IRIS SUMMARY FOR TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

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.

Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

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Tetrachloroethylene (Perchloroethylene); CASRN 127-18-4; 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/backgrd.html.

STATUS OF DATA FOR TETRACHLOROETHYLENE

File First On-Line: 01/31/1987

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 – TETRACHLOROETHYLENE
CASRN − 127-18-4
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/backgrd.html 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 IRIS 03/01/1988. The new RfD is based on the critical effect of neurotoxicity. The RfD was derived by quantitative evaluation of multiple (three) principal studies (Cavalleri et al., 1994; Echeverria et al., 1995; Seeber, 1989), and is the midpoint of the range of available values.

___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) in occupationally-exposed adults	LOAEL = 9.7	1,000	0.0097	0.006
Seeber (1989): neurotoxicity (neurobehavioral) in occupationally - exposed adults	LOAEL = 5.0	1,000	0.0050	
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).
**RfD is supported by these multiple 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 inhalation and oral reference values. The application of pharmacokinetic models for a route-to-route extrapolation of the inhalation studies expands the database of studies suitable for RfD calculation. 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 judged to be associated with lower tetrachloroethylene exposures.

The nervous system is an expected target with lower oral tetrachloroethylene exposures, because tetrachloroethylene and many 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 also common targets associated with both inhalation and either oral routes of subchronic or chronic exposure. The similarity of effects in these organ systems with either oral or inhalation exposure to tetrachloroethylene 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 three inhalation neurotoxicity studies used to derive the RfC are chosen as principal studies for the RfD: Echeverria et al. (1995); Cavalleri et al. (1994) and Seeber, (1989).

The evidence for human neurotoxicity includes 12 well-conducted epidemiological studies of tetrachloroethylene exposure by inhalation. Of these, seven examined occupational exposure (i.e., Cavalleri et al., 1994; Echeverria et al., 1995; Ferroni et al., 1992; Gobba et al., 1998; Schreiber et al., 2002; Seeber, 1989; Spinatonda et al., 1997), three examined residential exposure (i.e., Altmann et al., 1995; NYSDOH, 2010; Schreiber et al., 2002; Storm et al., In Press) and two were acute-duration experimental chamber studies (i.e., Altmann et al., 1990; Hake and Stewart, 1977). The animal database comprises acute-duration and subchronic-duration studies of the effects of tetrachloroethylene on functional neurological endpoints (functional observation battery, motor activity) (i.e., Kjellstrand et al., 1985; Oshiro et al., 2008), on sensory system function as assessed by evoked potential (i.e., Boyes et al., 2009; Mattsson et al., 1998; U.S. EPA, 1998), or pathological changes in the brain (i.e., Wang et al., 1993).

Principal study selection from these candidate studies of central nervous system effects involved evaluation of study characteristics (see Table 5-2). To summarize, human studies are preferred to animal studies, as are studies of chronic duration and in residential settings. Residential exposure is more likely to be continuous and of lower concentrations compared with the more intermittent, higher concentration exposures experienced in work settings. Three human studies were considered to be more methodologically sound based on study quality attributes, including study population selection, exposure measurement methods, and endpoint measurement methods. Thus, three studies—Seeber (1989), Cavalleri et al. (1994), and Echeverria et al. (1995)—were judged to be principal studies for deriving a reference concentration [RfC], none of which is a clearly superior candidate for identifying the point of departure [POD]. Endpoints selected for the RfC were reaction time measures (Echeverria et al., 1995), cognitive changes (Echeverria et al., 1995; Seeber, 1989), 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 [$LOAEL_{HEC}$ = 56 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. 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, however, 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 selected as a principal study.

Seeber (1989) evaluated the neurobehavioral effects of tetrachloroethylene on 101 dry-cleaning workers (employed in coin-operated or while-you-wait shops), and reported effects on several measures of cognition at a LOAEL of 83 mg/m^3 [$LOAEL_{HEC}$ = 29 mg/m^3]

(time-weighted average mean concentration), compared to referents from several department stores and receptionists from large hotels. A strength of the study was the relatively large sample sizes used for all three groups, 57, 44, and 84 subjects in the lowest, highest and referent groups, respectively. No information was provided on the methods used to identify subjects or their reasons for participating in the study, although the authors reported that 29 service technicians were excluded from participation because of either discontinuous exposure conditions with peak concentrations or long periods of no exposure. The exposure assessment targeted estimates of long-term exposure from interview data, active sampling of room air, and passive sampling of personal air, including during entire shifts in summer and in winter. This information was used in assigning dry cleaners to two exposed groups (83 and 364 mg/m^3). The administered tests of neuropsychological function included standardized tests of symptoms and personality; tests of sensorimotor function, including finger tapping and aiming; and the Mira and Santa Ana dexterity tests. Another strength of this study is its use of blinded examiners to test subjects. Because the dry-cleaner groups and the control group differed in gender ratios, age, and scores on the intelligence test, stratified regression analysis was used to statistically control for the influence of these potentially confounding factors on test scores. Additional adjustment for group differences in alcohol consumption did not alter the results. Seeber (1989) had relatively good quality in terms of the addressing comparability of referent and exposed groups, measurement of effect, and measurement of exposure. Therefore, it was selected as a principal study.

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 [$LOAEL_{HEC}$ = 15 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 was assessed by the Lanthony D-15 Hue desaturated panel. 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). Multiple logistic regression analyses 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/m^3 to 29 mg/m^3 over the 2-year period. No improvement was observed among 14 subjects whose geometric mean exposure had decreased from 20 mg/m^3 to 5 mg/m^3. 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 study. 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) as a principal study for 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 study (1998)did not include

unexposed controls, and therefore cannot distinguish the possible impact of age on the CCI scores of subjects who were two 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. study also demonstrated further deficits in those whose exposure increased after the first study (n = 19), it is not straightforward 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 (Allen et al., 1988). The point of departure (POD) was therefore taken from the Cavalleri et al. (1994) study. The exposure level for the full study sample is used as the LOAEL, using the following reasoning. Although no apparent CCI deficit was seen in ironers, their reported exposure range (0.52−11.28 ppm, or 3.5−76 mg/m^3) was completely contained within the range of exposures for dry cleaners (0.38−31.19 ppm, or 2.6−210 mg/m^3). Yet elevated CCI scores were observed at exposures lower than the mean exposure of the ironers (4.8 ppm, or 33 mg/m^3), indicating that the mean exposure of the ironers cannot be considered a NOAEL. For these reasons, Cavalleri et al. (1994) is selected as a principal study.

___I.A.3. UNCERTAINTY FACTORS

Each of the candidate studies provided lowest-observed-adverse-effect levels (LOAELs) that were selected as PODs. No adjustment of the PODs was needed for animal-to-human extrapolation uncertainty. Additionally, no adjustment was needed for subchronic-to-chronic uncertainty because the principal studies involved chronic exposures. An overall uncertainty factor of 1,000 was applied to each selected POD, comprised of the following uncertainty factors (UFs):

Human Variation

The UF of 10 was applied for human variation for all of the studies that were selected in derivation of the RfD. These studies are from 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.

LOAEL-to-NOAEL Uncertainty

A UF of 10 is generally applied when the POD is a LOAEL due to a lack of a no-observed-adverse-effect level [NOAEL]. For all of the human studies and endpoints selected (Cavalleri et al., 1994; Echeverria et al., 1995; Seeber, 1989), PODs were LOAELs and a UF of 10 was applied to these endpoints.

Database Uncertainty

A database UF of 10 has been applied to address the lack of data to adequately characterize the hazard and dose-response in the human population. A number of data gaps were identified from both the human and animal literature, including the need for high quality epidemiologic studies of residential exposures, and chronic-duration animal studies (including in developing animals) designed to define and characterize the exposure-response relationships for the observed neurotoxicological effects, particularly, reaction time, cognitive and visual function. Additionally, the available studies of immunologic and hematologic toxicity studies (e.g., Emara et al., 2010; Marth, 1987) are limited, but do raise concern for risk at exposures lower than those evaluated. The relative lack of data taken together with the concern that other structurally related solvents have been associated with immunotoxicity, particularly relating to autoimmune disease (Cooper et al., 2009), contributes to uncertainty in the database for tetrachloroethylene.

In addition, the available epidemiologic studies of residential exposures were judged to be more limited for developing an RfD (Altmann et al., 1995; NYSDOH, 2010; Schreiber et al., 2002; Storm et al., In Press) based on consideration of selection bias, residual confounding (population comparability) and/or selection of neurological methods. Yet the residential studies yielded the most sensitive neurotoxic endpoint associated with tetrachloroethylene exposure, decrement in visual contrast sensitivity (VCS). Because this specific endpoint was not evaluated in any of the occupational studies, it cannot be concluded that similar or even greater VCS changes would not occur at the higher exposures of the occupational studies. There were impairments in Color Confusion Index for one set of occupationally exposed subjects (Cavalleri et al., 1994; Gobba et al., 1998), but this effect was not evaluated in other occupational studies. There is also a lack of studies which evaluated the critical effects of reaction time, cognitive and visual functional deficits in populations exposed to tetrachloroethylene at lower than the studied occupational exposure levels, including at residential levels.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

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

Study -- High
Data Base -- Medium
RfD -- High

The overall confidence in this RfD assessment high because it is supported by medium- to high-confidence estimates from multiple human neurotoxicity studies. Additionally, quantitative dose-response analyses of the findings in other toxicity domains (i.e., kidney, liver, immunologic and hematologic, and reproductive and developmental toxicity), detailed in Section 5 (U.S. EPA, 2011), are considered to be supportive of these values.

___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 A of the

Toxicological Review of Tetrachloroethylene (Perchloroethylene)(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 – Tetrachloroethylene (Perchloroethylene)
CASRN – 127-18-4
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 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.

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

___I.B.1. CHRONIC INHALATION RfC SUMMARY

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

Seeber (1989): neurotoxicity (neurobehavioral) in occupationally-exposed adults	LOAEL = 29	1,000	0.029	
Cavalleri et al. (1994): neurotoxicity (color vision) in occupationally-exposed adults	LOAEL = 15	1,000	0.015	

* RfC is supported by these multiple 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 inhalation and oral reference values. 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 judged to be associated with lower tetrachloroethylene exposures.

The evidence for human neurotoxicity includes 12 well-conducted epidemiological studies of tetrachloroethylene exposure by inhalation. Of these, seven examined occupational exposure (i.e., Cavalleri et al., 1994; Echeverria et al., 1995; Ferroni et al., 1992; Gobba et al., 1998; Schreiber et al., 2002; Seeber, 1989; Spinatonda et al., 1997), three examined residential exposure (i.e., Altmann et al., 1995; NYSDOH, 2010; Schreiber et al., 2002; Storm et al., In Press) and two were acute-duration experimental chamber studies (i.e., Altmann et al., 1990; Hake and Stewart, 1977). The animal database comprises acute-duration and subchronic-duration studies of the effects of tetrachloroethylene on functional neurological endpoints (functional observation battery, motor activity) (i.e., Kjellstrand et al., 1985; Oshiro et al., 2008), on sensory system function as assessed by evoked potential (i.e., Boyes et al., 2009; Mattsson et al., 1998; U.S. EPA, 1998), or pathological changes in the brain (i.e., Wang et al., 1993).

Principal study selection from these candidate studies of central nervous system effects involved evaluation of study characteristics (Table 5-2; U.S. EPA, 2011). To summarize, human studies are preferred to animal studies, as are studies of chronic duration and in residential settings. Residential exposure is more likely to be continuous and of lower concentrations compared with the more intermittent, higher concentration exposures experienced in work settings. Three human studies were considered to be more methodologically sound based on study quality attributes, including study population selection, exposure measurement methods, and endpoint measurement methods. Thus, three studies—Seeber (1989), Cavalleri et al. (1994), and Echeverria et al. (1995)—were judged to be principal studies for deriving a reference concentration [RfC], none of which is a clearly superior candidate for identifying the point of departure [POD]. Endpoints selected for the RfC were reaction time measures (Echeverria et al., 1995), cognitive changes (Echeverria et al., 1995; Seeber, 1989), 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 [$LOAEL_{HEC}$ = 56 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. 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, however, 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 selected as a principal study.

Seeber (1989) evaluated the neurobehavioral effects of tetrachloroethylene on 101 dry-cleaning workers (employed in coin-operated or while-you-wait shops), and reported effects on several measures of cognition at a LOAEL of 83 mg/m^3 [$LOAEL_{HEC}$ = 29 mg/m^3] (time-weighted average mean concentration), compared to referents from several department stores and receptionists from large hotels. A strength of the study was the relatively large sample sizes used for all three groups, 57, 44, and 84 subjects in the lowest, highest and referent groups, respectively. No information was provided on the methods used to identify subjects or their reasons for participating in the study, although the authors reported that 29 service technicians were excluded from participation because of either discontinuous exposure conditions with peak concentrations or long periods of no exposure. The exposure assessment targeted estimates of long-term exposure from interview data, active sampling of room air, and passive sampling of personal air, including during entire shifts in summer and in winter. This information was used in assigning dry cleaners to two exposed groups (83 and 364 mg/m^3). The administered tests of neuropsychological function included standardized tests of symptoms and personality; tests of sensorimotor function, including finger tapping and aiming; and the Mira and Santa Ana dexterity tests. Another strength of this study is its use of blinded examiners to test subjects. Because the dry-cleaner groups and the control group differed in gender ratios, age, and scores on the intelligence test, stratified regression analysis was used to statistically control for the influence of these potentially confounding factors on test scores. Additional adjustment for group differences in alcohol consumption did not alter the results. Seeber (1989) had relatively good quality in terms of the addressing comparability of referent and exposed groups, measurement of effect, and measurement of exposure. Therefore, it was selected as a principal study.

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 [$LOAEL_{HEC}$ = 15 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 was assessed by the Lanthony D-15 Hue desaturated panel. 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). Multiple logistic regression analyses 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/m^3 to 29 mg/m^3 over the 2-year period. No improvement was observed among 14 subjects whose geometric mean exposure had decreased from 20 mg/m^3 to 5 mg/m^3. 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 study. 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) as a principal study for 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 study (1998)did not include unexposed controls, and therefore cannot distinguish the possible impact of age on the CCI scores of subjects who were two 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. study also demonstrated further deficits in those whose exposure increased after the first study (n = 19), it is not straightforward 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 (Allen et al., 1988). The point of departure (POD) was therefore taken from the Cavalleri et al. (1994) study. The exposure level for the full study sample is used as the LOAEL, using the following reasoning. Although no apparent CCI deficit was seen in ironers, their reported exposure range (0.52−11.28 ppm, or 3.5−76 mg/m^3) was completely contained within the range of exposures for dry cleaners (0.38−31.19 ppm, or 2.6−210 mg/m^3). Yet elevated CCI scores were observed at exposures lower than the mean exposure of the ironers (4.8 ppm, or 33 mg/m^3), indicating that the mean exposure of the ironers cannot be considered a NOAEL. For these reasons, Cavalleri et al. (1994) is selected as a principal study.

___I.B.3. UNCERTAINTY FACTORS

Each of the candidate studies provided lowest-observed-adverse-effect levels (LOAELs) that were selected as PODs. No adjustment of the PODs was needed for animal-to-human extrapolation uncertainty. Additionally, no adjustment was needed for subchronic-to-chronic uncertainty because the principal studies involved chronic exposures. An overall uncertainty factor of 1,000 was applied to each selected POD, comprised of the following uncertainty factors (UFs):

Human Variation

The UF of 10 was applied for human variation for all of the studies that were selected in derivation of the RfC. These studies are from 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.

LOAEL-to-NOAEL Uncertainty

A UF of 10 is generally applied when the POD is a LOAEL due to a lack of a no-observed-adverse-effect level [NOAEL]. For all of the human studies and endpoints selected (Cavalleri et al., 1994; Echeverria et al., 1995; Seeber, 1989), PODs were LOAELs and a UF of 10 was applied to these endpoints.

Database Uncertainty

A database UF of 10 has been applied to address the lack of data to adequately characterize the hazard and dose-response in the human population. A number of data gaps were identified from both the human and animal literature, including the need for high quality epidemiologic studies of residential exposures, and chronic-duration animal studies (including in developing animals) designed to define and characterize the exposure-response relationships for the observed neurotoxicological effects, particularly, reaction time, cognitive and visual function. Additionally, the available studies of immunologic and hematologic toxicity studies (e.g., Emara et al., 2010; Marth, 1987) are limited, but do raise concern for risk at exposures lower than those evaluated. The relative lack of data taken together with the concern that other structurally related solvents have been associated with immunotoxicity, particularly relating to autoimmune disease (Cooper et al., 2009), contributes to uncertainty in the database for tetrachloroethylene.

In addition, the available epidemiologic studies of residential exposures were judged to be more limited for developing an RfC (Altmann et al., 1995; NYSDOH, 2010; Schreiber et al., 2002; Storm et al., In Press) based on consideration of selection bias, residual confounding (population comparability) and/or selection of neurological methods. Yet the residential studies yielded the most sensitive neurotoxic endpoint associated with tetrachloroethylene exposure, decrement in visual contrast sensitivity (VCS). Because this specific endpoint was not evaluated in any of the occupational studies, it cannot be concluded that similar or even greater VCS changes would not occur at the higher exposures of the occupational studies. There were impairments in Color Confusion Index for one set of occupationally exposed subjects (Cavalleri et al., 1994; Gobba et al., 1998), but this effect was not evaluated in other occupational studies. There is also a lack of studies which evaluated the critical effects of reaction time, cognitive and visual functional deficits in populations exposed to tetrachloroethylene at lower than the studied occupational exposure levels, including at residential levels.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

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

Study – High
Data Base -- Medium
RfC -- High

The overall confidence in this RfC assessment is high because it is supported by medium- to high-confidence estimates from multiple human neurotoxicity studies. Additionally, quantitative dose-response analyses of the findings in other toxicity domains (i.e., kidney, liver,

immunologic and hematologic, and reproductive and developmental toxicity), detailed in Section 5, are considered to be supportive of these values.

___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 A of the *Toxicological Review of Tetrachloroethylene (Perchloroethylene)* (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 – Tetrachloroethylene (Perchloroethylene)
CASRN – 127-18-4
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* (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 $\mu g/m^3$ 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.

No previous cancer assessment of tetrachloroethylene is 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; NCI, 1977; NTP, 1986b).

___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 results from five of the six studies with relatively high quality exposure-assessment methodologies provide additional evidence of an association with effect estimates ranging from 1.44 to 4.03 (Aschengrau et al., 1993; Blair et al., 2003; Lynge et al., 2006, >90th percentile exposure), (Calvert et al., In Press; Pesch et al., 2000). The Lynge et al. (2006) risk estimates were slightly higher among the subgroup from Denmark and Norway, in which the number of subjects with unclassifiable data was negligible (relative risk: 1.69, 95% CI: 1.18, 2.43). An exposure-response gradient was seen in a large case-control study by Pesch et al. (2000), using a semiquantitative cumulative exposure assessment but not in Lynge et al. (2006) using employment duration without consideration of exposure concentration. 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, based on the JTEM approach. 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 (Ji et al., 2005; Pukkala et al., 2009; Travier et al., 2002; Wilson et al., 2008). 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. There is little evidence of an association in the large cohort studies examining risk in relation to a broad occupational category of work in laundry or dry cleaning (i.e., relative risk estimates ranging from 0.95 to 1.05 in females in Andersen et al. (1999), females and males in Ji and Hemminki (2006); and Pukkala et al. (2009)). 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 (Anttila et al., 1995; Boice et al., 1999; Calvert et al., In Press; Radican et al., 2008; Seldén and Ahlborg, 2011). There is also some evidence of exposure-response gradients in studies with tetrachloroethylene-specific exposure measures based on intensity, duration, or cumulative exposure (Boice et al., 1999; Miligi et al., 2006; Seidler et al., 2007). 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). 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 (Andersen et al., 1999; Ji and Hemminki, 2006; Pukkala et al., 2009). 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., (2010); tetrachloroethylene exposure). Gold et al. also reported increasing risks with increasing exposure duration (based on job titles) Gold et al., (2010) and based on a cumulative tetrachloroethylene exposure metric (Gold et al., 2010). Two smaller studies with tetrachloroethylene-specific exposure measures based on intensity, duration, or cumulative exposure did not observe an exposure-response trend: a study by Seidler et al. (2007) observed no cases among the highest exposure groups, and a 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, 1986b) 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, 1986b) or F344/DuCrj (JISA, 1993) strain. Tetrachloroethylene reduced MCL latency in females in both studies. In addition, the NTP 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. Additionally, the NTP (1986b) 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, 1986b) or oral gavage (NCI, 1977) significantly increased the incidence of hepatocellular adenomas and carcinomas. The NCI (1977) and NTP (1986b) studies employed the $B6C3F_1$ 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 (1986b)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

In terms of the role of metabolism, the specific toxic moieties have not been identified for any endpoint. However, for mouse liver tumors and rat kidney tumors there are data that identify the likely metabolic pathway involved—oxidation and GSH conjugation, respectively. For oxidation, toxicokinetic data and modeling indicate that this pathway represents a greater fraction of tetrachloroethylene disposition in mice than in humans, a difference that can be accounted for quantitatively through use of the PBPK model. Therefore, this factor leads to decreasing the weight accorded to mouse liver tumors, but the extent of the difference can be carried through quantitatively and addressed in the comparison of resulting low-dose extrapolation predictions. For rat kidney tumors, the range of estimates for GSH conjugation is very wide, with some estimates based on this dose metric being higher than those based on the AUC of tetrachloroethylene in blood, which was selected as the preferred surrogate dose metric. Therefore, it is unclear whether the weight accorded to rat kidney tumors should be increased or decreased, as the toxicokinetic data are inadequate to quantify the extent of interspecies differences. For the endpoints other than mouse liver and rat kidney tumors, toxicokinetic data are not informative as to the choice of data set that may best reflect human carcinogenic potency

In terms of MOA, only for rat kidney tumors and mouse liver tumors are there any concrete hypotheses. 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 MOA hypotheses concern mutagenicity, epigenetic effects (especially DNA hypomethylation), oxidative stress, and receptor activation (focusing on a hypothesized PPARα activation MOA). 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. Although target organ concordance is not a prerequisite for evaluating the implications of animal study results for humans (U.S. EPA, 2005a), it is notable that the leukemias (in both sexes of rats) support the observation of lymphopoietic cancers in individuals employed as dry cleaners and degreasers, and the liver tumors (in both sexes of mice) support the observation of liver tumors in dry cleaners (see Section 4.10.1.1.2). Overall, the MOAs involved in the carcinogenicity of tetrachloroethylene and its metabolites are not known, and mechanistic data are not informative as to the choice of data set that may best reflect human carcinogenic potency.

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

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1. Oral Slope Factor - **6×10^{-2} per mg/kg-day**

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

$BMDL_{10}$, lower 95% bound on exposure at 10% extra risk – 1.7 mg/kg-day
BMD_{10}, central estimate of exposure at 10% extra risk – 10 mg/kg-day

The slope of the linear extrapolation from the central estimate BMD_{10} is $0.1/(1.7 \text{ mg/kg-day}) = 1 \times 10^{-2}$ per mg/kg-day.

The slope factor for tetrachloroethylene should not be used with exposures exceeding the point of departure ($BMDL_{10}$), 2 mg/kg-day, because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of tetrachloroethylene.

____II.B.1.2. Drinking Water Unit Risk* - 2×10^{6} per µg/L

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	60 µg/L
E-5 (1 in 100,000)	6 µg/L

E-6 (1 in 1,000,000)	0.6	µg/L

* The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human.

____II.B.1.3. Extrapolation Method

Michaelis-Menten model (see II.C.3.) with linear extrapolation from the point of departure ($BMDL_{10}$), 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 – Mononuclear cell leukemia
Test species – Male and female F344; DuCrj rats
Route – Inhalation
Reference –JISA (1993)
See II.C.2 for dose-response data and II.C.3.

___II.B.3. ADDITIONAL COMMENTS

The oral slope factor was developed from inhalation data because the only available oral bioassay had several limitations for extrapolating to lifetime risk in humans (see also Section 5.4.1). First, the study was conducted by gavage at relatively high doses. Human exposures are less likely to occur in boluses, and high doses are associated at least with saturable metabolism processes which may involve a different profile of toxicological processes than those prevalent at more likely environmental exposure levels. Also, the animals were dosed for only approximately 75% of the more usual 2-year period (NCI, 1977), 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.4. DISCUSSION OF CONFIDENCE

There is high confidence in the oral slope factor. The estimate is supported by those from other tumor sites using preferred dose metrics (total oxidative metabolites for hepatocellular tumors, tetrachloroethylene AUC in blood for all other tumors), which are lower by between three- and 50-fold. The recommended oral slope factor is less than threefold higher than estimates of total tumor risk from multiple sites (brain, kidney, testes, and MCL) in the NTP (1986b) rat bioassay, using tetrachloroethylene AUC in blood as the preferred dose metric. Estimates using alternative dose metrics (TCA AUC for hepatocellular tumors, GST metabolism for kidney tumors) spanned a range from almost three orders of magnitude below to almost fourfold above the recommended oral slope factor.

Confidence in the recommended oral slope factor is further increased by the concordance of the recommended inhalation unit risk estimate (from which the oral slope factor was derived) with estimates based on the available human data, discussed above. Although estimates based on human data are not sufficient to serve as a primary basis for dose-response assessment, they support the plausibility of the cancer risk estimates based on rodent bioassays.

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

___II.C.1. SUMMARY OF RISK ESTIMATES

____II.C.1.1. Inhalation Unit Risk: 7×10^{-2} per ppm, or 1×10^{-5} per $\mu g/m^3$

The inhalation unit risk is derived from the $BMCL_{10}$, the 95% lower bound on the exposure associated with a 10% extra cancer risk, by dividing the risk (as a fraction) by the $BMCL_{10}$, and represents an upper bound, continuous lifetime exposure risk estimate:

$BMCL_{10}$, lower 95% bound on exposure at 10% extra risk – 1.5 ppm, or 10^4 $\mu g/m^3$.
BMC_{10}, central estimate of exposure at 10% extra risk – 8.6 ppm, or 5.8×10^4 $\mu g/m^3$.

The slope of the linear extrapolation from the central estimate BMC_{10} is $0.1/(5.8 \times 10^4\ \mu g/m^3) = 2 \times 10^{-6}$ per $\mu g/m^3$.

The unit risk for tetrachloroethylene should not be used with exposures exceeding the point of departure ($BMCL_{10}$), 10^4 $\mu g/m^3$ or 1.5 ppm, because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of tetrachloroethylene.

Air Concentrations at Specified Risk Levels:

Risk Level	Lower Bound on Concentration Estimate
E-4 (1 in 10,000)	10 $\mu g/m^3$
E-5 (1 in 100,000)	1 $\mu g/m^3$
E-6 (1 in 1,000,000)	0.1 $\mu g/m^3$

____II.C.1.2. Extrapolation Method

Michaelis-Menten model (see II.C.3) with linear extrapolation from the point of departure ($BMCL_{10}$).

___II.C.2. DOSE-RESPONSE DATA

Tumor type – Mononuclear cell leukemia
Test species – Male and female F344; DuCrj rats
Route – Inhalation
Reference – JISA (1993)

Administered Concentration (ppm)	Tetrachloroethylene AUC in blood (mg-hr/L-d)	Sex	MCL Incidence
0	0	Male	11/50
50	20.		14/50
200	81		22/50
600	248		27/50
0	0	Female	10/50
50	20		17/50
200	81		16/50
600	248		19/50
0	0	Male and Female	21/100
50	20		31/100
200	81		38/100
600	248		46/100

___II.C.3. ADDITIONAL COMMENTS

A number of alternative analyses were performed in an attempt to obtain better model fits to the nonmonotonic and supralinear datasets. The datasets that did not exhibit supralinearity were all fit well by the multistage model, and carry the greatest weight from this perspective. These include the female mouse hepatocellular tumors, male mouse hemangiosarcomas, and all the NTP (1986a) datasets. For the male mouse hepatocellular tumors, none of the alternative analyses were successful in obtaining better model fits to the supralinear dose response shape, so these data carry somewhat less weight from this perspective. The most challenging datasets were the rat MCL data from JISA (1993), which necessitated trying multiple approaches. Among those results, the results of the male MCL data and the combined male and female MCL data carry the greatest weight, since the Michaelis-Menten model both fit the supralinear shape and resulted in a stable BMCL estimate. Less weight is accorded to results of the female MCL data, which necessitated use of only the control and lowest dose group. Another indicator related to the dose-response fit is the statistical uncertainty at the POD. For the selected dose-response models this uncertainty is quite modest at around twofold or less for all data sets except the combined male and female MCL fits, which had statistical uncertainty at the POD of around fivefold. In addition, for the male MCL fits, the use of some alternative dose-response models led to poorly bounded BMCs, suggesting that this dataset may carry somewhat less weight due to its more limited ability to bound the BMC.

The dose-response analyses using the Michaelis-Menten model of the combined male and female rat MCL from the JISA study were selected. These data showed a strong and robust observed response; the dose response modeling was able to fit the dataset's supralinearity as well as estimate a reasonable BMDL; and it is the most sensitive unit risk estimate using a preferred dose metric. Therefore, this analysis is accorded the greatest overall weight among the available choices. Supporting this selection are two analyses given slightly less weight: the Michaelis-Menten model-based analysis of the male MCL from the JISA bioassay (1993), and the analysis of the total tumor risk among four sites from male rats in the NTP bioassay (1986b). Each of these results is also based on strong and robust observed responses and fits that accounted for any supralinearity, and lead to only slightly less sensitive unit risk estimates. However, the male

MCL data from JISA (1993) led to a much wider range of BMDL estimates when a range of alternative dose-response models were applied; and the NTP (1986a) data are based on fewer dose groups and on several endpoints that were not reproduced in other bioassays. Finally, the results from the analysis of only the control and low dose group from the female MCL JISA (1993) data were of similar sensitivity, but where based on dose-response modeling that could not account for any supralinearity below the lowest dose, and thus were accorded less overall weight.

The slope factors in terms of the internal dose metric (tetrachloroethylene AUC in blood) were converted to unit risks in terms of human equivalent environmental inhalation using the pharmacokinetic modeling of Chiu and Ginsberg (2011).

___II.C.4. DISCUSSION OF CONFIDENCE

There is high confidence in the inhalation unit risk estimate. The estimates are supported by those from other tumor sites using preferred dose metrics (total oxidative metabolites for hepatocellular tumors, tetrachloroethylene AUC in blood for all other tumors), which are lower by between three- and 30-fold. The recommended inhalation unit risk is also within threefold of estimates of total tumor risk from multiple sites (brain, kidney, testes, and MCL) in the NTP (1986a) rat bioassay, using tetrachloroethylene AUC in blood as the preferred dose metric, thereby providing support for the recommended value. Estimates using alternative dose metrics (TCA AUC for hepatocellular tumors, GST metabolism for kidney tumors) spanned a range from almost three orders of magnitude below to more than twofold above the recommended inhalation unit risk.

Confidence in the recommended inhalation unit risk estimate is further increased by its concordance with estimates reported by VanWinjngaarden and Hertz-Piccioto (2004) and Finkel, (201?), based on two epidemiologic studies (Lynge et al., 2006; Vaughan et al., 1997), which have central estimates ranging from 2×10^{-6} to 8×10^{-6} per $\mu g/m^3$ and upper bound estimates ranging from 8×10^{-6} to 16×10^{-6} per $\mu g/m^3$. The two such estimates available use average tetrachloroethylene concentration as the exposure surrogate, either the time-weighted average or average level from industrial monitoring studies, they assume that bladder cancer or laryngeal cancer are the only carcinogenic hazard in humans, and they may be subject to some other sources of bias, but provide information without extrapolation from animals to humans. Therefore, although the studies lack estimates of tetrachloroethylene exposure intensity to individual study subjects, precluding their use as a primary basis for dose-response assessment, the estimates based on these human data support the plausibility of the cancer risk estimates based on rodent bioassays.

__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 A of the *Toxicological Review of Tetrachloroethylene (Perchloroethylene)* (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

Tetrachloroethylene
CASRN -- 127-18-4
Section VI. Last Revised -- 00/00/0000

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_VII. REVISION HISTORY

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

Date	Section	Description
12/23/1987	I.A.	RfD withdrawn pending further review
03/01/1988	I.A.	Revised Oral RfD summary added - RfD changed
03/01/1988	III.A.	Health Advisory added
07/01/1989	VI.	Bibliography on-line
06/01/1990	IV.A.1.	Area code for EPA contact corrected
06/01/1990	IV.F.1.	EPA contact changed
01/01/1992	IV.	Regulatory actions updated
04/01/1992	IV.	Regulatory action section withdrawn
08/01/1995	II.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.

04/01/1997 III., IV., V. Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.

_VIII. SYNONYMS

Tetrachloroethylene
CASRN -- 127-18-4
Section VIII. Last Revised -- 00/00/0000

- 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
- Perchlorethylene
- Perchlorethylene, per
- Perchloroethylene
- Perclene
- Percloroetilene
- Percosolv
- Percosolve

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