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Tetrachloroethylene (Perchloroethylene) (CASRN: 127-18-4)

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Reference Dose for Chronic Oral Exposure (RfD)

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Tetrachloroethylene (Perchloroethylene); CASRN 127-18-4; 02/10/2012

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

STATUS OF DATA FOR Tetrachloroethylene (Perchloroethylene)

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	02/10/2012
Chronic Inhalation RfC Assessment (I.B.)	on-line	02/10/2012

Carcinogenicity Assessment (II.)

on-line

02/10/2012

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS**I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE**

Substance Name — Tetrachloroethylene (Perchloroethylene)

CASRN — 127-18-4

Section I.A. Last Revised — 02/10/2012

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the [guidance documents](#) for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The RfD of 0.006 mg/kg-day replaces the previous RfD of 0.01 mg/kg-day entered on the IRIS database on 03/01/1988. The previous RfD was based on a NOAEL of 14 mg/kg-day ([Buben and O'Flaherty, 1985](#)), and a composite UF of 1,000 (10 for extrapolation from rats to humans, 10 for human variation, and 10 for extrapolating to chronic exposure conditions).

I.A.1. CHRONIC ORAL RfD SUMMARY

Principal Study / Critical Effect	POD (mg/kg-day) *	UF	Candidate RfDs (mg/kg-day)	RfD (mg/kg-day) **
Echeverria et al. (1995): neurotoxicity (reaction time, cognitive effects) in occupationally-exposed adults	LOAEL = 9.7	1,000	0.0097	0.006
Cavalleri et al. (1994): neurotoxicity (color vision) in occupationally-exposed adults	LOAEL = 2.6	1,000	0.0026	

*Derived by route-to-route extrapolation from inhalation exposure using PBPK model of Chiu and Ginsberg ([2011](#)).

**The RfD is supported by the two principal studies, as a midpoint of the range of available values (then rounded to one significant figure).

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

The database of human and animal studies of tetrachloroethylene is adequate to support derivation of an oral reference value. To derive an RfD, the application of pharmacokinetic

models for a route-to-route extrapolation of the inhalation studies was utilized because the available oral studies were less well suited for dose-response analysis. Please refer to Section 5.1 of the IRIS *Toxicological Review of Tetrachloroethylene* (U.S. EPA, 2012) for further discussion of the database of inhalation studies. A number of targets of toxicity from chronic exposure to tetrachloroethylene have been identified in published animal and human studies. These targets include the central nervous system, kidney, liver, immune and hematologic system, and development and reproduction. In general, neurological effects were found to be associated with lower tetrachloroethylene inhalation exposures.

The nervous system is an expected target with oral tetrachloroethylene exposures because tetrachloroethylene and metabolites produced from inhalation exposures will also reach the target tissue via oral exposure. In addition, other organ systems such as the liver and kidney are common targets associated with both inhalation and oral routes of exposure which supports the use of route extrapolation to compare PODs for oral and inhalation exposure. In addition, differences in first-pass metabolism between oral and inhalation exposures can be adequately accounted for by the PBPK model (Chiu and Ginsberg, 2011). For these reasons, the inhalation neurotoxicity studies used to derive the RfC (see I.B.2) are chosen as principal studies for the RfD: Echeverria et al. (1995) and Cavalleri et al. (1994). Candidate RfDs span a range from 2.6×10^{-3} to 9.7×10^{-3} mg/kg-day. The RfD for tetrachloroethylene is 6×10^{-3} mg/kg-day, the midpoint of this range rounded to one significant figure.

I.A.3. UNCERTAINTY FACTORS

Candidate RfDs for tetrachloroethylene were derived by dividing the route-to-route extrapolated points of departures (PODs) of 2.6 mg/kg-day (Cavalleri et al., 1994) and 9.7 mg/kg-day (Echeverria et al., 1995) by a total UF of 1,000, comprised of 10 for interindividual variability, 10 for extrapolation from a LOAEL to a NOAEL, and 10 for database uncertainty. The application of uncertainty factors is based on EPA's *A Review of the Reference Dose and Reference Concentration Processes* [U.S. EPA (2002); Section 4.4.5], which addresses five areas of uncertainty.

- A UF of 10 was applied for to account for human variability in the effects that were used for the for the derivation of the RfD. The principal studies are based on occupationally exposed subjects, who are generally healthier than the overall population, and, thus, provide no data to determine the relative effects of susceptible population including children, elderly, and/or people with compromised health. Additionally, no information was presented in the human studies with which to examine variation among subjects. Quantitative analyses have been carried out by Clewell et al. (2004) and Pelekis et al. (2001) evaluating pharmacokinetic variation between adults and children for tetrachloroethylene and its metabolites using physiologically based pharmacokinetic (PBPK) models. However, validation of these results for various life-stages and further refinement of the parameters in the model have not been conducted.
- A UF of 1 was applied to account for interspecies variability in extrapolation from laboratory animals to humans because the studies and critical endpoints were from human studies.
- A UF of 1 was applied for the use of data from subchronic study to assess potential effects from chronic exposure because, as with the RfC derivation described in Section 5.1.3 (U.S. EPA, 2011) for the human studies, the PODs are based on studies involving chronic exposure.

- A UF of 10 was applied for the extrapolation from a LOAEL to a NOAEL because the PODs from the studies were LOAELs.
- A UF of 10 has been applied to address the lack of data to adequately characterize the hazard and dose response in the human population. The following critical data gaps have been identified: uncertainties associated with database deficiencies on neurological, developmental, and immunological effects. The two studies (Echeverria et al., 1995; Cavalleri et al., 1994) used to derive the RfD evaluated neurotoxicity following occupational exposures with PODs 3- to 100-fold higher than those identified from residential studies [Storm et al. (2011), previously reported in NYSDOH, 2010; Schreiber et al., 2002; Altmann et al., 1995]. In comparison to the occupational studies, the available residential studies were judged to be more limited for developing an RfD, based on consideration of the study design (population comparability) and/or selection of neurological methods. However, they provide human evidence of neurotoxicity following tetrachloroethylene exposure in a residential setting, with reaction time deficits, visual system dysfunction, and cognitive performance deficits.

In addition, data characterizing dose-response relationships and chronic visuospatial functional deficits and the cognitive effects of tetrachloroethylene exposure under controlled laboratory conditions are lacking. Data from acute studies in animals (Oshiro et al., 2008; Umezue et al., 1997; Warren et al., 1996) suggest that cognitive function is affected by exposure to tetrachloroethylene. These studies do not address the exposure-response relationship for subchronic and chronic tetrachloroethylene exposures on cognitive functional deficits observed in humans [e.g., Altmann et al. (1995); Echeverria et al. (1995); Seeber (1989)]. There is also a lack of cognitive testing following exposures of longer than acute duration, including beginning during development. Visual system dysfunction and processing of visuospatial information are sensitive endpoints in human studies. The exposure-response relationship of these functional deficits could be evaluated more definitively with studies using homologous methods that examine retinal and visual function in experimental animals. However, there has been a limited evaluation of effects of chronic exposure to tetrachloroethylene on visual function in rodents, with the exception of the evoked potential studies by Mattsson et al. (1998). These types of studies could help determine whether there are both peripheral and central effects of tetrachloroethylene exposure on visual perception, and they could be used as an animal model to better define the exposure-response relationships in humans.

Finally, additional data are needed to assess the potential hematological and immunological effects of tetrachloroethylene. In humans, Emara et al. (2010) reported changes in various standard hematological measures in subjects with mean tetrachloroethylene blood levels of 1.685 mg/L. The limited laboratory animal studies of hematological toxicity demonstrated an effect of tetrachloroethylene exposure on red blood cells [decreased RBCs (Ebrahim et al., 2001), or decreased erythrocyte colony-forming units (Seidel et al., 1992)], with reversible hemolytic anemia observed in female mice exposed to low drinking water levels (0.05 mg/kg-day) of tetrachloroethylene beginning at 2 weeks of age in one series of studies (Marth et al., 1989; Marth, 1987; Marth et al., 1985a; Marth et al., 1985b). Ebrahim et al. (2001) also observed decreased hemoglobin, platelet counts, and packed cell volume, and increased WBC counts. Although additional corroborating studies are lacking, the observation of an effect at a low exposure level raises additional concern about hematological and immunological effects. The fact that other solvents [e.g., toluene, and the structurally similar solvent trichloroethylene (Cooper et al., 2009)] have been associated with immunotoxicity contributes further concern about this gap in the database for tetrachloroethylene.

In summary, candidate RfDs for tetrachloroethylene were developed through a route-to-route extrapolation from the PODs for the following endpoints from neurotoxicological studies of occupational tetrachloroethylene exposure: color vision changes (Cavalleri et al., 1994) and cognitive and reaction time changes (Echeverria et al., 1995). The oral exposure POD equivalent to the continuous inhalation exposure NOAELs or LOAELs was estimated via PBPK

modeling. The resulting PODs were 2.6 mg/kg-day (Cavalleri et al., 1994) and 9.7 mg/kg-day (Echeverria et al., 1995). The same composite UF of 1,000 that was used for the RfC derivation was applied to each of these PODs. The candidate RfDs from these studies span a range from 2.6×10^{-3} to 9.7×10^{-3} mg/kg-day. The RfD for tetrachloroethylene is **6×10^{-3} mg/kg-day**, the midpoint of this range rounded to one significant figure. This RfD is equivalent to a drinking water concentration of 0.21 mg/L, assuming a body weight of 70 kg and a daily water consumption of 2 L.

I.A.4. ADDITIONAL STUDIES/COMMENTS

The present analysis defines a POD using the traditional NOAEL/LOAEL approach. As discussed in Section 5.1.2 of the *Toxicological Review of Tetrachloroethylene* (U.S. EPA, 2012), the data from the principal studies were not amenable to dose-response modeling. This assessment has attempted to expand the database for derivation of an RfD using relevant inhalation data and route-to-route extrapolation with the aid of a PBPK model (refer to Section 3.5 of the *Toxicological Review of Tetrachloroethylene* (U.S. EPA, 2012)). Several factors support the use of route-to-route extrapolation for tetrachloroethylene. Tetrachloroethylene has been shown to be rapidly and well absorbed by both the oral and inhalation routes of exposure (ATSDR, 1997). Additionally, the metabolic pathways and kinetics of excretion with oral exposure are similar to those of inhalation exposure (ATSDR, 1997). Furthermore, the data for oral administration indicate a pattern of effects similar to that of inhalation exposure. PBPK modeling was also used with suitable studies in animals in order to extrapolate to human equivalent doses (HEDs). It is not clear if the noncancer effects observed in humans are the result of tetrachloroethylene itself and/or one or more metabolites. However, tetrachloroethylene in the blood can be presumed to be a step in the toxicity pathway. Therefore, area under the curve (AUC) of blood tetrachloroethylene concentration derived from PBPK modeling is considered the best surrogate for an internal dose. The use of blood tetrachloroethylene provides an attempt to account for breathing rates and to adjust for processes related to tetrachloroethylene toxicokinetics, and it is assumed to better reflect tetrachloroethylene toxicokinetics than use of default methodologies. Moreover, based on the results of the harmonized PBPK model (Chiu and Ginsberg, 2011), the sensitivity to the choice of dose metric for route-to-route extrapolation is low, with alternative dose metrics such as GSH metabolism, oxidative metabolism, or trichloroacetic acid (TCA) in blood giving route-to-route conversions within 1.4-fold of the conversion based on tetrachloroethylene in blood. Importantly, the PBPK model accounts for the potential first-pass effect of liver metabolism from oral exposure, which was found to be minimal.

The harmonized PBPK model of Chiu and Ginsberg (2011) was used to derive the continuous oral dose (i.e., in mg/kg-day) that would result in the same tetrachloroethylene in blood AUC as that following a continuous inhalation exposure from the two studies (Echeverria et al., 1995; Cavalleri et al., 1994). While the model utilizes data from some healthy adult volunteers, it cannot be considered to address pharmacokinetic variation in the full human population. The oral exposure scenario was also modeled as continuous (i.e., a constant oral dose rate in mg/kg-day), because at these exposure levels, the AUC of tetrachloroethylene in blood is insensitive to the exposure pattern.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

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

Study — Medium
Database — Medium
RfD — Medium

A confidence level of high, medium, or low is assigned to the study used to derive the RfD, the overall database, and the RfD itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). The overall confidence in the RfD is medium. Although the confidence in the evidence of neurotoxicological hazard is high, the estimates from studies for which candidate RfDs were calculated are of medium confidence. These studies were considered to be methodologically sound based on study quality attributes, including study population selection, exposure measurement methods, and endpoint measurement methods. Other strengths are that they are human studies of chronic duration, obviating the need for extrapolation across species and exposure duration. However, high confidence was not attained for the studies for which candidate RfDs were calculated because they identified a LOAEL rather than a NOAEL, and dose-response modeling could not be used for POD derivation due to lack of sufficient data [e.g., no control group (Echeverria et al., 1995) or lack of an important covariate (age) (Cavalleri et al., 1994)]. Additionally, the studies for which candidate RfDs were calculated are of occupationally exposed subjects; no data concerning potential susceptibility or variability among subjects were available. Because of the adequacy of the PBPK model (Chiu and Ginsberg, 2011) for extrapolating from inhalation to oral exposures, the use of inhalation studies for deriving the RfD did not decrease confidence.

Medium confidence in the database is based on a number of limitations of both the human and animal literature. Regarding neurotoxicity, there is a need for high quality epidemiologic studies of residential exposures and chronic-duration animal studies (including in developing animals). A fuller characterization is also needed of the noncancer effects other than the critical effect of neurotoxicity, particularly immunological and hematological effects.

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

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

Source Document — U.S. EPA ([2012](#))

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and has been 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 A of the *Toxicological Review of Tetrachloroethylene (Perchloroethylene)* (U.S. EPA, 2012). ***To review this appendix, exit to [the toxicological review, Appendix A, EPA Response to Major External Peer-Review and Public Comments \(PDF\)](#).***

Agency Completion Date — 02/10/2012

___ 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 —Tetrachloroethylene (Perchloroethylene)

CASRN – 127-18-4

Section I.B. Last Revised –02/10/2012

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 toxic effects for both the respiratory system (portal-of-entry) and for 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.

An RfC for tetrachloroethylene was not previously available on the IRIS database.

___ I.B.1. CHRONIC INHALATION RfC SUMMARY

Principal Study / Critical Effect	POD (mg/m^3)	UFs	Candidate RfDs (mg/m^3)	RfC (mg/m^3)*
Echeverria et al. (1995): neurotoxicity (reaction time, cognitive effects) in occupationally-exposed adults	LOAEL = 56	1,000	0.056	0.04
Cavalleri et al. (1994): neurotoxicity (color vision) in occupationally-exposed adults	LOAEL = 15	1,000	0.015	

*RfC is supported by the two principal studies, as the midpoint of the range of available values (then rounded to one significant figure).

___ I.B.2. PRINCIPAL AND SUPPORTING STUDIES

The database of human and animal studies of tetrachloroethylene is adequate to support derivation of an inhalation reference value. A number of targets of toxicity from chronic exposure to tetrachloroethylene have been identified in animal and human studies. These targets include the central nervous system, kidney, liver, immune and hematologic system,

and development and reproduction. In general, neurological effects were found to be associated with lower tetrachloroethylene exposures.

The evidence for neurotoxicity in humans includes controlled experimental chamber (Altmann et al., 1990; Hake and Stewart, 1977) and epidemiologic (Spinatonda et al., 1997; Altmann et al., 1995; Echeverria et al., 1995; Ferroni et al., 1992; Seeber, 1989; Hake and Stewart, 1977) studies that used standardized neurobehavioral batteries or employed assessment of visual function [Storm et al. (2011), previously reported in NYSDOH (2010); Schreiber et al., 2002; Gobba et al., 1998; Cavalleri et al., 1994], a neurological outcome known to be sensitive to volatile organic compounds. Of the 12 candidate studies in humans, seven epidemiological studies of tetrachloroethylene examined occupational exposure (Schreiber et al., 2002; Gobba et al., 1998; Spinatonda et al., 1997; Echeverria et al., 1995; Cavalleri et al., 1994; Ferroni et al., 1992; Seeber, 1989), three epidemiological studies examined residential exposure to tetrachloroethylene [Storm et al. (2011), previously reported in NYSDOH (2010); Schreiber et al., (2002); Altmann et al. (1995)], and 2 were acute experimental chamber studies (Altmann et al., 1990; Hake and Stewart, 1977). Together, the epidemiologic evidence supports an inference of a broad range of cognitive, motor, behavioral, and visual functional deficits following tetrachloroethylene exposure (U.S. EPA, 2004).

The research in animal models comprises acute and subchronic studies of the effects of tetrachloroethylene on functional neurological endpoints (functional observation battery, motor activity) (Oshiro et al., 2008; Kjellstrand et al., 1985), on sensory system function as assessed by evoked potential (Boyes et al., 2009; Mattsson et al., 1998) or pathological changes in the brain (Wang et al., 1993). The studies in animal models support the human studies, with notable effects on motor activity and motor function following exposure to tetrachloroethylene during either adulthood or the developmental period. Changes in evoked potentials following acute and subchronic exposures were also seen. In addition, postmortem effects in animals were observed with pathological alterations in brain DNA, RNA, or protein levels and brain-weight changes.

Three epidemiological studies of residential exposures were examined as candidate principal studies for deriving an RfC [Storm et al. (2011), previously reported in NYSDOH (2010); Schreiber et al., 2002; Altmann et al., 1995]. Residential exposures come closest to the chronic, continuous exposures addressed by reference values. The exposed populations in these studies lived in buildings colocated with dry cleaners. Additional strengths of all of these studies included high quality exposure assessment, matching of controls by age and sex, and use of standardized testing. In addition, statistical analyses adjusted for race/ethnicity, age, and other covariates such as smoking or alcohol use. On the other hand, there were differences in comparability between referent and exposed groups in each of these studies for which statistical analyses could not sufficiently adjust, limiting their use as principal studies. These studies nonetheless provide qualitative evidence for hazard identification of neurological deficits in visual function, reaction time, and cognitive function. The database of residential studies also adds support for the choice of key endpoints in principal studies and informs the selection of UFs.

The two human controlled exposure studies (Altmann et al., 1990; Hake and Stewart, 1977) were of fewer subjects and shorter exposure durations, and effects were observed at higher exposure concentrations than chronic studies of residential and occupational exposure. While subjects in the Altmann et al. (1990) study could serve as their own controls, there was not an unexposed group. Therefore, neither study was selected as a principal study given the availability of suitable human data of chronic duration. These studies do provide qualitative

evidence for hazard identification of neurological deficits in visual function and neurological function and add support for choice of key endpoints in principal studies.

Seven occupational studies assessed visual function or other neurobehavioral effects and were considered as candidate studies for deriving the RfC (Schreiber et al., 2002; Gobba et al., 1998; Spinatonda et al., 1997; Echeverria et al., 1995; Cavalleri et al., 1994; Ferroni et al., 1992; Seeber, 1989). The primary strength of each of these studies is their use of standardized test methodology to evaluate neurobehavioral or visual function. Additional details regarding the evaluation of occupational study characteristics that informed selection of candidate studies are provided in Section 5.1.1 of the *Toxicological Review of Tetrachloroethylene* (U.S. EPA, 2012). Of these studies, Cavalleri et al. (1994) and Echeverria et al. (1995) are considered principal studies for the derivation of the RfC. Endpoints selected for the candidate RfCs were reaction time measures (Echeverria et al., 1995), cognitive changes (Echeverria et al., 1995), and visual function changes (Cavalleri et al., 1994).

Echeverria et al. (1995) examined 65 dry cleaners in Detroit, MI, using a standardized neurobehavioral battery and found changes in cognitive and visuospatial function. A LOAEL of 156 mg/m^3 [$\text{LOAEL}_{\text{HEC}} = 56 \text{ mg/m}^3$] (time-weighted average mean concentration) was identified, based on comparison of the two higher exposure categories with an internal referent group comprising mainly counter clerks, who were matched to exposed dry cleaners on age and education. Changes of 4–14% from internal referent levels, depending on subtest, were observed at the LOAEL. The study had a high quality exposure-assessment approach and appropriate statistical analyses that adjusted for covariates including alcohol. A potential selection bias may have resulted from the 18% participation rate among dry-cleaning shop owners, if the low participation could be explained by the health status of employees. The study also lacked an unexposed referent group; subjects were categorized into three exposure groups. Without an unexposed control group, the exposure level for the lowest exposure group (i.e., the internal referent group) cannot be classified as a NOAEL or a LOAEL. This study was of relatively good quality in terms of the comparability of referent and exposed groups, measurement of effect, and measurement of exposure and, although there are concerns about the lack of an unexposed referent group, this study was used to derive a candidate RfC.

Cavalleri et al. (1994) and Gobba et al. (1998) are two studies of the same exposed population. Cavalleri et al. (1994) reported poorer performance (6% decrement on average) on a test of color vision among 35 dry cleaning and laundry workers compared to 35 controls matched on age, alcohol consumption, and smoking. The LOAEL for all workers in this study was 42 mg/m^3 [$\text{LOAEL}_{\text{HEC}} = 15 \text{ mg/m}^3$] (time-weighted average mean concentration). Controls were not matched on education or intelligence, but these factors have not been shown to be associated with color vision. Exposure was assessed for individual subjects from personal monitoring over the full work shift and represented an 8-hour time-weighted average. Standard testing methods, including an established protocol, were used to detect changes in color vision, which were assessed by the Lanthony D-15 Hue desaturated panel. The investigators' statistical analyses included comparison of group mean Color Confusion Indexes (CCIs) by the arithmetic mean of three exposure groupings: all workers (42 mg/m^3), dry cleaners (49 mg/m^3), and ironers (33 mg/m^3), and multiple logistic regression analyses which adjusted for effects of age, alcohol consumption, and smoking.

Gobba et al. (1998) examined color vision in 33 of these 35 dry cleaners and laundry workers after a 2-year period and reported a further decrement in color vision (9% decrement on

average) among 19 subjects whose geometric mean exposure had increased from 12 mg/m³ to 29 mg/m³ over the 2-year period. No improvement was observed among 14 subjects whose geometric mean exposure had decreased from 20 mg/m³ to 5 mg/m³. The mean responses of both subgroups supported a persistence of deficits in visual function and suggested a worsening of effects when exposure increased for individuals. A strength of Gobba et al. (1998) is subjects serving as their self-controls, with scores on the test of color vision compared from the initial and follow-up studies. Given the vision deficits reported by Cavalleri et al. (1994), Gobba et al. (1998) serves to confirm and extend those findings.

Cavalleri et al. (1994) is preferred to Gobba et al. (1998) for candidate reference value derivation, for several reasons. First, the earlier study more clearly associated a deficit in color vision with tetrachloroethylene exposure, through comparison to a suitable and well characterized, unexposed reference group. The Gobba et al. (1988) study did not include unexposed controls and, therefore, cannot distinguish the possible impact of age on the CCI scores of subjects who were 2 years older at the second evaluation. Second, the Gobba et al. (1998) study suggests that the earlier exposure was sufficient to cause the CCI deficit in at least those subjects ($n = 14$) whose exposure decreased after the earlier evaluation. While the Gobba et al. (1998) study also demonstrated further deficits in workers whose exposure increased after the first study ($n = 19$), it is unclear how to relate the higher measurement to the incremental deficit, given the lack of improvement in the subset with decreased exposure and the lack of information concerning the other confounding variables considered in the first evaluation—absolute age, smoking, and alcohol status. In any case, a deficit existed in this subset before the follow-up period, at a lower exposure than that of the second evaluation. Third, the exposures in Cavalleri et al. (1994) were reported as time-weighted average arithmetic means, which are expected to represent total risk better than time-weighted average geometric means [as reported in Gobba et al. (1998)] when data are grouped (Crump, 1998). The POD was, therefore, taken from the Cavalleri et al. (1994) study. The exposure level for the full study sample is used as the LOAEL for several reasons. Although no apparent CCI deficit was observed in ironers, their reported exposure range (0.52–11.28 ppm, or 3.5–76 mg/m³) was completely contained within the range of exposures for dry cleaners (0.38–31.19 ppm, or 2.6–210 mg/m³). Yet elevated CCI scores were observed at exposures lower than the mean exposure of the ironers (4.8 ppm, or 33 mg/m³), indicating that the mean exposure of the ironers cannot be considered a NOAEL. For these reasons, Cavalleri et al. (1994) is used to derive a candidate RfC.

The present analysis defines a POD using the traditional NOAEL/LOAEL approach. The NOAELs/LOAELs were adjusted to an equivalent continuous exposure (U.S. EPA, 1994), so that comparisons could be made between studies. Ambient (inhaled) concentration of tetrachloroethylene was used as the dose metric in deriving the RfC. Because the application of dose-response modeling offers advantages over the use of NOAELs/LOAELs, the data sets from the endpoints in the two studies (Echeverria et al., 1995; Cavalleri et al., 1994) were evaluated for feasibility of dose-response modeling. In both studies, it was determined that PODs could not be derived using dose-response modeling.

____ I.B.3. UNCERTAINTY FACTORS

Candidate RfCs for tetrachloroethylene were derived by dividing the PODs of 15 mg/m³ (Cavalleri et al., 1994) and 56 mg/m³ (Echeverria et al., 1995) by a total UF of 1,000, comprised of 10 for interindividual variability, 10 for extrapolation from a LOAEL to a NOAEL, and 10 for database uncertainty. The application of uncertainty factors is based on EPA's A

Review of the Reference Dose and Reference Concentration Processes [U.S. EPA (2002); Section 4.4.5], which address five areas of uncertainty.

- A UF of 10 was applied for to account for human variability in the effects that were used for the derivation of the RfC. The principal studies are based on occupationally exposed subjects, who are generally healthier than the overall population, and, thus, provide no data to determine the relative effects of susceptible population including children, elderly, and/or people with compromised health. Additionally, no information was presented in the human studies with which to examine variation among subjects. Quantitative analyses have been carried out by Clewell et al. (2004) and Pelekis et al. (2001) evaluating pharmacokinetic variation between adults and children for tetrachloroethylene and its metabolites using physiologically based pharmacokinetic (PBPK) models. However, validation of these results for various life-stages and further refinement of the parameters in the model have not been conducted.
- A UF of 1 was applied to account for interspecies variability in extrapolation from laboratory animals to humans because the principal studies and critical endpoints were from human studies.
- A UF of 1 was applied for the use of data from subchronic study to assess potential effects from chronic exposure because the PODs are based on studies involving chronic exposure (refer to Section 5.1.3).
- A UF of 10 was applied for the extrapolation from a LOAEL to a NOAEL because the PODs from the studies were LOAELs.
- A UF of 10 has been applied to address the lack of data to adequately characterize the hazard and dose response in the human population. The following critical data gaps have been identified: uncertainties associated with database deficiencies on neurological, developmental, and immunological effects. The two studies (Echeverria et al., 1995; Cavalleri et al., 1994) used to derive the RfC evaluated neurotoxicity following occupational exposures with PODs 3- to 100-fold higher than those identified from residential studies [Storm et al. (2011), previously reported in NYSDOH (2010); Schreiber et al., 2002; Altmann et al., 1995]. In comparison to the occupational studies, the available residential studies were judged to be more limited for developing an RfC, based on consideration of the study design (population comparability) and/or selection of neurological methods. However, they provide human evidence of neurotoxicity following tetrachloroethylene exposure in a residential setting, with reaction time deficits, visual system dysfunction, and cognitive performance deficits.

In addition, data characterizing dose-response relationships and chronic visuospatial functional deficits and the cognitive effects of tetrachloroethylene exposure under controlled laboratory conditions are lacking. Data from acute studies in animals (Oshiro et al., 2008; Umezue et al., 1997; Warren et al., 1996) suggest that cognitive function is affected by exposure to tetrachloroethylene. These studies do not address the exposure-response relationship for subchronic and chronic tetrachloroethylene exposures on cognitive functional deficits observed in humans [e.g., Altmann et al. (1995); Echeverria et al. (1995); Seeber (1989)]. There is also a lack of cognitive testing following exposures of longer than acute duration, including beginning during development. Visual system dysfunction and processing of visuospatial information are sensitive endpoints in human studies. The exposure-response relationship of these functional deficits could be evaluated more definitively with studies using homologous methods that examine retinal and visual function in experimental animals. However, there has been a limited evaluation of effects of chronic exposure to tetrachloroethylene on visual function in rodents, with the exception of the evoked potential studies by Mattsson et al. (1998). These types of studies could help determine whether there are both peripheral and central effects of tetrachloroethylene exposure on visual perception, and they could be used as an animal model to better define the exposure-response relationships in humans.

Finally, additional data are needed to assess the potential hematological and immunological effects of tetrachloroethylene. In humans, Emara et al. (2010) reported changes in various standard hematological measures in subjects with mean tetrachloroethylene blood levels of 1.685 mg/L. The limited laboratory animal studies of hematological toxicity demonstrated an effect of tetrachloroethylene exposure on red blood cells [decreased RBCs (Ebrahim et al., 2001), or decreased erythrocyte colony-forming units (Seidel et al., 1992)], with reversible hemolytic anemia observed in female mice exposed to low drinking water levels (0.05 mg/kg-day) of tetrachloroethylene beginning at 2 weeks of age in one series of studies (Marth et al., 1989; Marth, 1987; Marth et al., 1985a; Marth et al., 1985b). Ebrahim et al. (2001) also observed decreased hemoglobin, platelet counts, and packed cell volume, and increased WBC counts. Although additional corroborating studies are lacking, the observation of an effect at a low exposure level raises additional concern about hematological and immunological effects. The fact that other solvents [e.g., toluene, and the structurally similar solvent trichloroethylene (Cooper et al., 2009)] have been associated with immunotoxicity contributes further concern about this gap in the database for tetrachloroethylene.

These UFs were applied to each of the following endpoints from the selected neurotoxicological studies of occupational tetrachloroethylene exposure: color vision changes (Cavalleri et al., 1994) and cognitive and reaction time changes (Echeverria et al., 1995).

The candidate RfCs from these two studies span a range from 0.015 to 0.056 mg/m³. The RfC for tetrachloroethylene is **0.04 mg/m³**, the midpoint of this range rounded to one significant figure.

___ I.B.4. ADDITIONAL STUDIES/COMMENTS

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

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

Study — Medium

Data Base — Medium

RfC — Medium

A confidence level of high, medium, or low is assigned to the study used to derive the RfC, the overall database, and the RfC itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). The overall confidence in the RfC is medium. Although the confidence in the evidence of neurotoxicological hazard is high, the estimates from studies for which candidate RfCs were calculated are of medium confidence. These studies were considered to be methodologically sound based on study quality attributes, including study population selection, exposure measurement methods, and endpoint measurement methods. Other strengths are that they are human studies of chronic duration, obviating the need for extrapolation across species and exposure duration. However, high confidence was not attained for the studies for which candidate RfCs were calculated because they identified a LOAEL rather than a NOAEL, and dose-response modeling could not be used for POD derivation due to lack of sufficient data [e.g., no control group (Echeverria et al., 1995) or lack of an important covariate (age) (Cavalleri et al., 1994)]. Additionally, the studies for which candidate RfCs were calculated are of occupationally exposed subjects; no data concerning potential susceptibility or variability among subjects were available.

Medium confidence in the database is based on a number of limitations of both the human and animal literature. Regarding neurotoxicity, there is a need for high quality epidemiologic studies of residential exposures and chronic-duration animal studies (including in developing animals). A fuller characterization is also needed of the noncancer effects other than the critical effect of neurotoxicity, particularly immunological and hematological effects.

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

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

Source Document — U.S. EPA ([2012](#))

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and has been 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 A of the *Toxicological Review of Tetrachloroethylene (Perchloroethylene)* (U.S. EPA, 2012). **To review this appendix, exit to the toxicological review, Appendix A, EPA Response to Major External Peer-Review and Public Comments (PDF).**

Agency Completion Date — 02/10/2012

___ 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 — Tetrachloroethylene (Perchloroethylene)

CASRN — 127-18-4

Section II. Last Revised — 02/10/2012

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* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). 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, either per µg/L drinking water (see Section II.B.1.) or per µg/m³ air breathed (see Section II.C.1.). Second,

the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A cancer assessment of tetrachloroethylene was not previously available on the IRIS database.

___II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

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

Following EPA (2005a) *Guidelines for Carcinogen Risk Assessment*, tetrachloroethylene is "likely to be carcinogenic in humans by all routes of exposure." This characterization is based on suggestive evidence of carcinogenicity in epidemiologic studies and conclusive evidence that the administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence (JISA, 1993; NTP, 1986; NCI, 1977).

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

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

___II.A.2. HUMAN CARCINOGENICITY DATA

The available epidemiologic studies provide a pattern of evidence associating tetrachloroethylene exposure and several types of cancer, specifically bladder cancer, non-Hodgkin lymphoma and multiple myeloma. Associations and exposure response relationships for these cancers were reported in studies using higher quality (more precise) exposure-assessment methodologies for tetrachloroethylene. Confounding by common lifestyle factors such as smoking are unlikely explanations for the observed results. For other sites, including esophageal, kidney, lung, liver, cervical, and breast cancer, more limited data supporting a suggestive effect are available.

With respect to bladder cancer, the pattern of results from this collection of studies is consistent with an elevated risk for tetrachloroethylene of a relatively modest magnitude (i.e., a 10–40% increased risk). The effect estimates from five of the six studies with relatively high quality exposure-assessment methodologies ranged from 1.44 to 4.03 (Calvert et al., 2011; Lynge et al., 2006; Blair et al., 2003; Pesch et al., 2000; Aschengrau et al., 1993). An exposure-response gradient was seen in a large case-control study by Pesch et al. (2000), using a semiquantitative cumulative exposure assessment, with an adjusted odds ratio of 0.8 (95% CI: 0.6, 1.2), 1.3 (95% CI: 0.9, 1.7), and 1.8 (95% CI: 1.2, 2.7) for medium, high, and substantial exposure, respectively, compared to low exposure. A similar exposure-response pattern was not seen in the study by Lynge et al. (2000). This study examined exposure duration, however, rather than a measure that incorporated information on exposure concentration. In addition, relative risk estimates between bladder cancer risk and ever having a job title of dry-cleaner or laundry worker in four large cohort studies ranged from 1.01 to 1.44 (Pukkala et al., 2009; Wilson et al., 2008; Ji et al., 2005; Travier et al., 2002). As expected, the results from the smaller studies are more variable and less precise, reflecting their reduced statistical power. Confounding by smoking is an unlikely explanation for the findings, given the adjustment for smoking by Pesch et al. (2000) and in other case-control studies.

The results from the collection of studies pertaining to non-Hodgkin lymphoma also indicate an elevated risk for tetrachloroethylene. The results from five cohort studies that used a relatively high quality exposure-assessment methodology generally reported relative risks between 1.7 and 3.8 ([Calvert et al., 2011](#); [Seldén and Ahlborg, 2011](#); [Radican et al., 2008](#); [Boice et al., 1999](#); [Anttila et al., 1995](#)). There is also some evidence of exposure-response gradients in studies with tetrachloroethylene-specific exposure measures based on intensity, duration, or cumulative exposure ([Seidler et al., 2007](#); [Milligi et al., 2006](#); [Boice et al., 1999](#)). Higher non-Hodgkin lymphoma risks were seen in these studies in the highest exposure categories, with the strongest evidence from the large case-control study in Germany in which a relative risk of 3.4 (95% CI: 0.7, 17.3) was seen in the highest cumulative exposure category (trend p -value = 0.12) ([Seidler et al., 2007](#)). Effect estimates in studies with broader exposure assessments showed a more variable pattern ([Seldén and Ahlborg, 2011](#); [Pukkala et al., 2009](#); [Ji and Hemminki, 2006](#); [Blair et al., 2003](#); [Travier et al., 2002](#); [Cano and Pollán, 2001](#); [Lynge and Thygesen, 1990](#)). Confounding by life-style factors are unlikely explanations for the observed results because common behaviors, such as smoking and alcohol use, are not strong risk factors for non-Hodgkin lymphoma ([Besson et al., 2006](#); [Morton et al., 2005](#)).

Results from the multiple myeloma studies are based on a smaller set of studies than those of non-Hodgkin lymphoma, but results are similar. The larger cohort studies that use a relatively nonspecific exposure measure (broad occupational title of launderers and dry cleaners, based on census data) do not report an increased risk of multiple myeloma, with effect estimates ranging from 0.99 to 1.07 ([Pukkala et al., 2009](#); [Ji and Hemminki, 2006](#); [Andersen et al., 1999](#)). Some uncertainty in these estimates arises from these studies' broader exposure-assessment methodology. Results from the cohort and case-control studies with a higher quality exposure-assessment methodology, with an exposure measure developed specifically for tetrachloroethylene, do provide evidence of an association, however, with relative risks of 7.84 (95% CI: 1.43, 43.1) in women and 1.71 (95% CI: 0.42, 6.91) in men in the cohort of aircraft maintenance workers ([Radican et al., 2008](#)) and 1.5 (95% CI: 0.8, 2.9) in a case-control study in Washington [[Gold et al. \(2010b\)](#); tetrachloroethylene exposure]. [Gold et al. \(2010a; 2010b\)](#) also reported increasing risks with increasing exposure duration (based on job titles) ([Gold et al., 2010a](#)) and based on a cumulative tetrachloroethylene exposure metric ([Gold et al., 2010b](#)). A smaller case-control study ($n = 76$ cases) with tetrachloroethylene-specific exposure measures based on intensity, duration, or cumulative exposure, [Seidler et al. \(2007\)](#), observed no cases among the highest exposure groups. A small cohort study by [Boice et al. \(1999\)](#) of aerospace workers observed one death among routinely exposed subjects and six deaths among subjects with a broader definition of routine or intermittent exposure.

Suggestive but limited evidence was also seen in the collection of epidemiologic studies pertaining to tetrachloroethylene exposure and esophageal, kidney, lung, liver, cervical, and breast cancer. One difference between these sets of data and the data for bladder cancer, non-Hodgkin lymphoma, and multiple myeloma is a more mixed pattern of observed risk estimates and an absence of exposure-response data from the studies using a quantitative tetrachloroethylene-specific cumulative exposure measure.

II.A.3. ANIMAL CARCINOGENICITY DATA

One oral gavage ([NCI, 1977](#)) and two inhalation ([JISA, 1993](#); [NTP, 1986](#)) cancer bioassays provide evidence of tetrachloroethylene carcinogenicity in rats and mice. In male and female rats, inhalation exposure to tetrachloroethylene significantly increased the incidence of mononuclear cell leukemia (MCL) in independent bioassays of the F344/N ([NTP, 1986](#)) or

F344/DuCrj (JISA, 1993) strain. Tetrachloroethylene reduced MCL latency in females in both studies. In addition, the NTP (1986) bioassay reported dose-related increases in the severity of MCL in males and females. Additional tumor findings in rats included significant increases in the NTP bioassay of two rare tumor types, kidney tumors in males, and brain gliomas in males and females. The NTP (1986) bioassay reported increases in the rate of testicular interstitial cell tumors, a tumor type of high incidence in unexposed male F344 rats. Other evidence, including that brain gliomas occurred earlier with tetrachloroethylene exposure than in control animals and that the related compound trichloroethylene is a kidney carcinogen in rats and humans and a testicular carcinogen in rats, support the significance of these findings. A third rat bioassay, of oral gavage exposure in Osborne-Mendel rats, was inconclusive with respect to carcinogenicity due to a high incidence of respiratory disease in all animals and shortened survival in tetrachloroethylene-exposed animals (NCI, 1977).

In male and female mice, tetrachloroethylene exposure via inhalation (JISA, 1993; NTP, 1986) or oral gavage (NCI, 1977) significantly increased the incidence of hepatocellular adenomas and carcinomas. The NCI (1977) and NTP (1986) studies employed the B6C3F₁ strain, while the JISA study examined the Crj:BDF1 strain. The JISA study reported increases in hemangiomas or hemangiosarcomas of the liver, spleen, fat, and subcutaneous skin in exposed male Crj:BDF1 mice.

In summary, tetrachloroethylene increased the incidence of liver tumors (hepatocellular adenomas and carcinomas) in male and female mice and of MCL in both sexes of rats. These findings were reproducible in multiple lifetime bioassays employing different rodent strains and, in the case of mouse liver tumors, by inhalation and oral exposure routes. Additional tumor findings in rats included significant increases in the NTP bioassay (1986) of testicular interstitial cell tumors and kidney tumors in males, and brain gliomas in males and females. In mice, hemangiosarcomas in liver, spleen, fat, and subcutaneous skin were reported in males in the JISA study (1993).

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

There are hypothesized mode(s) of action only for rat kidney tumors and mouse liver tumors. For rat kidney tumors, the hypothesized modes of action include mutagenicity, peroxisome proliferation, $\alpha_2\mu$ -globulin nephropathy, and cytotoxicity not associated with $\alpha_2\mu$ -globulin accumulation. For mouse liver tumors, the hypothesized mode(s) of action include mutagenicity, epigenetic effects (especially DNA hypomethylation), oxidative stress, and receptor activation (focusing on a hypothesized PPAR α activation mode of action). However, the available evidence is insufficient to support the conclusion that either rat kidney or mouse liver tumors are mediated solely by one of these hypothesized modes of action. In addition, no data are available concerning the mechanisms that may contribute to the induction of other rodent tumors (including MCL, brain gliomas, or testicular interstitial cell tumors in exposed rats and hemangiosarcomas in exposed mice). Furthermore, no mechanistic hypotheses have been advanced for the human cancers suggested to be increased with tetrachloroethylene exposure in epidemiologic studies, including bladder cancer, non Hodgkin lymphoma and multiple myeloma.

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

___II.B.1. SUMMARY OF RISK ESTIMATES

____ II.B.1.1. Oral Slope Factor - 2.1×10^{-3} per mg/kg-day (2×10^{-3} per mg/kg-day, rounded to one significant figure)

The oral slope factor is derived from the BMDL₁₀, the 95% lower bound on the exposure associated with a 10% extra cancer risk, by dividing the risk (as a fraction) by the BMDL₁₀, and represents an upper bound, continuous lifetime exposure risk estimate:

BMDL₁₀, lower 95% bound on exposure at 10% extra risk – 47 mg/kg-day

BMD₁₀, central estimate of exposure at 10% extra risk – 67 mg/kg-day

The slope of the linear extrapolation from the central estimate BMD₁₀ is

$0.1/(67 \text{ mg/kg-day}) = 1.5 \times 10^{-3}$ per mg/kg-day.

The slope factor for tetrachloroethylene should not be used with exposures exceeding the point of departure (BMDL₁₀), 50 mg/kg-day (rounded to one significant figure), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of tetrachloroethylene.

The oral slope factor was developed from inhalation data (JISA, 1993) because the only available oral bioassay (NCI, 1977) had several limitations for extrapolating to lifetime risk in humans [see also Section 5.4.1 of the *Toxicological Review of Tetrachloroethylene* (U.S. EPA, 2012)]. First, the oral gavage study (NCI, 1977) used relatively high doses. Human exposures are less likely to occur in boluses, and high doses are associated with saturable metabolism processes which may involve a different profile of toxicological processes than those prevalent at environmental exposure levels. Also, the animals were dosed for only approximately 75% of the more usual 2-year period, making the oral study less useful for estimating lifetime risk. Route-to-route extrapolation from the inhalation PODs developed from the JISA study (1993) (see II.C.3.) was carried out using the human pharmacokinetic model (Chiu and Ginsberg, 2011).

____ II.B.1.2. Drinking Water Unit Risk* - 6.1×10^{-8} per µg/L (6×10^{-8} per µg/L, rounded to one significant figure)

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	2000 µg/L
E-5 (1 in 100,000)	200 µg/L
E-6 (1 in 1,000,000)	20 µg/L

* The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human, rounded to one significant figure.

____ II.B.1.3. Extrapolation Method

Multistage model (with linear extrapolation from the point of departure (BMDL₁₀), followed by route-to-route extrapolation to the oral route and interspecies extrapolation using the PBPK model of Chiu and Ginsberg (2011) .

II.B.2. DOSE-RESPONSE DATA

Tumor type — Hepatocellular adenomas or carcinomas

Test species — Male Crj:BDF1 mice

Route — Inhalation

Reference — JISA 1993)

See II.C.2 for dose-response data and II.C.3 for additional information.

II.B.3. ADDITIONAL COMMENTS

The majority of the NRC peer review panel (NRC, 2010) recommended that the mouse hepatocellular tumors be used for cancer risk estimation as described above. Some members of the NRC peer review panel recommended that the MCL data be used for cancer risk estimation. The oral slope factor would be 6×10^{-2} per mg/kg-day (rounding to one significant digit) if it were based on the male and female rat MCL data from the JISA 1993) bioassay.

II.B.4. DISCUSSION OF CONFIDENCE

A number of uncertainties underlie the cancer unit risk for tetrachloroethylene, including the choice of study, PBPK modeling and dose metrics, cross-species scaling, low-dose extrapolation, model uncertainty, statistical uncertainty in the POD, the species/gender/tumor type combination selected, and sensitive subpopulations. Some suggest risks could be higher than was estimated (e.g., selection of MCL rather than mouse liver tumors, sensitive subpopulations), while others would decrease risk estimates [e.g., use of central tendency instead of lower 95% confidence bound on the POD], or have an impact of an uncertain direction. Several uncertainties are quantitatively characterized for the significantly increased rodent tumors. These include the statistical uncertainty in the POD, the range of uncertainty in PBPK modeling and dose metrics, dose-response model uncertainty, and the species/gender/tumor type combination selected. The latter three of these could either increase or decrease risk estimates. Due to limitations in the data, particularly regarding the mode of action and relative human sensitivity and variability, the quantitative impact of other uncertainties, which may have equal or greater impact, has not been explored.

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

II.C.1. SUMMARY OF RISK ESTIMATES

II.C.1.1. Inhalation Unit Risk: 1.8×10^{-3} per ppm, or 2.6×10^{-7} per $\mu\text{g}/\text{m}^3$ (2×10^{-3} per ppm, or 3×10^{-7} per $\mu\text{g}/\text{m}^3$, rounded to one significant figure)

The inhalation unit risk is derived from the BMCL₁₀, the 95% lower bound on the exposure associated with a 10% extra cancer risk, by dividing the risk (as a fraction)

by the BMCL₁₀, and represents an upper bound, continuous lifetime exposure risk estimate:

BMCL₁₀, lower 95% bound on exposure at 10% extra risk – 57 ppm, or $3.9 \times 10^5 \mu\text{g}/\text{m}^3$.

BMC₁₀, central estimate of exposure at 10% extra risk – 80 ppm, or $5.4 \times 10^5 \mu\text{g}/\text{m}^3$.

The slope of the linear extrapolation from the central estimate BMC₁₀ is $0.1/(5.4 \times 10^5 \mu\text{g}/\text{m}^3) = 1.9 \times 10^{-7}$ per $\mu\text{g}/\text{m}^3$.

The unit risk for tetrachloroethylene should not be used with exposures exceeding the point of departure (BMCL₁₀), $4 \times 10^4 \mu\text{g}/\text{m}^3$ or 60 ppm (rounded to one significant figure), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of tetrachloroethylene.

The slope factor in terms of the internal dose metric (total liver oxidative metabolism) was converted to a unit risk in terms of human equivalent environmental inhalation using by the pharmacokinetic modeling of Chiu and Ginsberg (2011).

Air Concentrations at Specified Risk Levels:

Risk Level	Lower Bound on Concentration Estimate
E-4 (1 in 10,000)	400 $\mu\text{g}/\text{m}^3$
E-5 (1 in 100,000)	40 $\mu\text{g}/\text{m}^3$
E-6 (1 in 1,000,000)	4 $\mu\text{g}/\text{m}^3$

II.C.1.2. Extrapolation Method

Multistage model with linear extrapolation from the point of departure (BMCL₁₀), followed by extrapolation to humans using the PBPK model of Chiu and Ginsberg (2011).

II.C.2. DOSE-RESPONSE DATA

Tumor type — Hepatocellular adenomas or carcinomas

Test species — Male Crj:BDF1 mice

Route — Inhalation

Reference — JISA 1993)

Administered Concentration (ppm)	Total liver oxidative metabolism, $\text{mg}/\text{kg}^{0.75}\text{-d}$	Tumor Incidence
0	0	13/46
10	2.25	21/49
50	8.25	19/48
250	33.6	40/49

II.C.3. ADDITIONAL COMMENTS

A majority of the NRC peer review panel recommended that the mouse hepatocellular tumors be used for cancer risk estimation, as described above. Some members of the NRC peer review panel recommended that the MCL data be used for cancer risk estimation. The inhalation unit risk would be 7×10^{-2} per ppm, or 1×10^{-5} per $\mu\text{g}/\text{m}^3$ (rounding to one significant digit) if it were based on the male and female rat MCL data from the JISA 1993) bioassay.

II.C.4. DISCUSSION OF CONFIDENCE

A number of uncertainties underlie the cancer unit risk for tetrachloroethylene, including the choice of study, PBPK modeling and dose metrics, cross-species scaling, low-dose extrapolation, model uncertainty, statistical uncertainty in the POD, the species/gender/tumor type combination selected, and sensitive subpopulations. Some suggest risks could be higher than was estimated (e.g., selection of MCL rather than mouse liver tumors, sensitive subpopulations), while others would decrease risk estimates [e.g., use of central tendency instead of lower 95% confidence bound on the POD], or have an impact of an uncertain direction. Several uncertainties are quantitatively characterized for the significantly increased rodent tumors. These include the statistical uncertainty in the POD, the range of uncertainty in PBPK modeling and dose metrics, dose-response model uncertainty, and the species/gender/tumor type combination selected. The latter three of these could either increase or decrease risk estimates. Due to limitations in the data, particularly regarding the mode of action and relative human sensitivity and variability, the quantitative impact of other uncertainties, which may have equal or greater impact, has not been explored.

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

II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA (2012)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and has been 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 A of the *Toxicological Review of Tetrachloroethylene (Perchloroethylene)* (U.S. EPA, 2012). **To review this appendix, exit to the toxicological review, Appendix A, EPA Response to Major External Peer-Review and Public Comments (PDF).**

II.D.2. EPA REVIEW

Agency Completion Date — 02/10/2012

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 — Tetrachloroethylene

CASRN — 127-18-4

Section VI. Last Revised — 02/10/2012

VI.A. ORAL RfD REFERENCES

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VII. REVISION HISTORY

Substance Name — Tetrachloroethylene
 CASRN — 127-18-4
 File First On-Line 01/31/87

Date	Section	Description
12/23/1987	I.A.	RfD withdrawn.
03/01/1988	I.A.	Revised Oral RfD summary added.
02/10/2012	I., II., VI.	RfD updated. RfC and cancer assessment added.
02/11/2012	NA	<u>Archived review drafts and comments from the development of this assessment</u> are available.

VIII. SYNONYMS

Substance Name — Tetrachloroethylene
 CASRN — 127-18-4
 Section VIII. Last Revised — 02/10/2012

- 127-18-4
- Ankilostin
- Antisal 1
- Antisol 1
- Carbon bichloride
- Carbon dichloride
- Czterochloroetylen
- Dee-Solv
- Didakene
- Didokene
- Dowclene EC
- Dow-Per
- ENT 1,860
- Ethene, tetrachloro-
- Ethylene tetrachloride
- Ethylene, tetrachloro-
- Fedal-Un
- NCI-C04580
- Nema
- PCE
- PER
- Perawin
- PERC
- Perchloorethyleen, per
- Perchlor
- Perchloraethylen, per
- Perchloroethylene
- Perchloroethylene, per
- Perchloroethylene
- Perclene
- Perchloroetilene
- Percosolv
- Percosolve
- PERK
- Perklone

- Persec
- Tetlen
- Tetracap
- Tetrachlooretheen
- Tetrachloraethen
- Tetrachlorethylene
- Tetrachloroethene
- Tetrachloroethylene
- 1,1,2,2-Tetrachloroethylene.
- Tetracloroetene
- Tetraguer
- Tetraleno
- Tetralex
- Travvec
- Tetroguer
- Tetropil

IRIS Home**Chronic Health
Hazards for Non-
Carcinogenic Effects****Reference Dose for
Chronic Oral
Exposure (RfD)**

- Oral RfD
Summary
- Principal and
Supporting
Studies
- Uncertainty and
Modifying Factors
- Additional
Studies/Comments
- Confidence in the
Oral RfD
- EPA
Documentation
and Review

**Reference
Concentration for
Chronic Inhalation
Exposure (RfC)**

- Inhalation RfC
Summary
- Principal and
Supporting
Studies
- Uncertainty and
Modifying Factors
- Additional
Studies/Comments
- Confidence in the
Inhalation RfC
- EPA
Documentation
and Review

**Carcinogenicity
Assessment for
Lifetime Exposure**

**Evidence for Human
Carcinogenicity**

- Weight-of-Evidence Characterization
- Human Carcinogenicity Data
- Animal Carcinogenicity Data
- Supporting Data for Carcinogenicity

**Quantitative
Estimate of
Carcinogenic Risk
from Oral Exposure**

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

**Quantitative
Estimate of
Carcinogenic Risk
from Inhalation
Exposure**

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence
- EPA Documentation, Review and, Contacts

Bibliography

Revision History

Synonyms