June, 2011

This document is a ***Final Agency/Interagency Science Discussion* draft**. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for review of its technical accuracy and science policy implications.

0199
Trichloroethylene; CASRN 79-01-6; 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review 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 at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR Trichloroethylene

File First On-Line 03/31/1987

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	on-line	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_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 -- 00/00/0000

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 at http://www.epa.gov/iris/backgr-d.htm 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 on the IRIS database.

___I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD**
Multiple (see below)	Multiple (see below)	Multiple (see below)	0.0005 mg/kg/day
Decreased thymus weight in female B6C3F1 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 PFC response (3 and 8 weeks), increased delayed-type hypersensitivity in B6C3F1 mice Drinking water exposure from GD0 to 3- or 8-weeks of age Peden-Adams et al. (2006)	LOAEL: 0.37 mg/kg/day	1000 (Candidate RfD = 0.00037 mg/kg/day)	
Increased fetal cardiac malformations in Sprague-Dawley rats Drinking water exposure from GD1 to GD22 Johnson et al. (2003)	$HED_{99,BMDL}$: 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 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent dose to the mouse 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 $HED_{99,BMDL}$ is the 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent dose 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 a RfD of 0.0005 mg/kg/d. This estimate is within 20% of the estimates for the critical effects—0.0004 mg/kg/d for developmental immunotoxicity (decreased PFC and increased delayed-type hypersensitivity) in mice, and 0.0005 mg/kg/d both for heart malformations in rats and for decreased thymus weights in mice.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

The Toxicological Review of Trichloroethylene (TCE) reviews and summarizes the available data on non-cancer effects caused by TCE (for summary, see U.S. EPA, 2011, Section 4.11.1). Adverse non-cancer effects associated with oral TCE exposure include decreased body weight, liver and kidney effects, and neurological, immunological, reproductive, and developmental effects. Candidate RfD values 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 on the basis of PBPK model-derived internal dose (U.S. EPA, 2011, Section 5.1.3). The most sensitive observed adverse effects, which were used as the principal bases of the RfD, were those affecting the immune system and the developing fetus. Additional support for the RfD was based on adverse effects in the kidney.

In particular, 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/d, at the low end of the overall range of candidate RfDs for all adverse effects. Given the somewhat imprecise nature of the individual candidate RfD values, and the fact that multiple effects/studies lead to similar candidate RfD values, the approach taken in this assessment is to select a RfD supported by multiple effects/studies. The advantages of this approach, which is only possible when there is a relatively large database of studies/effects and when multiple candidate values happen to fall within a narrow range at the low end of the overall range, 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 (Johnson et al., 2003; Keil et al., 2009; Peden-Adams et al., 2006) and two supporting (NTP, 1988; Woolhiser et al., 2006) studies/effects have been chosen as the basis of the RfD for TCE noncancer effects (see Table below). Two of the lowest candidate RfDs for the primary dose metrics—0.0008 mg/kg/d for increased kidney weight in rats and 0.0005 mg/kg/d 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/d 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/d 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) and 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 developmental effects, 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 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 3.3.3.2), 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 RfD value for toxic nephropathy had greater dose-response uncertainty since the estimation of its 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 a RfD of 0.0005 mg/kg/d. This estimate is within 20% of the estimates for the critical effects—0.0004 mg/kg/d for developmental immunotoxicity (decreased PFC and increased delayed-type hypersensitivity) in mice, and 0.0005 mg/kg/d both for heart malformations in rats and for decreased thymus weights in mice. This estimate is also within approximately a factor of two of the supporting effect estimates of 0.0003 mg/kg/d for toxic nephropathy in rats and 0.0008 mg/kg/d for increased kidney weight in rats. Thus, there is strong, robust support for a RfD of 0.0005 mg/kg/d 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 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/d** based on the critical effects of heart malformations (rats), adult immunological effects (mice), and developmental immunotoxicity (mice), all from oral studies. This RfD value 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 critical studies, effects, PODs, and UFs used to derive the RfD

Keil et al. (2009)—Decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water. • Internal dose POD = 0.139 mg TCE metabolized/kg^{¾}/d, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/d (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape) (U.S. EPA, 2011, Appendix F, Section F.6.4). • HED_{99} = 0.048 mg/kg/d (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model. • UF = 100. • Primary candidate RfD = HED_{99}/UF = 0.048/100 = 0.00048 mg/kg/d.
Peden-Adams et al. (2006)—Decreased PFC response (3 and 8 weeks), increased delayed-type hypersensitivity (8 weeks) in pups exposed from GD 0 to 3- or 8-weeks-of-age through drinking water (placental and lactational transfer, and pup ingestion). • POD = 0.37 mg/kg/d 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.6.6). • UF = 1000. • Primary candidate RfD = HED_{99}/UF = 0.37/1000 = 0.00037 mg/kg/d.
Johnson et al. (2003)—fetal heart malformations in S-D rats exposed from GD 1–22 by drinking water • Internal dose POD = 0.0142 mg TCE metabolized by oxidation/kg^{¾}/d, 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% (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.6.5). • HED_{99} = 0.0051 mg/kg/d (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model. • UF = 10 • Primary candidate RfD = HED_{99}/UF = 0.0051/10 = 0.00051 mg/kg/d.

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

Woolhiser et al. (2006)—Increased kidney weight in female S-D rats exposed for 4 weeks by inhalation (6 h/d, 5 d/wk).

- Internal dose POD = 0.0309 mg DCVC bioactivated/kg¾/d, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 10%, and Hill model with constant variance (U.S. EPA, 2011, Appendix F, Section F.6.3).
- HED_{99} = 0.0079 mg/kg/d (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- UF = 10.
- Supporting candidate RfD = HED_{99}/UF = 0.0079/10 = 0.00079 mg/kg/d.

___I.A.3. UNCERTAINTY FACTORS

Uncertainty factors are used to address differences between study conditions and conditions of human environmental exposure (U.S. EPA, 2002). These include

(a) *Extrapolating from laboratory animals to humans:* If a POD is derived from experimental animal data, it is divided by an UF to reflect pharmacokinetic and pharmacodynamic differences that may make humans more sensitive than laboratory animals. For oral exposures, the standard value for the interspecies UF is 10, which breaks down (approximately) to a factor of three for pharmacokinetic differences (which is removed if the PBPK model is used) and a factor of three for pharmacodynamic differences. For inhalation exposures, ppm equivalence across species is generally assumed, in which case pharmacokinetic differences are considered to be negligible, and the standard value used for the interspecies UF is 3, which is ascribed to pharmacodynamic differences. These standard values were used for all the candidate RfCs and RfDs based on laboratory animal data in this assessment.

(b) *Human (intraspecies) variability:* RfCs and RfDs apply to the human population, including sensitive subgroups, but studies rarely examine sensitive humans. Sensitive humans could be adversely affected at lower exposures than a general study population; consequently, PODs from general-population studies are divided by an UF to address sensitive humans. Similarly, the animals used in most laboratory animal studies are considered to be "typical" or "average" responders, and the human (intraspecies) variability UF is also applied to PODs from such studies to address sensitive subgroups. The standard value for the human variability UF is 10, which breaks down (approximately) to a factor of three for pharmacokinetic variability (which is removed if the PBPK model is used) and a factor of three for pharmacodynamic variability. This standard value was used for all the PODs in this assessment with the exception of the PODs for a few immunological effects that were based on data from a sensitive (autoimmune-prone) mouse strain; for those PODs, an UF of 3 was used for human variability.

(c) *Uncertainty in extrapolating from subchronic to chronic exposures:* RfCs and RfDs apply to lifetime exposure, but sometimes the best (or only) available data come from less-than-lifetime studies. Lifetime exposure can induce effects that may not be apparent or as large in magnitude in a shorter study; consequently, a dose that elicits a specific level of response from a lifetime exposure may be less than the dose eliciting the same

level of response from a shorter exposure period. Thus, PODs based on subchronic exposure data are generally divided by a subchronic-to-chronic UF, which has a standard value of 10. If there is evidence suggesting that exposure for longer time periods does not increase the magnitude of an effect, a lower value of three or one might be used. For some reproductive and developmental effects, chronic exposure is that which covers a specific window of exposure that is relevant for eliciting the effect, and subchronic exposure would correspond to an exposure that is notably less than the full window of exposure.

(d) *Uncertainty in extrapolating from LOAELs to NOAELs:* PODs are intended to be estimates of exposure levels without appreciable risk under the study conditions so that, after the application of appropriate UFs for interspecies extrapolation, human variability, and/or duration extrapolation, the absence of appreciable risk is conveyed to the RfC or RfD exposure level to address sensitive humans with lifetime exposure. Under the NOAEL/LOAEL approach to determining a POD, however, adverse effects are sometimes observed at all study doses. If the POD is a LOAEL, it is divided by an UF to better estimate a NOAEL. The standard value for the LOAEL-to-NOAEL UF is 10, although sometimes a value of three is used if the effect is considered minimally adverse at the response level observed at the LOAEL or even one if the effect is an early marker for an adverse effect. For one POD in this assessment, a value of 30 was used for the LOAEL-to-NOAEL UF because the incidence rate for the adverse effect was ≥90% at the LOAEL.

(e) *Additional database uncertainties*: A database UF of 1, 3 or 10 is used to reflect the potential for deriving an underprotective toxicity value as a result of an incomplete characterization of the chemical's toxicity. No database UF was used in this assessment. See U.S. EPA (2011, Section 5.1.4.1) for additional discussion of the uncertainties associated with the overall database for TCE.

Specific UFs used in the principal and supporting studies for the RfD are summarized in the following tables. (Note that UF values of "3" actually represent √10, and, when 2 such values are multiplied together, the result is 10 rather than 9.)

Summary of critical studies, effects, and UFs used to derive the RfD

Keil et al. (2009)—Decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water. • $UF_{composite}$ = 100. • UF_{loael} = 10 because POD is a LOAEL for an adverse effect. • UF_{is} = 3 because the PBPK model was used for interspecies (is) extrapolation. • UF_{h} = 3 because the PBPK model was used to characterize human (h) toxicokinetic variability.
Peden-Adams et al. (2006)—Decreased PFC response (3 and 8 weeks), increased delayed-type hypersensitivity (8 weeks) in pups exposed from GD 0 to 3- or 8-weeks-of-age through drinking water (placental and lactational transfer, and pup ingestion). • $UF_{composite}$ = 1000. • UF_{loael} = 10 because POD is a LOAEL for multiple adverse effects. • UF_{is} = 10 for interspecies extrapolation because PBPK model was not used. • UF_{h} = 10 for human variability because PBPK model was not used.

Johnson et al. (2003)—fetal heart malformations in S-D rats exposed from GD 1–22 by drinking water • $UF_{composite}$ = 10 • UF_{is} = 3 because the PBPK model was used for interspecies extrapolation. • UF_h = 3 because the PBPK model was used to characterize human toxicokinetic variability.

GD = gestation day.

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

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by oral gavage (5 d/wk). • $UF_{composite}$ = 10. • UF_{is} = 3 because the PBPK model was used for interspecies extrapolation. • UF_h = 3 because the PBPK model was used to characterize human toxicokinetic variability.
Woolhiser et al. (2006)—Increased kidney weight in female S-D rats exposed for 4 weeks by inhalation (6 h/d, 5 d/wk). • $UF_{composite}$ = 10. • UF_{sc} = 1 because Kjellstrand et al. (1983) reported that in mice, kidney effects after exposure for 120 d was no more severe than those after 30 d exposure. • UF_{is} = 3 because the PBPK model was used for interspecies extrapolation. • UF_h = 3 because the PBPK model was used to characterize human toxicokinetic variability.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

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

Study – High-medium/medium/low-medium (for each endpoint individually)
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 for immulological 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 immulogical effects, so PBPK modeling applied to Kiel 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 there 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 critical 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 (NTP, 1988; Woolhiser et al., 2006), 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). Morever, 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.

___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).

Agency Completion Date -- __/__/__

___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 -- 00/00/0000

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 trichloroethylene on the IRIS database.

___I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC**
Multiple (see below)	Multiple (see below)	Multiple (see below)	0.002 mg/m^3 (0.0004 ppm)
Decreased thymus weight in female B6C3F1 mice 30 week drinking water study 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 GD1 to GD22 Johnson et al. (2003)	$HEC_{99,BMDL}$: 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 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 $HEC_{99,BMDL}$ is the route-to-route extrapolated 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent concentration 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 a RfC of 0.0004 ppm (0.4 ppb or 2 $\mu g/m^3$). This estimate essentially 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.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES

The Toxicological Review of Trichloroethylene (TCE) reviews and summarizes the available data on non-cancer effects caused by TCE (for summary, see U.S. EPA, 2011, Section 4.11.1). Adverse non-cancer effects associated with TCE exposure by inhalation include hepatic, renal, neurological, immunological, reproductive, and developmental effects. Candidate RfC values 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 on the basis of PBPK model-derived internal dose (U.S. EPA, 2011, Section 5.1.3). The most sensitive observed adverse effects, which were used as the principal bases of the RfC, were those affecting the immune system and the developing fetus. 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 RfC values, and the fact that multiple effects/studies lead to similar candidate RfC values, the approach taken in this assessment is to select a RfC supported by multiple effects/studies. The advantages of this approach, which is only possible when there is a relatively large database of studies/effects and when multiple candidate values happen to fall within a narrow range at the low end of the overall range, 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 (Johnson et al., 2003; Keil et al., 2009) and one supporting (NTP, 1988) studies/effects have been chosen to as the basis of the RfC for TCE noncancer effects (see Table below). Each of these lowest candidate RfCs, ranging from 0.0003−0.0006 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 studies 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 3.3.3.2), there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, the p-cRfC 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 primary 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 a RfC of 0.0004 ppm (0.4 ppb or 2 μg/m^3). This estimate essentially 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. This estimate is also within a factor of two of the candidate RfC estimate of 0.00006 ppm for the supporting effect of toxic nephropathy in rats. Thus, there is robust support for a 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 (TotOxMetabBW34 for the heart malformations). There is high confidence that ABioactDCVCBW34 and AMetGSHBW34 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 value is further supported by route-to-route extrapolated results from an oral study of toxic nephropathy (rats).

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

Keil et al. (2009)—Decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water. • Internal dose POD = 0.139 mg TCE metabolized/kg^{¾}/d, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/d (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape) (U.S. EPA, 2011, Appendix F, Section F.6.4). • HEC_{99} = 0.033 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model. • UF = 100. • Principal candidate RfC = HEC_{99}/UF = 0.033/100 = 0.00033 ppm (2 μg/m^3).
Johnson et al. (2003)—fetal heart malformations in S-D rats exposed from GD 1–22 by drinking water. • Internal dose POD = 0.0142 mg TCE metabolized by oxidation/kg^{¾}/d, 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% (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.6.5). • HEC_{99} = 0.0037 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model. • UF = 10. • Principal candidate RfC = HEC_{99}/UF = 0.0037/10 = 0.00037 ppm (2 μg/m^3).

GD = gestation day.

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

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by oral gavage (5 d/wk). • Internal dose POD = 0.0132 mg DCVC bioactivated/kg^{¾}/d, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 5% (clearly toxic effect), and log-logistic model (U.S. EPA, 2011, Appendix F, Section F.6.1). • HEC_{99} = 0.0056 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model. • UF = 10. • Supporting candidate RfC = HEC_{99}/UF = 0.0056/10 = 0.00056 ppm (3 μg/m^3).

___I.B.3. UNCERTAINTY FACTORS

General discussion of uncertainty factors is presented above in I.A.3. Specific UFs used in the principal and supporting studies for the RfC are summarized in the following tables. (Note that UF values of "3" actually represent √10, and, when 2 such values are multiplied together, the result is 10 rather than 9.)

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

Keil et al. (2009)—Decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water. • $UF_{composite}$ = 100. • UF_{loael} = 10 because POD is a LOAEL for an adverse effect. • UF_{is} = 3 because the PBPK model was used for interspecies extrapolation. • UF_h = 3 because the PBPK model was used to characterize human toxicokinetic variability.
Johnson et al. (2003)—fetal heart malformations in S-D rats exposed from GD 1–22 by drinking water. • $UF_{composite}$ = 10. • UF_{is} = 3 because the PBPK model was used for interspecies extrapolation. • UF_h = 3 because the PBPK model was used to characterize human toxicokinetic variability.

GD = gestation day.

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

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by oral gavage (5 d/wk). • $UF_{composite}$ = 10. • UF_{is} = 3 because the PBPK model was used for interspecies extrapolation. • UF_h = 3 because the PBPK model was used to characterize human toxicokinetic variability.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

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

Study – High-medium/medium/low-medium (for each endpoint individually)
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 for immulological effects (Keil et al., 2009) precluded application of BMD modeling. There are inadequate data on the active moiety for TCE-induced immulogical effects, so PBPK modeling applied to Kiel 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 there 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 critical study coupled with the higher confidence in the dose-response analysis, the confidence in the candidate RfC derived from this studies 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). Morever, 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.

___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).

Agency Completion Date -- __/__/__

___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 -- 00/00/0000

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) (U.S. EPA, 2005c). 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 trichloroethylene 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 site-specific tumors in rodents given TCE by oral gavage and inhalation. 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 MOA is operative for TCE-induced kidney tumors, and this MOA is clearly relevant to humans. MOAs have not been established for other TCE-induced tumors in rodents, and no mechanistic data indicate that any hypothesized key events are biologically precluded in humans.

___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. Eighteen studies in which there is 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 studies reporting risks of kidney cancer (Anttila et al., 1995; Axelson et al., 1994; Boice et al., 1999; Brüning et al., 2003; Charbotel et al., 2006; Dosemeci et al., 1999; Greenland et al., 1994; Hansen et al., 2001; Moore et al., 2010; Morgan et al., 1998; Pesch et al., 2000; Raaschou-Nielsen et al., 2003; Radican et al., 2008; Siemiatycki, 1991; Zhao et al., 2005), most estimated relative risks 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 (Brüning et al., 2003; Dosemeci et al., 1999; Moore et al., 2010; Raaschou-Nielsen et al., 2003) or for one of the highest TCE exposure group (Charbotel et al., 2006; Moore et al., 2010; Raaschou-Nielsen et al., 2003; Zhao et al., 2005). 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, Sections 4.1. and 4.4.2).

The consistency of 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 TCE exposure potential to individual subjects. These

analyses observed a statistically significant increased summary relative risk estimate (RRm) for kidney cancer of 1.27 (95% CI: 1.13, 1.43) for overall TCE. The summary relative risk were robust and did not change appreciably with the removal of any individual study or with the use of alternate relative risk estimates from individual studies. In addition, there was no evidence for heterogeneity or publication bias.

The consistency of increased kidney cancer relative risk 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 is 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 relative risk estimates for NHL between 0.8 and 3.1 for overall TCE exposure (U.S. EPA, 2011, Section 4.1 and 4.6.1.2). Statistically significant elevated relative risk estimates for overall exposure were observed in two cohort (Hansen et al., 2001; Raaschou-Nielsen et al., 2003) and one case-control (Hardell et al., 1994) studies. The other 14 identified studies reported elevated relative risk estimates with overall TCE exposure that were not statistically significant (Anttila et al., 1995; Axelson et al., 1994; Boice et al., 1999; Cocco et al., 2010; Greenland et al., 1994; Miligi et al., 2006; Morgan et al., 1998; Nordström et al., 1998; Persson and Fredrikson, 1999; Purdue et al., 2011; Radican et al., 2008; Siemiatycki, 1991; Wang et al., 2009; Zhao et al., 2005). 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 relative risk 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, though 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 relative risk 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 is 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 (Anttila et al., 1995; Axelson et al., 1994; Boice et al., 1999; Boice et al., 2006; Greenland et al., 1994; Morgan et al., 1998; Radican et al., 2008) (Hansen et al., 2001; Raaschou-Nielsen et al., 2003), most reported relative risk 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 confidence intervals on the estimates, except for one study (Raaschou-Nielsen et al., 2003). This study has 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 (relative risk [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 relative risk 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 relative risk 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 relative risks or odds ratios for overall TCE exposure generally less than 2.0, and higher relative risks or odds ratios for high exposure categories. Among the highest statistically significant relative risks 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 relative risks, 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; 2009) (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) et al. may have contributed to their reported relative risks 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; 2009), and, as would be expected, observed relative risk estimates are lower (1.24 [95% CI: 1.03, 1.49]), Pesch et al., 2000a; 1.30 [95% CI: 0.9, 1.9], (Dosemeci et al., 1999). A few high-quality cohort and case-control studies reported statistically significant relative risks 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 relative risks reported for NHL were those of Hansen et al. (2001) (3.1 [95% CI: 1.3, 6.1]), 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-hr, and 7.9 [95% CI: 1.8, 34.3], >360 ppm-hr/week). Observed relative risk 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 relative risk 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 relative risk 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 are 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 can not fully explain the observed elevations in kidney cancer relative risks. All kidney cancer case-control studies included adjustment for possible confounding effects of smoking, and some studies included body mass index, hypertension, and co-exposure to other occupational agents such as cutting or petroleum oils. Cutting oils and petroleum oils, known as metalworking fluids, have not been associatied with kidney cancer (Mirer, 2010; NIOSH, 1998), and potential confounding by this occupational co-exposure is unable to explain the observed assocation 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, which 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 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 relative risk 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 (Miligi et al., 2006; Wang et al., 2009), two others adjusted for age, sex and education (Cocco et al., 2010; Purdue et al., 2011), and the other three case-control studies

adjusted for age only or age and sex (Hardell et al., 1994; Nordström et al., 1998; Persson and Fredrikson, 1999). 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 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 tumors that was specific to TCE exposure. There is some evidence suggesting particular 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. (2005; 2007) (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. (2007) 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 relative risk 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 relative risk 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 CH, TCA and DCA, are rodent hepatocarcinogens. Two other metabolites, DCVC and 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, 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 tumor findings, although there are insufficient data to support any one mode of action, and the available evidence does not preclude the relevance of the hypothesized modes of action to humans. Activation of macrophages, natural killer cells, and cytokine production (e.g., tumor necrosis factor), may also play an etiologic role in carcinogenesis, and so the immune-related effects of TCE should also be considered. In addition, the decreased in lymphocyte counts and subsets, including CD4+ T cells, and decreased lymphocyte activation seen in TCE-exposed workers (Lan et al., 2010) also support the biological plausibility of a role of TCE exposure in NHL.

(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, MA, after closure of the two wells contaminated with trichloroethylene 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 relative risk 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 relative risks are modest, 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 relative risk estimate was observed for overall TCE exposure (RRm: 1.27 [95% CI: 1.13, 1.43]). The summary relative risk estimate was greater for the highest TCE exposure groups (RRm: 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 relative risk estimate selections found the summary relative risk 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 (non-statistically 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 tumors 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 (Maltoni et al., 1986; NTP, 1988, 1990a). For instance, Maltoni et al. (1986) reported that although only 4/130 renal adenocarcinomas 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 (NCI, 1976; NTP, 1988, 1990a). 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 (Maltoni et al., 1986; NCI, 1976; NTP, 1990a). 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 B6C3F1 mice of both sexes (Anna et al., 1994; Bull et al., 2002; Herren-Freund et al., 1987; Maltoni et al., 1986; NCI, 1976; NTP, 1990a). In female Swiss mice, on the other hand, 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 (Henschler et al., 1980; Maltoni et al., 1986; NCI, 1976; NTP, 1988, 1990a) 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 (NCI, 1976; NTP, 1988, 1990a), 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 (Fukuda et al., 1983; Henschler et al., 1980; Maltoni et al., 1986). 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., Bull et al., 1990; DeAngelo et al., 1996; DeAngelo et al., 2008; DeAngelo et al., 1999; George et al., 2000; Leakey et al., 2003), 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 B6C3F1 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 B6C3F1 and Swiss mice.

Additionally, there is more limited evidence for TCE-induced lymphatic cancers in rats and mice, lung tumors in mice, and testicular tumors in rats. With respect to the 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 these lymphomas were of viral origin specific to this strain, subsequent studies reported increased lymphomas in female B6C3F1 mice treated via corn oil gavage (NTP, 1990a) and leukemias in male Sprague-Dawley and female August rats (Maltoni et al., 1986; NTP, 1988). However, these tumors 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 (Fukuda et al., 1983; Maltoni et al., 1988; Maltoni et al., 1986). Pulmonary tumors were not reported in other species tested (i.e., rats and hamsters) (Fukuda et al., 1983; Henschler et al., 1980; Maltoni et al., 1988; Maltoni et al., 1986). Chronic oral exposure to TCE led to a nonstatistically significant increase in pulmonary tumors in mice but, again, not in rats or hamsters (Henschler et al., 1984; Maltoni et al., 1986; NCI, 1976; NTP, 1988, 1990a; Van Duuren et al., 1979). 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 (Maltoni et al., 1986; NTP, 1988, 1990b). 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, 1988, 1990a).

In summary, there is clear evidence for TCE carcinogenicity in rats and mice, with multiple studies showing TCE to cause tumors at multiple sites. 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 indicates 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 CYPs and conjugation with glutathione via 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 (see 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 MOA 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 MOA is operative in TCE-induced kidney tumors. While supporting the biological plausibility of this hypothesized MOA, available data on the von Hippel-Lindau (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 MOA 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 MOA, 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. 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 MOA 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 MOA.

With respect to other tumor sites, data are insufficient to conclude that any of the other hypothesized MOAs are operant. In the liver, a mutagenic MOA 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 MOA 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 MOA 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 MOA 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 MOA 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 MOA for TCE-induced liver tumors. For mouse lung tumors, as with the liver, a mutagenic MOA involving CH has also been hypothesized, but there are insufficient data to conclude that it is operant. A second MOA 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 of duration 2 weeks or longer. See U.S. EPA (2011, Section 4.7.4) for additional discussion of the MOA for TCE-induced lung tumors. A MOA 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 MOA hypothesis for this tumor site (see U.S. EPA, 2011, Section 4.8.2.3 for additional discussion of the MOA 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 – EPA has concluded, by a weight of evidence evaluation, that trichloroethylene 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, 2005c) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for trichloroethylene 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 age-dependent adjustment factors (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), 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 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005c). The 10-fold 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 trichloroethylene. 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 trichloroethylene, 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*).

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 trichloroethylene's mutagenic mode of action for kidney tumors. A 1% extra risk level is used for the determination of the point of depature (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

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 trichloroethylene should not be used with exposures exceeding 10 mg/kg/d, 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 above (U.S. EPA, 2005b; 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 (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.

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

Drinking water unit risk and concentrations at specified risk levels are not provided for trichloroethylene. Since trichloroethylene 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 a specified risk levels will change based on the age of the individuals in the exposed group. 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/. 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).

____II.B.1.3. Modeling Approach and Extrapolation Method

The oral slope factor for trichloroethylene cancer risk, without consideration of increased early-life susceptibility due to trichloroethylene's mutagenic mode of action for kidney tumors, is derived from route-to-route extrapolation of the inhalation unit risk for trichloroethylene, using a PBPK model. As discussed in more detail below (II.C.2 and II.C.3), the inhalation unit risk for trichloroethylene is based on three separate target tissue sites – kidney, lymphoid tissue, and liver. 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. 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/d to internal dose per ppm. The expected value of the population mean for this conversion factor (in ppm per mg/kg/d) 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/d.

___II.B.2. DOSE-RESPONSE DATA

See II.C.2, below.

___II.B.3. ADDITIONAL COMMENTS

As discussed above, the weight of evidence supports a mutagenic mode of action for trichloroethylene 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, 2005c), 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 5.2.3.3.3 (U.S. EPA, 2011) when applying the ADAFs for oral TCE exposures.

The adult-based oral slope factor estimate presented above (4.6×10^{-2} per mg/kg/d) is for total cancer incidence, reflecting the incidence risks for kidney cancer (renal cell carcinoma, RCC), NHL, and liver cancer. The adult-based oral slope factor estimates for the separate cancer types were 9.33×10^{-3} per mg/kg/d for RCC, 2.16×10^{-2} per mg/kg/d for NHL, and 1.55×10^{-2} per mg/kg/d 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 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 2-fold range, and, for any particular dose metric, the 95% confidence interval for the extrapolated population mean risks for each site spanned a range of no more than about 3-fold.

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/d**. 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/d, 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/d. 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/d. In addition, the 90% confidence intervals for male Osborne-Mendel rat kidney tumors (NTP, 1988),

male F344 rat kidney tumors (NTP, 1990a), 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/d, 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/d. 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/d, with the preferred estimate based on human data falling within the route-to-route extrapolation of the 90% confidence interval. Finally, for all 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/d, 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 tumors at multiple sites (U.S. EPA, 2011, Section 5.2.2.2), 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 – EPA has concluded, by a weight of evidence evaluation, that trichloroethylene 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, 2005c) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for trichloroethylene 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 age-dependent adjustment factors (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), 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 to

<16 years, and 1 for 16 years and above (U.S. EPA, 2005c). The 10-fold 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 trichloroethylene. 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 trichloroethylene, 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*).

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 trichloroethylene's mutagenic mode of action for kidney tumors. A 1% extra risk level is used for the determination of the point of depature (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 $\mu g/m^3$

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 above (U.S. EPA, 2005; U.S. EPA, 2011, Section 5.2.3.3.1(U.S. EPA, 2005a).

*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 (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.

Air Concentrations at Specified Risk Levels

Air concentrations at specified risk levels are not provided for trichloroethylene. Since trichloroethylene 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. Risk assessors should use the unit risk 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/. 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).

____II.C.1.2. 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, RCC) incidence to obtain a slope estimate (regression coefficient) for the relative risk of RCC 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 RCC incidence was adjusted to account for potential increased risk of those tumor 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 tumor types combined versus the extra risk for RCC alone was estimated, and this factor was applied to the unit risk estimate for RCC to obtain a unit risk estimate for the three tumor types combined (i.e., lifetime extra risk for developing any of the 3 types of tumors). This factor was based on human surveillance data on the background risk of these tumors and human epidemiologic data on the relative risk of these tumors associated with TCE exposure.

___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 body mass index; 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)

CI = confidence interval.

For adjustment of the inhalation unit risk for multiple sites: The relative contributions to the extra risk for cancer from TCE exposure for multiple tumor types (NHL and liver cancer in

addition to RCC) 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 tumor types (U.S. EPA, 2011, Appendix C); the second calculation was based on the results of the Raaschou-Nielsen et al. (2003) study, the larget single human epidemiologic study by far with relative risk estimates for all three tumor types:

	RR	Ro	Rx	Extra risk	Ratio to kidney value
Calculation #1: using RR estimates from the meta-analyses					
Kidney (RCC)	1.27	0.0107	0.01359	0.002920	1
NHL	1.23	0.0202	0.02485	0.004742	1.62
Liver (& 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
Calculation #2: using RR estimates from Rasschou-Nielsen et al. (2003)					
Kidney (RCC)	1.20	0.0107	0.01284	0.002163	1
NHL	1.24	0.0202	0.02505	0.004948	2.29
Liver (& 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

RR = relative risk.
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 RCC alone to include the combined risk of RCC, NHL, and liver cancer.

___II.C.3. ADDITIONAL COMMENTS

As discussed above, the weight of evidence supports a mutagenic mode of action for trichloroethylene 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, 2005c), 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 above (4.1×10^{-6} per $\mu g/m^3$) is for total cancer incidence, reflecting the incidence risks for kidney cancer (RCC), NHL, and liver cancer. The adult-based unit risk estimates for the separate cancer types were 1.02×10^{-6} per $\mu g/m^3$ for RCC, 2.05×10^{-6} per $\mu g/m^3$ for NHL, and 1.02×10^{-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-dose to low-dose extrapolation. The unit risk estimate for RCC 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 RCC risk from peak exposures; however, there remained an apparent dose-response relationship for RCC 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 MOA is operative for TCE-induced kidney tumors supports the linear low-dose extrapolation that was used (U.S. EPA, 2005b).

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. study is a relatively small case-control study, with only 86 RCC 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 RCC incidence is about 2-fold.

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, report 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 RCC at a $p = 0.05$ significance level. Cutting fluids and other petroleum oils were associated with RCC at a $p = 0.1$ significance level; however, further modeling suggested no association with RCC 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. Body mass index (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 RCC, 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 RCC 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 tumor incidence data and summing across all the tumor 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 RCC only, and so the risk estimate derived from it does not represent all the tumor 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 tumor 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 tumor type approximate the relative values of the lifetime background incidence risks for those tumor types. In other words, at least on a proportional basis, the lifetime background incidence risks (for the United States population) for each site approximate the age-specific background incidence risks for the study populations. A further assumption is that the lifetime risk of RCC up to 85 years is an adequate approximation to the full lifetime risk, which is what was used for the other two tumor types. The first calculation, based on the results of the meta-analyses for the three tumor 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 relative risk estimates (RRm's) 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 tumor types. Second, it is assumed that the RRm's, 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 RRm for kidney cancer, for which RCC estimates from individual studies were used when available, is a good estimate for the overall RR for RCC and that the RRm 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 tumor types, has the advantage of having RR estimates that are directly comparable. In addition, the Raaschou-Nielsen et al. study provided data for the precise tumor types of interest for the calculation, i.e., RCC, 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 tumor 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 + 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 tumor type for which the weight of evidence was sufficient to conclude that TCE-induced carcinogenesis operates through a mutagenic MOA. However, it may be that TCE operates through a mutagenic MOA for other tumor types as well or that it operates through other MOAs 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 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).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___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]

_VI. BIBLIOGRAPHY

Substance Name – Trichloroethylene
CASRN – 79-01-6
Section VI. Last Revised -- 00/00/0000

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_VII. REVISION HISTORY

Substance Name – Trichloroethylene
CASRN – 79-01-6
File First On-Line 00/00/00

Date	Section	Description
__/__/__		
__/__/__		
__/__/__		
__/__/__		

_VIII. SYNONYMS

Substance Name – Trichloroethylene
CASRN – 79-01-6
Section VIII. Last Revised -- 00/00/0000

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