), is further increased by the similarity of this estimate to estimates based on multiple rodent data sets.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

II.C.1.1. Inhalation Unit Risk –

The inhalation unit risk, calculated from adult exposure, is equivalent to the risk (as a fraction, i.e., 0.01 here) divided by the LEC_{01}, the 95% lower bound on the exposure associated with an 1% extra cancer risk, and represents an upper bound risk estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to TCE's mutagenic mode of action for kidney tumors. A 1% extra risk level is used for the determination of the POD for low-exposure extrapolation because the exposure-response analysis is based on epidemiologic data, which normally demonstrate lower cancer response rates than rodent

bioassays; an LEC_{10} is not calculated because it would involve an upward extrapolation for these data.

Adult-based unit risk estimate - 4.1×10^{-6} per $\mu g/m^3$ (rounded to one significant figure = 4×10^{-6} per $\mu g/m^3$)

Adult-based LEC_{01}, lower 95% bound on exposure at 1% extra risk – 2.4 mg/m^3 *
Adult-based EC_{01}, central estimate of exposure at 1% extra risk – 5.2 mg/m^3 **

The slope of the linear extrapolation from the central estimate EC_{01} is
$0.01 / (5.2\ mg/m^3) = 1.9 \times 10^{-6}$ per $\mu g/m^3$

Additionally, it is recommended that the application of ADAFs to (the kidney cancer component of) this unit risk estimate be considered when assessing cancer risks to individuals exposed in early life (i.e., <16 years old), as discussed below (U.S. EPA (2011), Section 5.2.3.3.1).

*The inhalation unit risk estimate for TCE is calculated from the inhalation unit risk estimate for kidney cancer with a factor of 4 applied to include NHL and liver cancer risks (Section II.C.2, below; U.S. EPA (2011), Section 5.2.2.2). The LEC_{01} can be back-calculated, in abbreviated form, as follows: total cancer LEC_{01} = kidney cancer LEC_{01}/ 4 = 1.82 ppm / 4 = 0.455 ppm × $(5.374\ mg/m^3)$/ppm = 2.4 mg/m^3.

**The EC_{01} can be back-calculated as in the above footnote but using the kidney cancer EC_{01} in place of the LEC_{01}; thus, EC_{01} = 3.87 ppm / 4 = 0.968 ppm × $(5.374\ mg/m^3)$/ppm = 5.2 mg/m^3.

EPA has concluded, by a weight–of-evidence evaluation, that TCE is carcinogenic by a mutagenic mode of action for induction of kidney tumors. According to the *Supplemental Guidance* (U.S. EPA, 2005a), those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for TCE are not sufficient to develop separate risk estimates for childhood exposure. The inhalation unit risk of 4.1×10^{-6} per $\mu g/m^3$, calculated from data from adult exposure, does not reflect presumed increased early-life susceptibility to kidney tumors for this chemical. Generally, the application of ADAFs is recommended when assessing cancer risks for carcinogens with a mutagenic mode of action. However, as illustrated in the detailed example calculation for inhalation exposures to TCE in Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011 and related Excel spreadsheet). because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater

complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2–<16 years, and 1 for ≥16 years (U.S. EPA, 2005a). The 10- and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating kidney cancer risks from early life (<16 years age) exposure to TCE. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for TCE, age-specific values for cancer potency for kidney tumors are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, including adjusted kidney cancer potency values and unadjusted potency values for liver cancer and NHL, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance* and Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene*). For *full lifetime* exposure to a constant exposure level, the ADAF-adjusted unit risk estimate for TCE is 4.8×10^{-6} per $\mu g/m^3$ (U.S. EPA (2011), Section 5.2.3.3.1 and related Excel spreadsheet).

II.C.1.2. Air Concentrations at Specified Risk Levels

Since TCE is carcinogenic by a mutagenic mode of action for kidney tumors and increased susceptibility to kidney tumors is assumed for early-life exposures (<16 years of age), the concentrations at specified risk levels will change based on the age of the individuals in the exposed group. A detailed example application of ADAFs for TCE inhalation exposures is provided in Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). The results of that example for a lifetime exposure (ages 0-70) are as follows:

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	20 $\mu g/m^3$
E-5 (1 in 100,000)	2 $\mu g/m^3$
E-6 (1 in 1,000,000)	0.2 $\mu g/m^3$

*Assumes exposure from age 0-70 years, rounded to one significant figure (for details, see Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011) and related Excel spreadsheet).

However, as a general matter, risk assessors should use the unit risk estimate and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.C.1.3. Exposure-Response Model and Extrapolation Method

A weighted linear regression model was used to model the exposure-response data on kidney cancer (renal cell carcinoma) incidence to obtain a slope estimate (regression coefficient) for the RR of renal cell carcinoma versus cumulative exposure. The regression coefficient was used in a lifetable analysis to estimate the LEC_{01}, which was used as the POD for linear extrapolation to generate the unit risk estimate. Because there is evidence from human (and rodent) studies for increased risks of NHL and liver cancer, the inhalation unit risk estimate derived from human data for renal cell carcinoma incidence was adjusted to account for potential increased risk of those cancer types. To make this adjustment, a factor accounting for the relative contributions to the extra risk for cancer incidence from TCE exposure for these three cancer types combined versus the extra risk for renal cell carcinoma alone was estimated, and this factor was applied to the unit risk estimate for renal cell carcinoma to obtain a unit risk estimate for the three cancer types combined (i.e., lifetime extra risk for developing any of the three types of cancers). This factor was based on human surveillance data on the background risk of these cancers and human epidemiologic data on the RR of these cancers associated with TCE exposure.

A linear low-dose extrapolation approach was used to estimate human carcinogenic risk from TCE exposure for kidney cancer due to the mutagenic mode of carcinogenic action. In the absence of a mode of action for the lymphoid and liver cancers associated with exposure to TCE, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk for these target sites.

II.C.2. EXPOSURE-RESPONSE DATA

For the unit risk of kidney cancer (renal cell carcinoma): Conditional logistic regression results for renal cell carcinoma incidence, matching on sex and age, adjusted for tobacco smoking and BMI; data from the Charbotel et al. (2006) study in the Arve Valley of France (U.S. EPA (2011), Sections 4.4, 5.2.2.1.1, and Appendix B):

Cumulative exposure category	Mean cumulative exposure (ppm × years)	Adjusted OR (95% CI)
Nonexposed		1
Low	62.4	1.62 (0.75, 3.47)
Medium	253.2	1.15 (0.47, 2.77)
High	925.0	2.16 (1.02, 4.60)

OR = odds ratio

For adjustment of the inhalation unit risk for multiple cancer types: The relative contributions to the extra risk for cancer from TCE exposure for multiple cancer types (NHL and liver cancer in addition to renal cell carcinoma) was estimated based on two different data sets. The first calculation was based on the results of the meta-analysis of human epidemiologic data for the three cancer types (U.S. EPA (2011), Appendix C); the second calculation was based on the results of the Raaschou-Nielsen et al. (2003) study, the largest single human epidemiologic study by far with RR estimates for all three cancer types.

	RR	Ro	Rx	Extra risk	Ratio to kidney value
Calculation #1: using RR estimates from the meta-analyses					
Kidney (renal cell carcinoma)	1.27	0.0107	0.01359	0.002920	1
NHL	1.23	0.0202	0.02485	0.004742	1.62
Liver (and biliary) cancer	1.29	0.0066	0.008514	0.001927	0.66
			sum	0.009589	**3.28**
Kidney + NHL only			**sum**	0.007662	2.62

	RR	Ro	Rx	Extra risk	Ratio to kidney value
Calculation #2: using RR estimates from Raaschou-Nielsen et al. (2003)					
Kidney (renal cell carcinoma)	1.20	0.0107	0.01284	0.002163	1
NHL	1.24	0.0202	0.02505	0.004948	2.29
Liver (and biliary) cancer	1.35	0.0066	0.008910	0.002325	1.07
			sum	0.009436	**4.36**
Kidney + NHL only			**sum**	0.007111	3.29

Ro = lifetime risk in an unexposed population (from SEER statistics); Rx = lifetime risk in the exposed population = RR × Ro

Both of these calculations suggest that a factor of 4 (within 25% of either value; and equal to the arithmetic or geometric mean, rounded to 1 significant figure) is reasonable for adjusting the unit risk estimate based on renal cell carcinoma alone to include the combined risk of renal cell carcinoma, NHL, and liver cancer. This value differs from the factor of 5 used for the total cancer oral slope factor estimate (see II.B.1, above) because of differences in the relative values of the dose-metrics used for the different cancer types when the route-to-route extrapolation is performed.

II.C.3. ADDITIONAL COMMENTS

As discussed above, the weight of evidence supports a mutagenic mode of action for TCE kidney carcinogenicity. Generally, in the absence of chemical-specific data to evaluate differences in susceptibility, increased early-life susceptibility is assumed for carcinogens with a mutagenic mode of action and application of the ADAFs to the adult-based unit risk estimate, in accordance with the *Supplemental Guidance* (U.S. EPA, 2005a), is recommended. However, as illustrated in the example calculation in Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011), because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted,

given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases. Please consult the example in Section 5.2.3.3.1 (U.S. EPA, 2011) when applying the ADAFs for inhalation TCE exposures.

The adult-based unit risk estimate presented in II.C.1.1 (4.1×10^{-6} per $\mu g/m^3$) is for total cancer incidence, reflecting the incidence risks for kidney cancer (renal cell carcinoma), NHL, and liver cancer. The adult-based unit risk estimates for the separate cancer types were 1×10^{-6} per $\mu g/m^3$ for renal cell carcinoma, 2×10^{-6} per $\mu g/m^3$ for NHL, and 1×10^{-6} per $\mu g/m^3$ for liver cancer.

II.C.4. DISCUSSION OF CONFIDENCE

Some primary sources of uncertainty in the inhalation unit risk estimates are briefly discussed below. The two major sources of uncertainty in quantitative cancer risk estimates are generally interspecies extrapolation and high- to low-dose extrapolation. The unit risk estimate for renal cell carcinoma incidence derived from the Charbotel et al. (2006) results is not subject to interspecies uncertainty because it is based on human data. A major uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures. There was some evidence of a contribution to increased renal cell carcinoma risk from peak exposures; however, there remained an apparent dose-response relationship for renal cell carcinoma risk with increasing cumulative exposure without peaks, and the OR for exposure with peaks compared to exposure without peaks was not significantly elevated (Charbotel et al., 2006). Although the actual exposure-response relationship at low exposure levels is unknown, the conclusion that a mutagenic mode of action is operative for TCE-induced kidney tumors supports the linear low-dose extrapolation that was used (U.S. EPA, 2005b). The weight of evidence also supports involvement of a cytotoxicity and regenerative proliferation mode of action, although not with the extent of support as for a mutagenic mode of action (see II.A.4, above). Because any possible involvement of a cytotoxicity mode of action would be additional to mutagenicity, the dose-response relationship would nonetheless be expected to be linear at low doses. Therefore, the additional involvement of a cytotoxicity mode of action does not provide evidence against the use of linear extrapolation from the POD. In the absence of a mode of action for NHL and liver cancer associated with exposure to TCE, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk for these cancer types.

Another source of uncertainty in the cancer unit risk estimate is the dose-response model used to model the study data to estimate the POD. A weighted linear regression across the categorical ORs was used to obtain a slope estimate; use of a linear model in the observable

range of the data is often a good general approach for human data because epidemiological data are frequently too limited (i.e., imprecise) to clearly identify an alternate model (U.S. EPA, 2005b). The Charbotel et al. (2006) study is a relatively small case-control study, with only 86 renal cell carcinoma cases, 37 of which had TCE exposure; thus, the dose-response data upon which to specify a model are indeed limited. In accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment*, the lower bound on the EC_{01} is used as the POD; this acknowledges some of the uncertainty in estimating the POD from the available dose-response data. In this case, the statistical uncertainty associated with the EC_{01} is relatively small, as the ratio between the EC_{01} and the LEC_{01} for renal cell carcinoma incidence is about twofold.

An important source of uncertainty in the underlying Charbotel et al. (2006) study is the retrospective estimation of TCE exposures in the study subjects. This case-control study was conducted in the Arve Valley in France, a region with a high concentration of workshops devoted to screw cutting, which involves the use of TCE and other degreasing agents. Since the 1960s, occupational physicians of the region have collected a large quantity of well-documented measurements, including TCE air concentrations and urinary metabolite levels (Fevotte et al., 2006). The study investigators conducted a comprehensive exposure assessment to estimate cumulative TCE exposures for the individual study subjects, using a detailed occupational questionnaire with a customized task-exposure matrix for the screw-cutting workers and a more general occupational questionnaire for workers exposed to TCE in other industries (Fevotte et al., 2006). The exposure assessment even attempted to take dermal exposure from hand-dipping practices into account by equating it with an equivalent airborne concentration based on biological monitoring data. Despite the appreciable effort of the investigators, considerable uncertainty associated with any retrospective exposure assessment is inevitable, and some exposure misclassification is unavoidable. Such exposure misclassification was most likely for the 19 deceased cases and their matched controls, for which proxy respondents were used, and for exposures outside the screw-cutting industry (295 of 1,486 identified job periods involved TCE exposure; 120 of these were not in the screw-cutting industry).

Although the exposure estimates from Moore et al. (2010) were not considered to be as quantitatively accurate as those of Charbotel et al. (2006), as discussed in U.S. EPA (2011), Section 5.2.2, it is worth noting, in the context of uncertainty in the exposure assessment, that the exposure estimates in Moore et al. (2010) are substantially lower than those of Charbotel et al. (2006) for comparable OR estimates. For example, for all subjects and high-confidence assessments only, respectively, Moore et al. (2010) report OR estimates of 1.19 and 1.77 for cumulative exposures <1.58 ppm × years and 2.02 and 2.23 for cumulative exposures ≥1.58 ppm × years. Charbotel et al. (2006), on the other hand, reported OR estimates for all subjects of 1.62, 1.15, and 2.16 for mean cumulative exposures of 62.4, 253.2, and 925.0 ppm

× years, respectively. If the exposure estimates for Charbotel et al. (2006) are overestimated, as suggested by the exposure estimates from Moore et al. (2010), the slope of the linear regression model, and hence the unit risk estimate, would be correspondingly underestimated.

Another source of uncertainty in the Charbotel et al. (2006) study is the possible influence of potential confounding or modifying factors. This study population, with a high prevalence of metal-working, also had relatively high prevalences of exposure to petroleum oils, cadmium, petroleum solvents, welding fumes, and asbestos (Fevotte et al., 2006). Other exposures assessed included other solvents (including other chlorinated solvents), lead, and ionizing radiation. None of these exposures was found to be significantly associated with renal cell carcinoma at a $p = 0.05$ significance level. Cutting fluids and other petroleum oils were associated with renal cell carcinoma at a $p = 0.1$ significance level; however, further modeling suggested no association with renal cell carcinoma when other significant factors were taken into account (Charbotel et al., 2006). Moreover, a review of other studies suggested that potential confounding from cutting fluids and other petroleum oils is of minimal concern (U.S. EPA (2011), Section 4.4.2.3). Nonetheless, a sensitivity analysis was conducted using the OR estimates further adjusted for cutting fluids and other petroleum oils from the unpublished report by Charbotel et al. (2005), and an essentially identical unit risk estimate of 5.46×10^{-3} per ppm was obtained. In addition, the medical questionnaire included familial kidney disease and medical history, such as kidney stones, infection, chronic dialysis, hypertension, and use of anti-hypertensive drugs, diuretics, and analgesics. BMI was also calculated, and lifestyle information such as smoking habits and coffee consumption was collected. Univariate analyses found high levels of smoking and BMI to be associated with increased odds of renal cell carcinoma, and these two variables were included in the conditional logistic regressions. Thus, although impacts of other factors are possible, this study took great pains to attempt to account for potential confounding or modifying factors.

Some other sources of uncertainty associated with the epidemiological data are the dose metric and lag period. As discussed above, there was some evidence of a contribution to increased renal cell carcinoma risk from peak TCE exposures; however, there appeared to be an independent effect of cumulative exposure without peaks. Cumulative exposure is considered a good measure of total exposure because it integrates exposure (levels) over time. If there is a contributing effect of peak exposures, not already taken into account in the cumulative exposure metric, the linear slope may be overestimated to some extent. Sometimes cancer data are modeled with the inclusion of a lag period to discount more recent exposures not likely to have contributed to the onset of cancer. In an unpublished report, Charbotel et al. (2005) also present the results of a conditional logistic regression with a 10-year lag period, and these results are very similar to the unlagged results reported in their published paper, suggesting that the lag period might not be an important factor in this study.

Some additional sources of uncertainty are not so much inherent in the exposure-response modeling or in the epidemiologic data themselves but, rather, arise in the process of obtaining more general Agency risk estimates from the epidemiologic results. U.S. EPA cancer risk estimates are typically derived to represent an upper bound on increased risk of cancer incidence for all sites affected by an agent for the general population. From experimental animal studies, this is accomplished by using cancer incidence data and summing across all of the cancer sites that demonstrate significantly increased incidences, customarily for the most sensitive sex and species, to attempt to be protective of the general human population. However, in estimating comparable risks from the Charbotel et al. (2006) epidemiologic data, certain limitations are encountered. For one thing, these epidemiology data represent a geographically limited (Arve Valley, France) and likely not very diverse population of working adults. Thus, there is uncertainty about the applicability of the results to a more diverse general population. Additionally, the Charbotel et al. (2006) study was a study of renal cell carcinoma only, and so the risk estimate derived from it does not represent all the cancer sites that may be affected by TCE.

To attempt to account for the potential risk for other cancers associated with TCE exposure, in particular NHL and liver cancer, for which there were no exposure-response data available, an adjustment factor reflecting the relative potency of TCE across cancer sites was derived, using two different approaches. In both approaches, an underlying assumption in deriving the relative potencies is that the relative values of the age-specific background incidence risks for the person-years from the epidemiologic studies for each cancer type approximate the relative values of the lifetime background incidence risks for those cancer types. In other words, at least on a proportional basis, the lifetime background incidence risks (for the U.S. population) for each site approximate the age-specific background incidence risks for the study populations. A further assumption is that the lifetime risk of renal cell carcinoma up to 85 years is an adequate approximation to the full lifetime risk, which is what was used for the other two cancer types. The first calculation, based on the results of the meta-analyses for the three cancer types, has the advantage of being based on a large data set, incorporating data from many different studies. However, this calculation relies on a number of additional assumptions. First, it is assumed that the summary RR estimates from the meta-analyses, which are based on different groups of studies, reflect similar overall TCE exposures (i.e., that the overall TCE exposures are similar across the different groups of studies that went into the different meta-analyses for the three cancer types). Second, it is assumed that the summary RR estimates, which incorporate RR estimates for both mortality and incidence, represent good estimates for cancer incidence risk from TCE exposure. In addition, it is assumed that the summary RR for kidney cancer, for which renal cell carcinoma estimates from individual studies were used when available, is a good estimate for the overall RR for renal cell carcinoma and that the summary RR estimate for NHL, for which different studies used different classification schemes, is a good estimate for the overall RR for NHL. The second

calculation, based on the results of the Raaschou-Nielsen et al. (2003) study, the largest single study with RR estimates for all three cancer types, has the advantage of having RR estimates that are directly comparable. In addition, the Raaschou-Nielsen et al. (2003) study provided data for the precise cancer types of interest for the calculation (i.e., renal cell carcinoma, NHL, and liver [and biliary] cancer).

The fact that the calculations based on two different data sets yielded comparable values for the adjustment factor (both within 25% of the selected factor of 4) provides more robust support for the use of the factor of 4. Additional uncertainties pertain to the weight of evidence supporting the association of TCE exposure with increased risk of cancer for the three cancer types. As discussed above, it was found that the weight of evidence for kidney cancer was sufficient to classify TCE as "carcinogenic to humans." It was also concluded that there was strong evidence that TCE causes NHL as well, although the evidence for liver cancer was more limited. In addition, the rodent studies demonstrate clear evidence of multisite carcinogenicity, with cancer types including those for which associations with TCE exposure are observed in human studies, i.e., liver and kidney cancers and NHLs. Overall, the evidence was found to be sufficiently persuasive to support the use of the adjustment factor of 4 based on these three cancer types. Alternatively, if one were to use the factor based only on the two cancer types with the strongest human evidence (a factor of 3 for kidney cancer and NHL is suggested by the two calculations in the table above), the cancer inhalation unit risk estimate would be only slightly reduced (25%).

Finally, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The adjustment is made only for the kidney-cancer component of total cancer risk because that is the cancer type for which the weight of evidence was sufficient to conclude that TCE-induced carcinogenesis operates through a mutagenic mode of action. However, it may be that TCE operates through a mutagenic mode of action for other cancer types as well or that it operates through other modes of action that might also convey increased early-life susceptibility. Additionally, the ADAFs from the 2005 *Supplemental Guidance* are not specific to TCE, and it is uncertain to what extent they reflect increased early-life susceptibility to kidney cancer from exposure to TCE, if increased early-life susceptibility occurs.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA (2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix I, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

II.D.2. EPA Review

Agency Completion Date — 09/28/2011

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

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Substance Name —Trichloroethylene
CASRN — 79-01-6

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VII. Revision History

Substance Name —Trichloroethylene
CASRN — 79-01-6
File First On-Line 03/31/1987

Date	Section	Description
03/31/1987	II.	Cancer assessment added.
07/01/1989	II.	Cancer assessment withdrawn.
09/28/2011	I., II., VI.	RfD, RfC, and Cancer assessment added.

VIII. Synonyms

Substance Name —Trichloroethylene
CASRN — 79-01-6
Section VIII. Last Revised — 09/28/2011

- ACETYLENE TRICHLORIDE
- AI3-00052
- ALGYLEN
- ANAMENTH
- BENZINOL
- Caswell No 876
- CECOLENE
- CHLORILEN
- 1-CHLORO-2,2-DICHLOROETHYLENE
- Chlorylea, Chorylen, CirCosolv, Crawhaspol, Dow-Tri, Dukeron, Per-A-Clor, Triad, Trial, TRI-Plus M, Vitran
- DENSINFLUAT
- 1,1-Dichloro-2-chloroethylene
- Pesticide Code: 081202
- EPA Pesticide Chemical Code 081202
- ETHENE, TRICHLORO-
- ETHINYL TRICHLORIDE
- ETHYLENE TRICHLORIDE

- ETHYLENE, TRICHLORO-
- FLECK-FLIP
- FLOCK FLIP
- FLUATE
- GERMALGENE
- LANADIN
- LETHURIN
- NARCOGEN
- NARKOSOID
- NCI-C04546
- NIALK
- NSC 389
- PERM-A-CHLOR
- PETZINOL
- PHILEX
- THRETHYLEN
- THRETHYLENE
- TRETHYLENE
- TRI
- TRIASOL
- Trichloraethen (German)
- Trichloraethylen, tri (German)
- TRICHLORAN
- TRICHLOREN
- Trichlorethene (French)
- TRICHLORETHYLENE
- Trichlorethylene, tri (French)
- TRICHLOROETHENE
- 1,1,2-TRICHLOROETHYLENE
- TRICLENE
- Tricloretene (Italian)
- Tricloroetilene (Italian)
- Trielin
- Trielina (Italian)
- TRIKLONE
- TRILENE
- TRIMAR
- TRI-PLUS
- VESTROL

Appendix B

DEQ Division of Waste Management TCE Vapor Intrusion Guidance Documents

North Carolina Division of Waste Management
Supplemental Vapor Intrusion Guidance

Trichloroethylene (TCE) Indoor Air Inhalation Immediate Action Levels and Response

February 2, 2017

Introduction

In 2011, the U.S. Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) (http://www.epa.gov/iris) issued an update to the toxicological evaluation for trichloroethylene (also known as trichloroethene or "TCE"). In that update [TCE 2011], IRIS established revised toxicity values for oral and inhalation exposures to TCE. The current North Carolina Department of Environmental Quality (DEQ) Division of Waste Management (DWM) Preliminary Soil Remediation Goals (PSRG) and vapor intrusion screening levels reflect the revised IRIS values. In addition to the vapor intrusion screening levels, DWM has established additional indoor air inhalation exposure immediate action levels (Table 1) for TCE to protect sensitive populations (groups of people most likely to suffer adverse health effects) from short-term exposures that may result in long-term effects.

The TCE-sensitive population for short-term exposures is women of child-bearing age, defined as women of age 15–50 years, although site-specific consideration of the appropriate age range should be evaluated in concert with the exposed women and DWM. **When it is identified that TCE-sensitive populations may be exposed to concentrations greater than the DWM action levels found in Table 1, immediate steps are to be taken to eliminate the exposure or reduce the exposure concentration to less than the action level.**

Table 1. Division of Waste Management (DWM) Immediate Action Levels for Trichloroethylene (TCE) Inhalation Exposures

Exposure Scenario	TCE Action Level - Inhalation	Required Action by the State-Lead Contractor, Consultant or Remediation Party [1]
Residential	2.1 µg/m^3 (0.39 ppbv)	1. Notify DWM within 1 business day 2. Immediately provide fact sheets to potentially affected individuals and involve DWM 3. Initiate measures to reduce exposure below the action level immediately.
Non-residential	8.8 µg/m^3 (1.6 ppbv)	
TCE sensitive populations are defined as: Women of child-bearing age (15 to 50 years of age) [2]		

[1] The required action time frame begins when the remediating party, DWM State-Lead Program or Brownfields Program applicant's receives the validated laboratory data

[2] A site-specific evaluation of the appropriate age range for women of child-bearing age should be made in consultation with the exposed women and DWM

TCE = trichloroethylene (trichloroethene, CASN 79-01-6)

The USEPA IRIS toxicological review identifies as one of the non-cancer critical health effects for TCE as fetal cardiac malformations. Because cardiac development begins during the earliest stages of fetal development, at a time before a woman may realize she is pregnant, TCE exposure to women during their first trimester of pregnancy is of particular concern Permanent adverse effects to fetal cardiac development may occur as a result of short-term maternal exposures. The USEPA identifies that a single fetal exposure to a developmental toxicant may be sufficient to produce an adverse developmental effect (EPA 2014b). DWM's TCE short-term inhalation action levels are developed from the USEPA IRIS reference concentration (RfC) of 2.0 µg/m^3 [TCE 2011]. The DWM action levels found in Table 1 are equivalent to the USEPA TCE regional screening levels (RSLs) (https://www.epa.gov/risk/regional-screening-levels-rsls) for residential and "composite worker" (non-residential) exposure.

If TCE is a chemical currently in use in the building being investigated for vapor intrusion, the Occupational Safety and Health Administration (OSHA) standards govern the amount of chemical allowed in indoor air. The OSHA standard for TCE is higher than the EPA targets used for vapor intrusion, and while the DEQ environmental cleanup programs don't regulate the day-to-day operational emissions at a business, they do recommend that best management practices be used in the workplace setting to reduce operational TCE emissions to minimize potential health risks. In addition, for closure under risk-based rules which may require land-use restrictions, future exposure from TCE vapor intrusion may need to be evaluated to account for changes in use of the building or land use when OSHA standards no longer apply. For example, a property that is currently used for an active dry-cleaning business may be changed to residential or mixed use in the future when the dry-cleaning business is no longer in operation.

DWM recognizes that various EPA Regions and state/federal agencies have adopted a wide range of action levels regarding TCE in indoor air. At this time, DWM considers the USEPA TCE RfC published on IRIS to be health protective with respect to cardiac developmental effects. DMW's TCE action level response aligns with current recommendations from USEPA Region 4. DWM will continue to monitor recommendations from USEPA and other state/federal agencies and update this guidance to reflect relevant developments in the future.

Notification

State-Lead Programs:

When independent contractors working under DWM State-Lead programs receive analytical data indicating that women of child-bearing age may be exposed to TCE concentrations above the action level, they must notify the applicable DWM program they are working for within 1 business day of receipt of the data from the laboratory.

DWM Programs that are not State-Lead:

When remediating parties or Brownfields Program applicants and/or their environmental consultants receive analytical data indicating that women of child-bearing age may be exposed to TCE concentrations above the action level, the client (if applicable) and DWM must be contacted within 1 business day of receipt of the data from the laboratory. The client may notify DWM directly or instruct

the environmental consultant to do so. The environmental consultant should make clients aware of the reporting requirement.

Closed Sites:
DWM is currently evaluating and implementing plans to review and screen closed sites with known TCE contamination to identify ongoing exposures of concern, focused on the particular risks of TCE and the vapor intrusion pathway. Property owners and/or potentially responsible parties of previously closed TCE sites should not wait for DWM to make the initial contact. DWM encourages parties to review existing information about a site and begin to evaluate current conditions to determine if there is a potential for ongoing exposure to TCE. Parties should notify DWM if closed sites are discovered to have a potential for TCE. Updates on the progress of TCE closed sites review will be posted as they become available.

Sampling Considerations

DWM recommends time-integrated air sampling methods to account for temporal variability in vapor intrusion. Time-integrated samples provide a direct measurement of the average TCE concentration over a fixed period of time (e.g., 8 hours, 24 hours, 3 days, 7 days, etc.), which should be compared to the DWM action levels in Table 1. TCE concentrations are to be quantified using USEPA-approved volatile organic laboratory analytical methods. The time-integrated sampling periods should be chosen to enable identification of peak exposures that may exceed the applicable action level.

Response Actions

Since the exposure duration of concern for developmental effects is short, DWM will work with responding parties to identify appropriate mitigation options and begin implementation quickly for locations where women of child-bearing age are present. Women of child-bearing age should not be reintroduced to the contaminated area until laboratory data for two consecutive sampling events collected after temporary or permanent mitigation shows that TCE levels are below action levels.

Initial response actions that should be implemented immediately (typically within 24 hours) include:

- Risk communication with the potentially-at-risk population should be made by a toxicologist, health professional, human health risk assessor or qualified DWM personnel knowledgeable of the potential TCE health effects. A DWM risk assessor will be consulted by the DWM program with oversight. The DWM risk assessor can assist parties in providing health risk information to potentially affected individuals.
- Ensure appropriate fact sheets are provided to potentially affected individuals. (see links below).
- Vent the basement (if a basement exists in the building) or lowest level of the building by opening windows.
- Seal potential conduits where vapors may be entering the bottom floor of the building and any subsurface walls.
- Enclose and passively vent sumps.

Response actions that should be implemented <u>as soon as possible</u>, but which may require several days to two weeks to implement include:

- Adjust the building's pressurization (over-pressurize) by utilizing the HVAC system.
- Install carbon filtration on the HVAC system.
- Utilize portable air-purifying units in the building.

Response actions that should be implemented <u>as soon as possible</u>, but which may require several weeks to two months to design, install and test include:

- Installation of a sub-slab depressurization system.
- Installation of a soil vapor extraction system.
- Installation of new HVAC equipment to over-pressurize the building or bottom floor.

<u>Links to TCE factsheets including medical follow-up factsheets for primary care physicians:</u>

- DWM's *Frequently Asked Questions about Trichloroethylene (TCE) in Residential Indoor Air,* (insert web link)

- DWM's *Frequently Asked Questions about Trichloroethylene (TCE) in Workplace Indoor Air* (insert web link)

- NC DPH's *Trichloroethylene (TCE)* and *Trichloroethylene (TCE) Information of Health Professionals (*http://epi.publichealth.nc.gov/oee/az.html#tce

- ATSDR's *TCE ToxFAQs, TCE ToxGuide and Toxicological Profile for Trichloroethylene (TCE),* available at: **http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=30**

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Frequently Asked Questions about Trichloroethylene (TCE) in Residential Indoor Air

May 2016

Why am I receiving this notice?

You are receiving this information because trichloroethylene (also called trichloroethene or "TCE") has been measured in the air in your home at a level which exceeds the Division of Waste Management's (DWM) action level concentration. When an indoor air concentration greater than the action level is identified, DWM requires immediate action be taken to reduce or eliminate the exposure to TCE in indoor air to prevent short-term exposures that pose a potential health risk to persons that may be sensitive to the effects of TCE.

- A TCE concentration above 2.1 micrograms per cubic meter of air ($\mu g/m^3$) is the DWM action level for women exposed in their homes and who are or may be in the first trimester of pregnancy. The health concern with breathing TCE above the action level is to the developing fetus.
- When a woman who is or may be in the first trimester of a pregnancy may be exposed to TCE above the action level concentration, immediate steps should be taken to promptly reduce the risk to the developing fetus. Developmental effects will not necessarily occur at exposures above the action level, but they cannot be ruled out and steps to address the potential risk are required.

What is TCE? How might I be exposed?

TCE is a man-made, colorless liquid used mainly as a solvent to remove grease from metal parts. It has also been an ingredient in some consumer products such as glues and paint removers. When TCE is released to soil or groundwater as a result of spills or leaks at a facility, it can evaporate and enter into a building's indoor air through seams and cracks in building foundations. This process is called "vapor intrusion."

What is the safe level of TCE in a home?

The United States Environmental Protection Agency (US EPA) recommends an indoor air guideline for residential settings of 2.1 $\mu g/m^3$. At or below this level there are no indications of a significant risk of adverse health effects.

What are the possible health effects from indoor air TCE exposure?

The possible health effects from breathing TCE depends on the concentration in indoor air, the length of the exposure, and whether and when a pregnant woman is exposed. Women who are in the first trimester of pregnancy are most sensitive to TCE exposures. This exposure period is of special concern because a woman may not yet know that she is pregnant. TCE exposures may increase the risk of heart malformations in the developing fetus. Breathing TCE over a long period of time may affect the immune system and increase susceptibility to infections. Long-term exposures may increase an individual's risk of cancers of the kidney, liver and non-Hodgkin's lymphoma.

What should I know about TCE if I might be pregnant?

Because TCE exposure during the first trimester of pregnancy could affect fetal heart development, pregnant women are of special concern. Where residential indoor air TCE concentrations exceed 2.1 µg/m3, DWM requires immediate notification of all women that may be exposed and that are of "child-bearing age" and immediate action to reduce or eliminate the exposure concentrations to below these levels. .

For exposures during the first trimester of pregnancy, DWM recommends the following protective measures:

- At TCE levels above the 2.1 $\mu g/m^3$ action level, women who may be in the first trimester of pregnancy and are concerned about their risk should consult with their physician and/or an occupational doctor familiar with chemical exposures. Depending on their specific exposure situation, they may want to

limit exposure while efforts to reduce the concentration of TCE are underway, for example by avoiding areas with TCE concentrations higher than the 2.1 µg/m^3 if possible, or by improving ventilation. TCE exposure concentrations above the action level may present a lower risk to the pregnant woman, but levels above this range must ultimately be reduced to meet US EPA and DWM's indoor air guideline in situations where women of child-bearing age may be exposed.

For exposures before or after the first trimester of pregnancy:

Exposures that end two to four weeks or more before a pregnancy are not indicated to contribute to an elevated level of risk since most TCE is eliminated from the body within that period.

What measures might be taken to reduce indoor air TCE levels??

Parties responsible for the contamination should are required to contract environmental professionals to quickly take steps to reduce the indoor air levels. The first mitigation steps usually include sealing sumps and foundation cracks and increasing ventilation. Portable carbon filtration systems and changes to the heating and ventilation system to increase the proportion of clean air into the home may also help to temporarily reduce concentrations while more permanent measures are being designed and implemented. Installing a sub-slab depressurization (SSD) system can be an effective measure in the longer term. An SSD system, which is similar to a radon abatement system, is a series of pipes under the basement with a fan that vents vapors to the outdoors. Groundwater treatment or soil vapor extraction may also be employed to reduce the source of TCE contamination.

What should I do if I'm concerned that my health has been affected?

If you have concerns about your health status, you should talk to your family doctor and/or an occupational doctor familiar with chemical exposures. When you meet with them, provide a copy of your TCE sampling results and the N.C. Division of Public Health's factsheet, *Trichloroethylene (TCE) Information for Health Professionals*, available at http://epi.publichealth.nc.gov/oee/az.html#tce

Where can my physician and I get more information about potential TCE health effects?

More information on TCE health effects and the basis of DWM's action levels can be found on DWM's website at http://epi.publichealth.nc.gov/oee/az.html#tce and the Agency for Toxic Substances and Disease Registry's (ATSDR) website at http://www.atsdr.cdc.gov/. Your physician may also contact the N.C. Division of Public Health's Occupational and Environmental Epidemiology Branch in Raleigh to speak with physicians familiar with chemical exposures (telephone 919-707-5900).

Where can I get more information about TCE contamination and cleanup?

More information DWM's guidance for sites with TCE contamination can be found at (http://epi.publichealth.nc.gov/oee/az.html#tce)

More information on the health effects associated with TCE exposures is available on the Agency for Toxic Substances and Disease Registry's (ATSDR) website at http://www.atsdr.cdc.gov/.

Adapted from Massachusetts Department of Environmental Protection's 'Important Information on Trichloroehylene (TCE) in Residential Indoor Air'.

Frequently Asked Questions about Trichloroethylene (TCE) in Workplace Indoor Air

May 2016

The purpose of this fact sheet is to provide information on trichloroethylene (also known as "TCE" or trichloroethene) workplace exposures due to hazardous waste sites as the source of contamination and worker exposure through breathing contaminated air in the workplace. This information applies to workplaces that do not utilize TCE as part of its operations. OSHA standards cover workplaces that utilize TCE as part of its operations.

Why am I receiving this notice?

You are receiving this information because TCE has been measured in the air in your workplace at a level which exceeds DWM's action level concentration for inhalation exposures. DWM has determined that when the inhalation exposure action level concentration is exceeded and persons that may be particularly sensitive to TCE exposures at these concentrations may be exposed immediate actions must be taken to reduce the exposure to below the action level concentration as quickly as possible. The population at risk at the action level concentration are women that maybe in their first trimester of a pregnancy, a period when a woman may not yet realize that she is pregnant. The potential health risks are permanent developmental effects manifested as damage to the developing heart of the unborn child (fetus).

- The DWM TCE action level for workplace (non-residential) inhalation exposures is 8.8 micrograms per cubic meter ($\mu g/m^3$) for women who are or may be in the first trimester of pregnancy.
- Immediate action to reduce the workplace air concentration to below the TCE action level is required to reduce the risk to the developing fetus. Developmental effects will not necessarily occur at exposures above this level, but they cannot be ruled out and steps to address the potential risk are required.
- Women exposed to TCE concentrations above the inhalation action level should wait 3 to 4 weeks after their exposures reach concentrations below the action level before getting pregnant to allow the TCE to be removed from your body. Contacting your personal physician to discuss your TCE exposure is recommended.

What is TCE? How might I be exposed?

TCE is a man-made, colorless liquid used mainly as a solvent to remove grease from metal parts. It has also been an ingredient in some consumer products such as glues and paint removers. When TCE is released to soil or groundwater as a result of spills or leaks at a facility, it can evaporate and enter into a building's indoor air through seams and cracks in building foundations. This process is called "vapor intrusion."

What is the safe level of TCE in the workplace?

The indoor air guideline for workplace settings is 8.8 $\mu g/m^3$. This value is based on the United States Environmental Protection Agency's (EPA's) guideline for continuous exposure, which has been adopted by DWM. The value is based on a cautious interpretation of the data. At or below this level, significant health effects are not indicated.

What are the possible health effects from indoor air TCE exposure?

The possible health effects from breathing TCE depend on the levels in indoor air, the length of exposure, and whether and when a pregnant woman is exposed. Women who are in the first trimester of pregnancy are most sensitive to TCE exposures. TCE exposures may increase the risk of heart malformations in the developing fetus. Breathing TCE over a long period of time may affect the immune system and increase susceptibility to infections. Long-term exposures may increase an individual's risk of cancers of the kidney, liver and non-Hodgkin's lymphoma.

What should I know if I might be pregnant?
Because TCE exposure during the first trimester of pregnancy could affect fetal heart development, pregnant women are of special concern. Where workplace indoor air TCE concentrations exceed 8.8 µg/m^3, DWM requires immediate notification to workers and actions to reduce concentrations to below 8.8 µg/m^3, or if feasible, eliminate the exposures.

For exposures during the first trimester of pregnancy, DWM recommends the following protective measures:

- At TCE levels above 8.8 µg/m^3, women who may be in the first trimester of pregnancy and are concerned about their risk may want to consult with their physician and/or an occupational doctor familiar with chemical exposures. Depending on the specific situation, there may be ways to minimize or eliminate the risk, for example by avoiding areas of the workplace with higher TCE levels if possible. TCE levels below 8.8 µg/m^3 present a lower risk to the pregnant woman. Levels above this range must ultimately be reduced to meet EPA and DWM's indoor air guidelines.

For exposures before or after the first trimester of pregnancy:

- Exposures that end two to four weeks or more before a pregnancy are not indicated to contribute to an elevated level of risk since most TCE is eliminated from the body within that period.

What measures might be taken to reduce TCE levels in my workplace?
Parties responsible for the contamination are required to contract environmental professionals to quickly take steps to reduce the indoor air levels. The first mitigation steps usually include sealing sumps and foundation cracks and increasing ventilation. Portable carbon filtration systems and changes to the heating and ventilation system may also help to temporarily reduce concentrations while more permanent measures are being designed and implemented. Installing a sub-slab depressurization (SSD) system can be an effective measure in the longer term. An SSD system, which is similar to a radon abatement system, is a series of pipes under the basement with a fan that vents vapors to the outdoors. Groundwater treatment or soil vapor extraction may also be employed to reduce the source of TCE contamination.

What should I do if I'm concerned that my health has been affected?
If you have concerns about your health status, you should talk to your family doctor and/or an occupational doctor familiar with chemical exposures. When you meet with them, provide a copy of your TCE sampling results and the N.C. Division of Public Health's factsheet, *Trichloroethylene (TCE) Information for Health Professionals*, available at http://epi.publichealth.nc.gov/oee/az.html#tce.

Where can my physician and I get more information about potential TCE health effects?
More information on TCE health effects and the basis of DWM's action levels can be found on DWM's website at http://epi.publichealth.nc.gov/oee/az.html#tce and the Agency for Toxic Substances and Disease Registry's (ATSDR) website at http://www.atsdr.cdc.gov/. Your physician may also contact the N.C. Division of Public Health's Occupational and Environmental Epidemiology Branch in Raleigh to speak with physicians familiar with chemical exposures (telephone 919-707-5900).

Where can I get more information on TCE contamination and cleanup?
More information on DWM's guidance for sites with TCE contamination can be found at http://epi.publichealth.nc.gov/oee/az.html#tce. More information on the health effects associated with TCE exposures is available on the Agency for Toxic Substances and Disease Registry's (ATSDR) website at http://www.atsdr.cdc.gov/.

Adapted from Massachusetts Department of Environmental Protection's 'Important Information on Trichloroethylene (TCE) in Workplace Indoor Air'.

Appendix C

DWM TCE Short-Term Inhalation Action Level Presentation

August 2017

Nothing Compares
NORTH CAROLINA

Trichloroethylene (TCE)
Short-Term Inhalation Action Levels

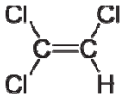
Sandra Amiss Mort, PhD
NC Department of Environmental Quality
Division of Waste Management

August 24, 2017

Short-term TCE Inhalation Health Risks

1. The most recent TCE health science
2. The population at risk
3. DWM response guidance

TCE = trichloroethylene



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Trichloroethylene -

- Trichloroethene, "TCE"
  - CASN 79-01-6
  - C_2HCl_3
- Volatile, colorless, nonflammable, sweet odor
- Uses:
  - Solvent, metal degreaser
  - Precursor for manufacture of refrigerant (HFC-134a) and other chemicals
  - Dry cleaning, textile industry
  - Component of adhesives, paints, lubricants, varnishes, paint strippers
  - Component of pesticides
  - Once used as an anesthetic

3

Environmental Impacts -

- Common soil and groundwater contaminant
  - US annual production - 270 million pounds (EPA, 2011)

- Mobile in soil
- Water soluble
- Highly volatile
- Degraded to toxic daughter products

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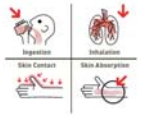
IRIS 2011 TCE Update -

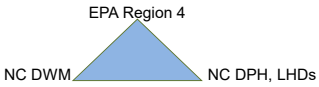
- Carcinogenic to humans by all routes (inhalation, ingestion, dermal)
  - Tumor types –
    - Renal cell, non-Hodgkin's lymphoma, liver
    - Mutagenic mode-of-action for kidney tumors
      - Children
- Established toxicity values for non-cancer endpoints
  - Critical effects, inhalation –
    - Immune (Thymus weight)
    - Developmental – Fetal cardiac malformation



TCE Vapor Intrusion Indoor Air Action Levels

- Calculation of the AL -
  - 2.0 µg/m^3 RfC TCE
  - Default EPA/DEQ inhalation exposure parameters

- **VI Action Levels**
  - **Residential - 2.1 µg/m^3** TCE in indoor air
  - **Occupational – 8.8 µg/m^3** TCE in indoor air
  - ❖***TCE VI ALs are not listed on the VI screening level tables***
- EPA Region 4, NC DEQ, NC DPH & County Health Dept. consensus
  - Coordinated response, risk communication
- *Science Advisory Board* review proposal



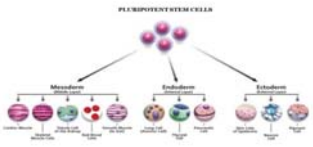
The Sensitive Receptor -

What we know about TCE uptake -
- It is rapidly absorbed and distributed throughout the body
- It crosses the placenta

Sensitive (critical) effect – developmental, fetal cardiac malformation
- *Cardiogenesis* = heart, vasculature system formation

Sensitive receptor = developing fetus during the 1st trimester

Exposure window of concern –
- 2-4 weeks prior to conception
- 1st trimester of pregnancy



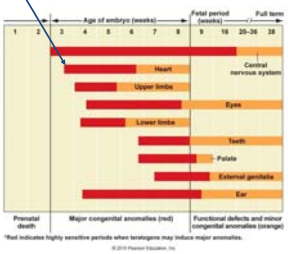
The Critical TCE Exposure Window

Developmental implications of TCE exposures in the 1st trimester –
- A period of rapid stem cell differentiation, migration
- Cardiac system one of earliest to develop
- Primary toxic insult response mechanisms not yet developed

** Result → a period of extreme vulnerability*

- Developmental effects with no apparent maternal toxicity
- Fetal risk increases with increased exposure frequency, duration and concentration

** Short-term exposure with long-term implications*



TCE Human Health References:

- IRIS
  - https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199
- ATSDR
  - https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=30
- USEPA Review article, 2016 –
  - Makris, S.L., Scott, C.S., Fox, J., *et.al.* A systematic evaluation of the potential effects of trichloroethylene exposure on cardiac development. *Reproductive Toxicology 2016, 65: 321-358*
    - Available at: *http://creativecommons.org/licenses/by-nc-nd/4.0/*

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Post-IRIS TCE Studies

Animal model identifies developmental critical-effect mechanism of action
- Wirbisky et al, *Chem. Res. Toxicol*. 2016, 29, 169−179

Altered cardiac function and development-associated gene expression in human embryonic stem cell cardiac differentiation model
- Jiang et al, *Environmental Toxicology.* DOI: 10.1002/tox.22142, Wiley Online Library. *2015*

Explains atypical dose-response curve shape
- *Trichloroethylene: Toxicity and Health Risks*. Gilbert and Blossom Editors. 2014

Texas birth registry study detected obstructive aorta and septal heart defects related to maternal TCE exposures
- Brender et al, *Environmental Health* 2014, 13:96

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Post-IRIS TCE Reviews

Makris et al, 2016 (USEPA). Reproductive Toxicology. 2016, 65:321-358. *http://creativecommons.org/licenses/by-nc-nd/4.0/*
- Updated literature search and weight-of-evidence analysis of epidemiological, toxicological, mechanistic data
- Concluded "*TCE has the potential to cause cardiac defects in humans when exposures occurs at sufficient doses during a sensitive window of fetal development*"
- Reaffirmed the suitability of the Johnson et al (2003) study in WOE

Massachusetts DEP (2014). *Assessing the Congenital Cardiac Toxicity of Trichloroethylene: Key Scientific Issues*
- Concluded that the WOE supports TCE exposure association with congenital cardiac defects and the Jones et al (2003) study is suitable for developing toxicity values

ATSDR, 2014. *Draft Toxicological Profile for Trichloroethylene*
- Epidemiological studies of 2 USA populations. Preconception exposures and living in proximity to TCE emission associated with elevated cardiac defects at birth
- Concluded Johnson et al (2003) study is "*valid and relevant to humans*"

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Desired Response Time-Line -

*the **Goal** – to quickly recognize and remove or reduce sensitive population exposures to < AL concentrations*

1. Identify Residential or Occupational TCE > AL
2. Within 1 business day –
   a. Notify DWM
   b. Verify presence of Sensitive Population
      - F (15-50 yrs. of age) → (-1 month – 1st trimester)
      - Risk Communication (on-site, factsheets, etc.)
   c. Notify NCDPH / County HD
   d. Initiate measures to reduce / eliminate exposure to < AL

**** DWM works with the facility to communicate risks, find a solution & reduce the exposure to <ALs ****

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Immediate Action Alternatives to Reduce / Remove TCE Exposures > Action Levels -

Alternatives to affect immediate reduction of exposure levels while long-term solutions are implemented -

- Adjust air-handling units
- Increase ventilation
- Temporarily relocate sensitive populations
- Seal obvious vapor conduits

Long-term solutions include -

- Vapor intrusion mitigation systems
- Remediation of the TCE source

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Indoor Air Monitoring -

- USEPA analytical method TO-15 for Toxic Organic Compounds in Ambient Air
  - GC/MS
  - SUMMA canister collection device
- 24-hour residential sample collection
- 8-hour occupational exposure sample collection
- Follow-up indoor air sampling to document successful intervention

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Contact information:

NC DWM Main:
919.707.8200

Sandy Mort
NC DEQ DWM
Office: 919.707.8217
sandy.mort@ncdenr.gov

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Appendix D

Time Line of Trichloroethylene (TCE) Inhalation Action Level

Toxicity References and Discussion Documents

N.C. Department of Environmental Quality

January 2017

Time Line of Trichloroethylene (TCE) Inhalation Action Level Toxicity References and Discussion Documents
N.C. Department of Environmental Quality
January 2017

2016, Apr., Trichloroethylene (TCE) Indoor Air Inhalation Immediate Action Levels and Response (Draft), NC DEQ DWM

2016, Aug., Makris et al., *A Systemic Evaluation of the Potential Effects of Trichloroethylene Exposure on Cardiac Development*. Reproductive Toxicology. 2016, 65:321-358. http://dx.doi.org/10.1016/j.reprotox.2016.08.014. [1]

2016, Jan., Wirbisky et al., *Mitochondrial Dysfunction, Disruption of F -Actin Polymerization, and Transcriptomic Alterations in Zebrafish Larvae Exposed to Trichloroethylene*. Chem. Res. Toxicol. 2016, 29, 169−179 [2]

2015, Mar., *Disruption of Cardiogenesis in Human Embryonic Stem Cells Exposed to Trichloroethylene*. Jiang et al. Environmental Toxicology DOI: 10.1002/tox.22142, Wiley Online Library [3]

2014, *Chapter 8, Environmental Sensitivity to Trichloroethylene (TCE) in the Developing Heart*, Ornella I. Selmin, Om Makwana, and Raymond B. Runyan. In *Trichloroethylene*: *Toxicity and Health Risks*, Kathleen M. Gilbert, Sarah J. Blossom Editors, Humana Press Molecular and Integrative Toxicology Series [4]

2014, Nov., *Maternal Residential Proximity to Chlorinated Solvent Emissions and Birth Defects in Offspring: A Case–Control Study*. Brender et al. Environmental Health 2014, 13:96 [5]

2014, Oct., *Draft Toxicological Profile for Trichloroethylene*, ATSDR, U.S. DHHS [includes discussions of human exposures resulting in fetal cardiac effects] [6,7,8]

2014, Aug., *Review and Recommendations for TCE Short-Term Action Levels in Indoor Air*, TRC Inc., http://www.trcsolutions.com/

2014, July, *EPA Region 9 Response Action Levels and Recommendations to Address Near-Term Inhalation Exposures to TCE in Air from Subsurface Vapor Intrusion*, U.S. EPA Region 9

2014, Mar., *Assessing the Congenital Cardiac Toxicity of Trichloroethylene: Key Scientific Issues*. Massachusetts Department of Environmental Protection Office of Research and Standards

2013, Mar., Makwana et al., *Low Dose Trichloroethylene Alters Cytochrome P450 - 2C Subfamily Expression in the Developing Chick Heart*. Cardiovasc Toxicol. 2013 March; 13(1): 77–84 [9]

2013, Feb., *Health Consultation, Millsboro TCE, Millsboro, Delaware*. U.S. DHHS, (ATSDR) Agency for Toxic Substances and Disease Registry.

2011 Sept., *Toxicological Review of Trichloroethylene*, IRIS, U.S. EPA [source of non-cancer RfD and RfC, and cancer potency values]

2003, Mar., Johnson et al., *Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat*. Environ Health Perspect. 111:289-292. [IRIS RfD / RfC critical effect study for fetal cardiac malformations]

[1] The U.S. EPA performed an updated literature search of TCE-related developmental cardiac defects and developed a putative adverse outcome pathway (AOP) construct to explore key events for the most commonly observed cardiac dysmorphologies, particularly those involved with epithelial-mesenchymal transition (EMT) of endothelial origin (EndMT). They concluded: "*A hypothesis-driven weight-of-evidence analysis of epidemiological, toxicological, in vitro, in ovo, and mechanistic/AOP data concluded that TCE has the potential to cause cardiac defects in humans when exposure occurs at sufficient doses during a sensitive window of fetal development. The study by Johnson et al. (2003) was reaffirmed as suitable for hazard characterization and reference value derivation, though acknowledging study limitations and uncertainties*."

[2] A laboratory study exposing zebrafish embryos to TCE identified mechanisms of cardiovascular toxicity associated with adverse developmental effects (zebrafish possess developmental genomic cardiovascular similarities to humans and are a common model for cardiac development). Observed TCE dose-response-related effects included loss of the vasculature network assembly, decreases in the development of new blood vessels (angiogenesis) and actin fibers, and mitochondrial function. These observations support human fetal cardiac malformation as the critical effect during early embryonic development. The heart is the first organ developed during embryogenesis and a competent vascular network is required for endothelial cell differentiation, proliferation and migration. Gene expression alterations to 70 genes associated with cardiovascular disease, organ morphology and function, cancer, liver and digestive system development and function, and kidney toxicity, and skeletal and muscular disorders were observed. In addition, TCE-induced abnormalities were observed to genes associated with cellular growth and proliferation, cell-to-cell signaling and cell cycle control, all of which are critical pathway components associated with tumor morphology and regulation. Significant effects were observed at the lowest test concentration, 10 ppb TCE.

[3] Cardiac function and development-associated gene expression levels were significantly altered in a human embryonic stem cell cardiac differentiation model. Species-specific inhibitory effects of TCE on heart development associated with the inhibition of human stem cell differentiation to cardiac muscle cells were reported. Significant interference with cardiac muscle cell Ca^{2+} (calcium) channel pathways were also observed and are implicated in TCE impacts to cardiac differentiation during early embryonic organogenesis, as well as subsequent cardiotoxicity and abnormal cardiac morphology.

[4] This review of the current-science of TCE toxicity includes the referenced chapter which discusses the observation of a non-monotonic dose-response (the response decreases with increasing dose) of TCE effects at environmentally-relevant concentrations observed in other studies. Significantly increased effects were seen on gene expression and cardiac function at exposure concentrations just above the TCE MCL (5 ppb). Examination of early heart valve development indicated that formation of valve progenitors were impaired. Changes in the expression of several genes involved in muscle cell calcium homeostasis and myocardial contraction were implicated. Calcium-mediated contraction in the heart was impaired and corresponded to changes in intracellular calcium flux and cardiac output. The non-monotonic dose-response characteristic reported in some studies was linked to the expression of a specific phase I metabolic enzyme (cytochrome P450 CYP2C) prior to the later development of the liver's phase I metabolic response capacity. Low doses of TCE were metabolized in the embryonic chick heart model by the localized CYP2C metabolizing enzyme family, providing a mechanism of early TCE and TCE metabolite-associated toxicity in the developing heart prior to the development of the liver and its ability to provide metabolizing enzyme systems in response to toxic insults in the embryo and fetus.

[5] A population-based case-control epidemiological study of the Texas Birth Defects Registry for births occurring during 1996-2008 examined the relationship between maternal residential proximity to industrial releases of chlorinated solvents and selected birth defects. The Texas database included >60k cases and >244k controls. Exposures were estimated using distance from the source and reported annual amounts of solvent releases (EPA TRI data). Logistic regression indicated a significant association of TCE exposure and obstructive heart defects in

offspring of mothers 35 years or older (odds ratio 1.43, 95% CI 1.08, 1.88; the odds ratio represents the odds of an exposed person developing the disease relative to a non-exposed person developing the disease). Other TCE and maternal proximity to emission-related associations identified in the Texas study included maternal age-related effects associated with oral cleft defects and the likelihood of any type of heart defect or septal heart defect, as well as an increased likelihood of spina bifida in the offspring of mothers of any age.

[6] A study of an Endicott NY residential population exposed via vapor intrusion. Findings included a significantly elevated risk of cardiac defects at birth. Total cardiac defects at birth were twice as prevalent as expected. A 2.5-fold increase in the rate of congenital heart disease in children was reported for parents exposed in drinking water during the month before conception and the 1st trimester of pregnancy.

[7] Milwaukee, WI residential exposures to TCE resulted in significant (3-fold) increased risk of congenital heart defects in children born to women living within 1.3-miles of a TCE-emitting site (as compared to those living outside the 1.3-mile range).

[8] ATSDR states, when discussing the Johnson et al. 2003 study, that "…*However, in the absence of convincing information to the contrary, the report of trichloroethylene-induced cardiac malformations in rat fetuses is considered valid and relevant to humans. The increased incidences of fetuses with cardiac malformations from the rat dams administered trichloroethylene during gestation serve as partial basis for the chronic-duration inhalation and oral MRLs for trichloroethylene*…", and they later state "…*EPA concluded that "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*".

[9] This study demonstrates that the earliest embryonic expression of phase I detoxification enzymes is in the developing heart. The expression of these enzymes is relevant to the unique susceptibility of the embryonic heart at the earliest stages of development to environmental teratogens, including TCE. Developing chick embryos were dosed with TCE at 8 and 800 ppb, followed by examination of genetic material-associated effects in cardiac and other tissues. The study reported TCE-induced adverse effects to cardiovascular development prior to development of the liver systems able to mediate xenobiotic insults. Increased expression of early embryo cardiac tissue-specific cytochrome P450 metabolizing enzyme genetic material (mRNA and cytochrome precursor proteins) were observed, with no detectable response in extra-cardiac tissue. In this study, the dose-response in the cardiac tissue was non-monotonic (the response was greater at 8 ppb TCE than at 800 ppb TCE), supporting observations in prior studies. A known cytochrome oxidative metabolite of TCE is trichloroacetic acid (TCA), which has been shown to elicit greater cardiac toxicity than TCE. One possible pathway of the non-monotonic dose-response is that in early stages of embryonic TCE exposures, the cardiac-specific enzyme system metabolizes TCE, producing toxic metabolites, that act in concert with the TCE to induce adverse cardiac effects. As exposure concentrations increase, response systems may be quickly overwhelmed, until additional metabolizing systems are developed in the liver and other tissues, producing toxic metabolites that increase the level of adverse effects.