1,1,1-Trichloroethane; CASRN 71-55-6

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

STATUS OF DATA FOR 1,1,1-Trichloroethane

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)		
Acute Oral RfD (I.A.1.)	qualitative discussion	09/28/2007
Short-term Oral RfD (I.A.2.)	qualitative discussion	09/28/2007
Subchronic Oral RfD (I.A.3.)	yes	09/28/2007
Chronic Oral RfD (I.A.4.)	yes	09/28/2007
Inhalation RfC (I.B.)		
Acute Inhalation RfC (I.B.1.)	yes	09/28/2007
Short-term Inhalation RfC (I.B.2.)	yes	09/28/2007
Subchronic Inhalation RfC (I.B.3.)	yes	09/28/2007

Category (section)	Assessment Available?	Last Revised
Chronic Inhalation RfC (I.B.4.)	yes	09/28/2007
Carcinogenicity Assessment (II.)	yes	09/28/2007

I. Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose (RfD) for Oral Exposure

Substance Name — 1,1,1-Trichloroethane
CASRN — 71-55-6
Section I.A. Last Revised -- 09/28/2007

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 (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr d.htm for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Acute Oral RfD

The acute RfD applies to exposures for 24 hours or less.

The acute oral data for 1,1,1-trichloroethane are inadequate to support derivation of an acute oral RfD. Human data are limited to the results of a single accidental exposure incident. Acute animal studies are limited to the following: several studies that investigated only hepatic endpoints, a gavage study that found no significant changes in levels of neurotransmitters in the brains of rats associated with 1,1,1-trichloroethane exposure, and some LD_{50} determinations. Data clearly establishing sensitive targets and associated dose-response relationships for acute oral exposure were not located.

I.A.2. Short-Term Oral RfD

The short-term RfD applies to exposures for more than 24 hours, up to 30 days.

The short-term oral data for 1,1,1-trichloroethane are inadequate to support derivation of a short-term oral RfD. No short-term human data are available. Several short-term animal studies identified dose levels associated with gross central nervous system (CNS) depression and death by gavage exposure but failed to conclusively identify targets or effect levels not associated with frank toxicity. Neurophysiological changes were observed in one study at a relatively low dose level (705 mg/kg-day); however, these effects were not confirmed in other studies that examined neurotoxicological endpoints and were considered to be of uncertain toxicological significance.

I.A.3. Subchronic Oral RfD

The subchronic RfD applies to exposures for more than 30 days, up to approximately 10% of the life span in humans (more than 30 days up to approximately 90 days in typically used laboratory animal species).

I.A.3.1. Subchronic Oral RfD Summary

Critical Effect	Point of Departure*	UF	Subchronic RfD
Reduced body weight **90-Day mouse dietary study** **NTP (2000)**	$BMDL_{10}$: 2155 mg/kg-day	300	7 mg/kg-day

*Conversion Factors and Assumptions -- NTP (2000) calculated the exposure (in mg/kg-day) from the dietary concentration (in ppm) by using measured food consumption and measured body weight data. Body weights were analyzed by benchmark dose modeling. The lower 95% confidence interval on the effective dose associated with a 10% change in mean terminal body weight relative to the control mean ($BMDL_{10}$) was selected as the point of departure.

I.A.3.2. Principal and Supporting Studies

The National Toxicology Program (NTP, 2000) fed groups of 10 male and 10 female F344/N rats and B6C3F1 mice diets containing 0 (untreated feed), 0 (placebo microcapsules), 5000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (> 99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 290, 600, 1200, 2400, and 4800 mg/kg in male rats; 310, 650, 1250, 2500, and 5000 mg/kg in female rats; 850, 1770, 3500, 7370, and 15,000 mg/kg in male mice; and 1340, 2820, 5600, 11,125, and 23,000 mg/kg in female mice.

All rats survived to study termination and no clinical signs of toxicity were observed (NTP, 2000). Body weight gain over the course of the study was significantly reduced in the 80,000 ppm male rats in comparison with both the untreated and vehicle controls. Final body weight was 10% less than vehicle controls (statistically significant) but only 4% less than untreated controls (not significant). Because of the nutritional value of the vehicle used (i.e., microcapsules composed of 80% food grade modified corn starch and 20% sucrose), the vehicle control was considered the most appropriate comparison group. In the 80,000 ppm females, final body weight was statistically significantly lower (4%) than vehicle controls. Body weight changes in lower dose groups were unremarkable. Feed consumption was similar to controls in all groups. No toxicologically meaningful changes were found in hematology, clinical chemistry, or urine analyses. Absolute and relative liver weights were significantly reduced in 80,000 ppm female rats by about 15% and 11%, respectively, in comparison with both untreated and vehicle controls. In 80,000 ppm male rats, absolute liver weight was significantly reduced by about 13% compared with vehicle controls but did not differ from untreated controls, and relative liver weight was unaffected. Male rats treated with 20,000 ppm 1,1,1-trichloroethane or above showed renal lesions considered by study investigators to be consistent with α_{2u}-globulin nephropathy. Renal changes associated with α_{2u}-globulin nephropathy in male rats are specific to this sex and species and are not considered to be predictive for effects in humans (U.S. EPA, 1991). No lesions in other tissues were observed in the males, and no lesions in any tissue were observed in the females. Treatment with 1,1,1-trichloroethane had no effect on vaginal cytology parameters in female rats. In males, epididymal spermatozoal concentration was significantly reduced by about 10% in the 80,000 ppm group compared with vehicle controls, but no other associated changes were found. Therefore, this study identified a LOAEL of 80,000 ppm (4800 mg/kg-day in males and 5000 mg/kg-day in females) and a NOAEL of 40,000 ppm (2400 mg/kg-day in males and 2500 mg/kg-day in females), based on reduced liver weights in males and females and reduced epididymal spermatozoal concentration in males.

Mice also showed no clinical signs of toxicity from 1,1,1-trichloroethane ingestion, and mortality was unaffected (NTP, 2000). Statistically significant, dose-related reductions in body weight gain and terminal body weight were observed in male mice treated with 5000 ppm or above and female mice treated with 10,000 ppm or above, in relation to both untreated

and vehicle controls. Terminal body weights for male mice relative to controls were as follows: 5,000 ppm—91%; 10,000 ppm—91%; 20,000 ppm—88%; 40,000 ppm—90%; and 80,000 ppm—85%; and for female mice were: 5,000 ppm—97%; 10,000 ppm—93%; 20,000 ppm—89%; 40,000 ppm—88%; and 80,000 ppm—84%.

Feed consumption was generally greater in treated mice than in controls. Any changes in organ weights were considered by NTP to be secondary to the changes in body weight, and not toxicologically significant. No gross or microscopic lesions due to 1,1,1-trichloroethane were seen in male or female mice. Vaginal cytology parameters in treated female mice were similar to those of controls. Male mice in the 80,000 ppm group had a significant (20%) reduction in epididymal spermatozoal concentration compared with vehicle controls but no other associated changes. Effects on body weight were the most sensitive indicators of 1,1,1-trichloroethane toxicity in both male and female mice. NTP (2000) estimated the dose of 10,000 ppm (1770 mg/kg-day in male mice) to be a NOAEL and 20,000 ppm (3500 mg/kg-day) to be a LOAEL based on decreases in terminal body weight greater than 10% of the control values.

Decreased body weight appears to be a sensitive effect in other subchronic and chronic studies by oral or inhalation routes of exposure, either in the absence of other toxicity (Bruckner et al., 2001; Prendergast et al., 1967; Adams et al., 1950) or at doses causing minimal liver histopathologic changes (some reflective of an adaptive physiologic response) (Quast et al., 1988, 1984; Calhoun et al., 1981). Reduced body weight has also been observed at levels causing reduced survival without clear indication of any target organ toxicity (Bruckner et al., 2001; NCI, 1977).

Method of Analysis
The subchronic RfD was derived by using benchmark dose (BMD) analysis of terminal body weight data from male and female mice exposed to 1,1,1-trichloroethane for 90 days (NTP, 2000). Continuous data models (linear, polynomial, power, and Hill) with a constant variance were fit to the data by using U.S. EPA Benchmark Dose Software (BMDS) (version 1.4). The software was used to calculate potential points of departure for deriving the subchronic RfD by estimating the effective dose at a specified level of response (BMD_x) and its 95% lower bound ($BMDL_x$). A 10% change in mean terminal body weight relative to the control mean was selected as the benchmark response (BMR) level as the minimal level of change generally considered to be biologically significant (U.S. EPA, 2000).

BMDS results for mouse body weight data are summarized in the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007), Section 5.1.3.2 and Appendix B. All models provided an adequate fit of the female body weight data; the Hill model provided the best fit of the data (based on a goodness-of-fit p-value ≥ 0.1 and the lowest Akaike Information

Criterion. Of the continuous data models, only the Hill model provided an adequate fit of the body weight data for the male mouse (i.e., p-value ≥ 0.1).

Visual inspection of plots of body weight data for the male and female mouse (see *Toxicological Review of 1,1,1-Trichloroethane* [U.S. EPA, 2007], Appendix B) reveals that the female data set provides a much better relationship of dose and response than does the male data set. In the case of the male data set, the first four dose groups show a flat dose-response relationship; in the dose range between 850 and 7370 mg/kg-day, the body weight decrease (relative to controls) approaches 10%, but male mouse body weights appear to be relatively insensitive to increasing doses of 1,1,1-trichloroethane. A decrease in body weight relative to the control appears to exceed 10% only in the high-dose (15,000 mg/kg-day) male mice. Although the Hill model provided an adequate fit of the male mouse data, the resulting $BMDL_{10}$ of 594 mg/kg-day is not consistent with the data that show no relationship between dose and reduction in body weight gain at a dose as high as 7370 mg/kg-day. NTP (2000) noted that feed consumption and estimates of average daily dose were determined by the disappearance of feed from the feeder and may not accurately represent intake. It is possible that imprecision in dose estimates may have contributed to the observed dose-response relationship in male mice.

Because male and female mice generally responded similarly to 1,1,1-trichloroethane in the diet (i.e., the decrease in body weight was similar, with terminal body weights in high-dose male and female mice at 84 to 85% of controls) and because the female body weight data showed a clearer relationship between dose and response, the female mouse data were used as the basis for the subchronic RfD. The $BMDL_{10}$ for female body weight data, based on the Hill model of 2155 mg/kg-day, was selected as the point of departure for the subchronic RfD.

I.A.3.3. Uncertainty Factors

UF = 300.

A 10-fold uncertainty factor (UF) was used to account for laboratory animal-to-human interspecies differences. This default UF accounts for differences in the toxicokinetics and toxicodynamics between the model species and humans.

A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

A UF to extrapolate from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure.

A UF to extrapolate from a shorter to a longer duration was not necessary because the subchronic RfD was derived from a study of subchronic duration.

A threefold uncertainty factor was used to account for deficiencies in the available 1,1,1-trichloroethane database. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats, none of which clearly demonstrated any effects. The principal study, a 13-week NTP (2000) toxicity study, was conducted under an interagency agreement with the Agency for Toxic Substances and Disease Registry (ATSDR) to address data needs identified by ATSDR. Specifically, ATSDR identified the need for data from intermediate-duration oral exposure studies to provide information that would help determine the NOAELs and LOAELs for systemic, neurological, reproductive, and developmental effects. NTP (2000) was a well-conducted repeat-dose oral study but did not examine the potential for subtle neurotoxicity. Acute neurotoxicity was observed by the oral route following bolus dosing (e.g., hyperexcitability and narcosis reported by Bruckner et al., 2001) and by the inhalation route, where signs of central nervous system depression have been extensively documented. As discussed more thoroughly in the justification of the database uncertainty factor used in the derivation of the subchronic RfC, some uncertainty exists with respect to the neurotoxicity database for 1,1,1-trichloroethane, notably associated with findings from the epidemiological literature and from the Rosengren et al. (1985) study in gerbils. Lack of endpoints for subtle neurotoxic potential following repeated exposure is considered a deficiency in the oral database for this chemical in light of its acute neurotoxicity and uncertainties in the inhalation neurotoxicity database.

I.A.3.4. Additional Studies/Comments

No subchronic human data are available. Animal studies in this duration category include studies of developmental and reproductive toxicity, which did not conclusively demonstrate the occurrence of effects due to 1,1,1-trichloroethane (Maurissen et al., 1994, 1993; George et al., 1989; NTP, 1987a,b; Dapson et al., 1984a,b; Lane et al., 1982), and studies of systemic toxicity by gavage (Bruckner et al., 2001) and dietary (NTP, 2000) exposure.

The primary target of 1,1,1-trichloroethane at high oral doses is the central nervous system (CNS), although CNS effects have not been consistently demonstrated in subchronic oral studies. Gross CNS depression was observed in rats given 1,1,1-trichloroethane by gavage in corn oil at an average dose of 1786 mg/kg-day or above for 90 days (Bruckner et al., 2001). The NTP (2000) 13-week feeding study in rats, however, reported no evidence of gross CNS effects at doses up to 5000 mg/kg-day in the rat and 23,000 mg/kg-day in the mouse.

Evidence for the liver as a potential target of orally administered 1,1,1-trichloroethane is equivocal. Some, but not all studies suggest that 1,1,1-trichloroethane may produce mild hepatotoxicity. Serum enzyme changes indicative of mild hepatotoxicity were seen in a 13-week gavage study at a dose (3571 mg/kg-day) that was lethal to 50% of the rats tested (Bruckner et al., 2001). NTP (2000) reported decreases in relative and/or absolute liver weight (12%) in female and male rats exposed to 4800—5000 mg/kg-day of 1,1,1-trichloroethane in the diet for 13 weeks (NTP, 2000), but no histopathologic changes in the liver were observed.

NTP (2000) provides evidence for the kidney as a target of 1,1,1-trichloroethane in male rats following oral exposure. Male rats exposed to 1200 mg/kg-day or more in the diet for 13 weeks showed renal lesions characteristic of α_{2u}-globulin nephropathy (NTP, 2000); the lesions are specific to male rats and not considered to be predictive for effects in humans (U.S. EPA, 1991). Specific analysis for α_{2u}-globulin was not, however, conducted by NTP. In a 21-day gavage study in rats, designed specifically to examine renal toxicity of halogenated ethanes (NTP, 1996), no renal lesions, including hyaline droplet nephropathy, tubule regeneration, or granular casts, were seen at the high dose of 165 mg/kg-day, and increases in mean urine protein and AST were not clearly related to 1,1,1-trichloroethane treatment. Male rats treated dermally with 240—320 mg/kg-day for 3 weeks showed no evidence of renal lesions (Viola et al., 1981). Parenteral studies found little evidence of nephrotoxicity even at lethal dose levels (e.g., Bernard et al., 1989; Klaassen and Plaa, 1967; Plaa et al., 1958); however, these studies were not conducted in male rats. The kidneys were not adequately evaluated as a potential endpoint of toxicity in other subchronic or chronic oral studies. Inhalation studies, including studies of subchronic and chronic durations, did not show renal effects in male rats or other species tested. The overall weight of evidence does not show the kidney to be a sensitive target organ for 1,1,1-trichloroethane.

Epididymal spermatozoal concentration was reduced in high-dose male rats (4800 mg/kg-day) and mice (15,000 mg/kg-day) in the 13-week NTP feeding study (NTP, 2000). The toxicological significance of these changes is uncertain because the magnitude was relatively small (10—20%), and no associated changes in sperm motility or the weight or histopathology of the reproductive organs were seen in either species. The epididymis was not evaluated as a potential endpoint of toxicity in other oral studies, and was not identified as a target in inhalation studies. Intratesticular injection of 1,1,1-trichloroethane produced a significant decrease in testicular DNA synthesis in male mice (Borzelleca and Carchman, 1982), but repeated intraperitoneal injections had no effect on the incidence of sperm head abnormalities in mice (Topham, 1981, 1980). No effect on male or female reproductive function was seen in mice tested in a multigeneration oral study at doses up to 1000 mg/kg-day (Lane et al., 1982).

For more detail on Susceptible Populations, exit to the [toxicological review, Section 4.8 (PDF)](.).

I.A.3.5. Confidence in the Subchronic Oral RfD

Study -- High
Data Base -- Low-medium
RfD -- Low-medium

The overall confidence in this subchronic RfD assessment is low-medium. Confidence in the principal study, NTP (2000), is considered high. The principal study (NTP, 2000), a 90-day feeding study in rats and mice, is a recently conducted, peer-reviewed study performed with standard protocols for NTP toxicity studies. 1,1,1-Trichloroethane was microencapsulated and administered in the diet to avoid chemical loss due to volatilization and to avoid toxicity that can occur when administered in a bolus dose. Although the principal study is considered of high confidence, the interpretation of the critical effect from this study, reduced mean terminal body weight, merits discussion. Reduction in body weight gain was a consistent finding in studies of 1,1,1-trichloroethane toxicity across studies, species, and routes of exposure, though effects on body weight were not associated with other target organ toxicity. External peer reviewers expressed various opinions about the use of reduced body weight as the critical effect. See Appendix A, Section B (question 3) of the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007) for a more thorough summary of the comments from external peer reviewers on endpoint selection. Confidence in the oral database is low-medium. Subchronic oral studies include studies using gavage and dietary administration. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats. Repeat-dose studies, including NTP (2000), did not include investigation of sensitive neurological endpoints; the neurological endpoints in repeat-dose oral studies were limited to clinical observations and brain histopathology. Considering the confidence in the principal study, the endpoint selection, and the database, the overall confidence in the subchronic RfD is low-medium.

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

I.A.4. Chronic Oral RfD

The chronic RfD applies to exposures for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).

A chronic oral reference dose for 1,1,1-trichloroethane was previously included on the IRIS database but was withdrawn in 1991. Thus, the previous IRIS record for this chemical did not provide an RfD.

I.A.4.1. Chronic Oral RfD Summary

Critical Effect	Point of Departure*	UF	Chronic RfD
Reduced body weight **90-Day mouse dietary study** **NTP (2000)**	$BMDL_{10}$: 2155 mg/kg-day	1000	2 mg/kg-day

*Conversion Factors and Assumptions -- NTP (2000) calculated the exposure (in mg/kg-day) from the dietary concentration (in ppm) by using measured food consumption and measured body weight data. Body weights were analyzed by benchmark dose modeling. The lower 95% confidence interval on the effective dose associated with a 10% change in mean terminal body weight relative to the control mean ($BMDL_{10}$) was selected as the point of departure.

I.A.4.2. Principal and Supporting Studies

The 90-day bioassay conducted by the National Toxicology Program (NTP, 2000), which was selected as the principal study for derivation of the subchronic RfD, was also selected as the basis for deriving the chronic RfD. Reduced terminal body weight was also selected as the critical effect. See Section I.A.3.2 for a description of this study and derivation of the point of departure of 2155 mg/kg-day.

I.A.4.3. Uncertainty Factors

UF = 1000.

A 10-fold UF was used to account for laboratory animal-to-human interspecies differences. This default UF accounts for differences in the toxicokinetics and toxicodynamics between the model species and humans.

A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

A UF to extrapolate from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure.

A threefold UF was used to extrapolate from subchronic to chronic exposure duration. The available body weight data from chronic toxicity studies suggest that body weight effects did not become more pronounced with duration of exposure. In the NCI (1977) cancer bioassay, body weight data are presented in graphic format only. Visual inspection of these graphs for rats shows reduction in mean body weight in treated animals in year one (beginning between weeks 10 and 20) to be similar to the weight reduction in year two (with the exception of low-dose females, where elevated mortality confounded body weight results). Similarly for mice, the mean body weight reduction in year one (beginning between weeks 10 and 20) was similar to year two for male mice; for females, the differences in mean body weight were slightly higher in year two.

The inhalation study by Quast et al. (1988), which included interim sacrifices at 6, 12, and 18 months, similarly revealed no progression in any 1,1,1-trichloroethane-related effects with length of exposure. Mean body weight reduction in female rats versus controls was similar in year one and two (1,1,1-trichloroethane did not produce statistically significant effects on body weight in male rats or male and female mice). Histopathologic changes of the liver in rats—the only other exposure-related effect in this study—showed no progression in incidence or severity from the first interim sacrifice (6 months) to study termination (2 years). For these reasons, a partial uncertainty factor of 3 is used for extrapolation from subchronic to chronic exposure duration.

Removing the UF for subchronic-to-chronic extrapolation (UF = 1) was not considered appropriate because lifetime oral data are not available to fully characterize the potential chronic toxicity of 1,1,1-trichloroethane. The Maltoni et al. (1986) study was designed as a cancer bioassay only and did not include evaluation of nonneoplastic lesions. In the NCI (1977) bioassay, high early mortality was observed in rats and mice, probably due to murine pneumonia, and thus NCI (1977) considered the study to be inadequate.

A threefold UF was used to account for deficiencies in the available 1,1,1-trichloroethane database. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats, none of which clearly demonstrated any effects. Neither the available chronic studies nor the 13-week NTP study included investigation of sensitive

neurological endpoints. As noted in the discussion of the subchronic database UF, the principal study, a 13-week NTP (2000) toxicity study, was conducted under an interagency agreement with the Agency for Toxic Substances and Disease Registry to address data needs identified by ATSDR. Specifically, ATSDR identified the need for data from intermediate-duration oral exposure studies to provide information that would help determine the NOAELs and LOAELs for systemic, neurological, reproductive, and developmental effects. NTP (2000) was a well-conducted repeat-dose oral study but did not examine the potential for subtle neurotoxicity. Acute neurotoxicity was observed by the oral route following bolus dosing (e.g., hyperexcitability and narcosis reported by Bruckner et al. [2001]) and by the inhalation route, where signs of central nervous system depression have been extensively documented. As discussed more thoroughly in the justification of the database uncertainty factor used in the derivation of the chronic RfC, some uncertainty exists with respect to the neurotoxicity database for 1,1,1-trichloroethane, notably associated with findings from the epidemiological literature and from the Rosengren et al. (1985) study in gerbils. Lack of endpoints for subtle neurotoxic potential following repeated exposure is considered a deficiency in the oral database for this chemical in light of evidence for acute neurotoxicity and uncertainty in the inhalation database.

I.A.4.4. Additional Studies/Comments

No chronic human data are available. Chronic oral animal studies were designed as cancer bioassays and included only limited investigation of noncancer endpoints.

Studies of 1,1,1-trichloroethane toxicity following repeat exposure and the targets of toxicity identified in these studies are summarized in Section I.A.3.4. The primary target of 1,1,1-trichloroethane at high oral doses is the CNS, although CNS effects have not been consistently demonstrated in subchronic or chronic oral studies. Evidence for the liver as a potential target of orally administered 1,1,1-trichloroethane is equivocal. NTP (2000) provides evidence for the kidney as a target of 1,1,1-trichloroethane in male rats following oral exposure. The weight of evidence suggests that these renal lesions are associated with α_{2u}-globulin nephropathy; the lesions are specific to male rats and not considered to be predictive for effects in humans (U.S. EPA, 1991) or an appropriate basis for derivation of a reference value. Epididymal spermatozoal concentration was reduced in high-dose male rats (4800 mg/kg-day) and mice (15,000 mg/kg-day) in the 13-week NTP (2000) feeding study. The toxicological significance of these changes is uncertain, however, and effects on male or female reproductive organs and function have not been observed in other studies.

For more detail on Susceptible Populations, exit to the [toxicological review, Section 4.8 (PDF)](#).

I.A.4.5. Confidence in the Chronic Oral RfD

Study -- High
Data Base -- Low-medium
RfD -- Low-medium

The overall confidence in this chronic RfD assessment is low-medium. Confidence in the principal study, NTP (2000), is considered high. The principal study (NTP, 2000), a 90-day feeding study in rats and mice, is a recently conducted, peer-reviewed study performed with standard protocols for NTP toxicity studies. 1,1,1-Trichloroethane was microencapsulated and administered in the diet to avoid chemical loss due to volatilization and to avoid toxicity that can occur when administered in a bolus dose. Although the principal study is considered of high confidence, the interpretation of the critical effect from this study, reduced mean terminal body weight, merits discussion. Reduction in body weight gain was a consistent finding in studies of 1,1,1-trichloroethane toxicity across studies, species, and routes of exposure, though effects on body weight were not associated with other target organ toxicity. External peer reviewers expressed various opinions about the use of reduced body weight as the critical effect. See Appendix A, Section B (question 3) of the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007) for a more thorough summary of the comments from external peer reviewers on endpoint selection. Confidence in the oral database is low-medium. Chronic oral animal studies were designed as cancer bioassays with only limited investigation of noncancer endpoints. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats. Repeat-dose studies, including NTP (2000), did not include investigation of sensitive neurological endpoints; the neurological endpoints in repeat-dose oral studies were limited to clinical observations and brain histopathology. Considering the confidence in the principal study, the endpoint selection, and the database, the overall confidence in the chronic RfD is low-medium.

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

I.A.5. EPA Documentation and Review of the Oral RfD

Source Document -- U.S. EPA (2007)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007). [*To review this appendix, exit to the*](#)

toxicological review, Appendix A Summary of External Peer Review and Public Comments and Disposition (PDF).

Agency Completion Date -- 09/28/2007

I.A.6. 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 Inhalation Exposure

Substance Name — 1,1,1-Trichloroethane
CASRN — 71-55-6
Section I.B. Last Revised -- 09/28/2007

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 (possibly 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.

I.B.1. Acute Inhalation RfC

The acute RfC applies to exposures for 24 hours or less.

I.B.1.1. Acute Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Acute RfC
Performance on neurobehavioral tests **Human subjects exposed for 3.5 hr** **Mackay et al. (1987)**	LOAEL: 950 mg/m^3	100	1 hour: 9 mg/m^3
			4 hours: 7 mg/m^3
			8 hours: 7 mg/m^3
			24 hours: 6 mg/m^3

*Conversion Factors and Assumptions -- The points of departure for the acute RfC values at 4, 8, and 24 hours were derived using PBPK modeling to extrapolate from a 1-hour exposure at the LOAEL (950 mg/m^3) to a concentration at 4, 8, and 24 hours that would yield the same internal (blood) concentration.

I.B.1.2. Principal and Supporting Studies

Mackay et al. (1987) chamber-exposed 12 adult male volunteers to 0, 950, and 1900 mg/m^3 (0, 175, and 350 ppm) of 1,1,1-trichloroethane (purity not reported) for 3.5 hours. The exposure chamber program adhered to the protocol approved by the local Brent and Harrow Area Health Authority Ethical Committee and appears to have been conducted consistent with the ethical standards prevailing at the time of the study. Each subject's three exposures were separated by at least 14 days. Peppermint oil was introduced into the chamber to mask the odor of the solvent. Neurobehavioral tests were performed 25 minutes before exposure and four times during exposure, starting at 20, 60, 120, and 180 minutes. Each test battery took 20—25 minutes to complete. Testing included five psychomotor performance tests (simple reaction time, four-choice reaction time, Stroop test [a measure of susceptibility to distraction], syntactic reasoning [via analysis of grammatical statements], and digital step-input tracking [a measure of eye-hand coordination]) and a subjective measure of mood (stress-arousal checklist). Measurements of 1,1,1-trichloroethane in blood, performed after 0, 20, 60, 120, and 180 minutes of exposure, showed that levels rose rapidly during the first 20 minutes and began leveling off after about 120 minutes. None of the subjects complained of

headache, discomfort, or nausea. Changes in neurobehavioral performance were observed at both exposure levels, including increased simple reaction time, increased choice reaction time, impaired performance in the tracking test, and improved performance in the Stroop test. The reaction time tests appeared to be the most sensitive; however, only simple reaction time was adequately quantified. The change in simple reaction time reportedly represented a 10—15% increase over baseline performance; the magnitudes of change in the other tests are unclear due to a lack of reported baseline performance values. For all tests, statistical analysis included analysis of variance to determine the main effects of exposure and duration (and their interaction) but did not include pair-wise tests to identify the specific exposure level at which a statistical difference from controls was achieved. When adjusted for both baseline (preexposure) and control (0 ppm) exposures, performance changes in the more sensitive tests (e.g., simple reaction time) followed the time-course of 1,1,1-trichloroethane levels in blood and correlated with absolute blood levels. Based on impaired psychomotor performance, particularly increased reaction time, the low exposure concentration of 950 mg/m^3 is a LOAEL for acute CNS effects.

The study by Mackay et al. (1987) is supported by studies by Muttray et al. (2000) and Gamberale and Hultengren (1973), which overall show a slight effect on neurobehavioral performance at exposure concentrations in the range of 1000—2000 mg/m^3 for up to 4 hours of exposure. Muttray et al. (2000) found EEG changes consistent with increased drowsiness, as well as with subjectively reported tiredness, in volunteers performing a choice reaction time test with eyes closed during 4-hour exposure to 1080 mg/m^3 1,1,1-trichloroethane. Gamberale and Hultengren (1973) observed performance deficits in tests of simple and choice reaction time, manual dexterity, and perceptual speed at concentrations of 1900 mg/m^3 for 30-minute exposure but not at 1350 mg/m^3 for 30-minute exposure.

Method of Analysis
The Reitz et al. (1988) PBPK model was used with data from Mackay et al. (1987) to predict effect levels at other acute exposure durations between 1 and 24 hours (Yang, 2006). Specifically, Yang (2006) estimated the internal dose (in venous blood) in humans exposed to 950 mg/m^3 1,1,1-trichloroethane for one hour (1.33 mg/L). The model was then used to predict the exposure concentration required to achieve the same target internal dose (1.33 mg/L) after 4, 8, and 24 hours of exposure by using continuous exposure assumptions (715, 693, and 650 mg/m^3, respectively). The PBPK modeling is more fully described in the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007).

I.B.1.3. Uncertainty Factors

UF = 100.

A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

An interspecies UF was not necessary because the critical effect is based on human data.

A default 10-fold UF for extrapolation from a LOAEL to a NOAEL was used because the lowest exposure concentration examined in the principal study was associated with a measurable deficit in a neurobehavioral test.

A UF to extrapolate from a shorter to a longer exposure duration was not necessary because the acute RfC was derived from a study using an acute exposure protocol; a PBPK model was used to extrapolate to other acute exposure durations.

A database UF was not applied because the acute database for this chemical was considered relatively complete. The inhalation database includes extensive testing for acute toxicity and inhalation developmental toxicity studies in three species. The neurobehavioral effects of 1,1,1-trichloroethane, the most sensitive effect following acute inhalation exposure, has been investigated in both animals and humans.

I.B.1.4. Additional Comments/Studies

There is extensive supporting evidence from the experimental animal literature that the CNS is a sensitive target for 1,1,1-trichloroethane. Neurological effects have been widely demonstrated in acute animal studies and have been shown to be by far the most sensitive endpoints in these studies. In comparison to the human data, however, neurological effects in animals have been reported only at considerably higher concentrations ($\geq$4000 mg/m^3 for effects of toxicological significance in acute studies).

Effects on respiration, blood pressure, and the heart have been associated with acute exposure to high levels of 1,1,1-trichloroethane (approximately 27,300 mg/m^3 and above) in both humans and animals (e.g., Herd et al., 1974; Reinhardt et al., 1973; Dornette and Jones, 1960). These effects have not been observed at lower levels and do not constitute sensitive measures of toxicity for 1,1,1-trichloroethane. There is some evidence to suggest that nasal tissue is a sensitive target for 1,1,1-trichloroethane by inhalation exposure, although such effects have not been widely or consistently reported.

There is little evidence of damage to the liver or other tissues in acute inhalation studies of 1,1,1-trichloroethane. Aside from a transitory increase in urinary urobilinogen in 2 of 4 subjects receiving 15-minute exposure to 14,310 mg/m^3 (Stewart et al., 1961), controlled

exposure studies in humans found no evidence for hepatotoxicity, as determined by liver function tests and serum chemistry, hematology, and urinalysis measurements (Stewart et al., 1969, 1961; Dornette and Jones, 1960; Torkelson et al., 1958). In animals, Adams et al. (1950) reported increased relative liver weight (12%) and slight histopathology (fatty change) in the liver of rats exposed to 43,200 mg/m^3 for 7 hours, as well as a larger increase in relative liver weight (27%) and slight-to-moderate liver lesions (including more marked fatty changes and, in some cases, congestion and hemorrhagic necrosis) in rats exposed to 64,700 mg/m^3 for 7 hours. Exposure for shorter durations, even to much higher concentrations, produced little evidence of hepatotoxicity in animal studies (Loizou et al., 1996; Carlson, 1973; Gehring, 1968; Cornish and Adefuin, 1966; Krantz et al., 1959; Adams et al., 1950).

For more detail on Susceptible Populations, exit to the [toxicological review, Section 4.8 (PDF)](#).

I.B.1.5. Confidence in the Acute Inhalation RfC

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

The overall confidence in the acute inhalation RfC assessment is medium. Confidence in the principal study (Mackay et al., 1987) is medium. The study included a battery of neurobehavioral tests and correlated test outcomes with blood 1,1,1-trichloroethane levels. The number of volunteers (12) was relatively small, and standard deviations/standard errors were not reported. Confidence in the acute inhalation database is high. The acute inhalation database is extensive, including both human and animal studies focused on the most sensitive endpoint, neurotoxicity. The inhalation database also includes inhalation developmental toxicity studies in three species.

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

I.B.2. Short-Term Inhalation RfC

The short-term RfC applies to exposures for more than 24 hours, up to 30 days.

I.B.2.1. Short-Term Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Short-term RfC
Performance on neurobehavioral tests **Human subjects exposed for 3.5 hr** **Mackay et al. (1987)**	LOAEL: 526 mg/m^3	100	5 mg/m^3

*Conversion Factors and Assumptions -- The point of departure was derived by using PBPK modeling to extrapolate from a one-hour exposure at the LOAEL (950 mg/m^3) as reported by Mackay et al. (1987) to a concentration at steady state (14 days) that would yield the same internal (blood) concentration.

I.B.2.2. Principal and Supporting Studies

The LOAEL of 950 mg/m^3 for neurobehavioral effects in humans following acute exposure to 1,1,1-trichloroethane (Mackay et al., 1987) is below the effect levels reported in the available short-term animal studies. This would suggest that protecting against neurobehavioral effects observed in human controlled-exposure studies of acute duration will protect against the effects reported in short-term, repeat-exposure studies in animals. This study was therefore used as the basis for the short-term inhalation RfC. See Section I.B.1.2 for a description of Mackay et al. (1987).

Use of acute data to establish a health-based limit for short-term exposure is supported by toxicokinetic evidence that 1,1,1-trichloroethane and its metabolites do not accumulate with repeated exposure (Nolan et al., 1984; Schumann et al., 1982a,b). The weight of evidence of the animal toxicity data suggests there is no lowering of the threshold for neurobehavioral effects with repeated versus acute exposure (despite limited data to the contrary) and development of only minimal tolerance to 1,1,1-trichloroethane with repeated exposure (Kjellstrand et al., 1990; Moser et al., 1985).

Method of Analysis

Yang (2006) used PBPK modeling with data from Mackay et al. (1987) to predict effect levels at short-term exposure durations (see *Toxicological Review of 1,1,1-Trichloroethane* [U.S. EPA, 2007], Sections 5.2.1.2 and 5.2.2.2). The internal dose of 1,1,1-trichloroethane (i.e., concentration in venous blood) in humans exposed to 950 mg/m^3 for 1 hour (i.e., the exposure considered to be associated with biologically significant changes in neurobehavioral performance) was identified. Yang (2006) used the Reitz et al. (1988) model to predict the exposure concentration required to achieve the same target internal dose once steady state had been reached at 336 hours (14 days). This predicted exposure concentration, 526 mg/m^3, served as the point of departure.

I.B.2.3. Uncertainty Factors

UF = 100.

A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

An interspecies UF was not necessary because the critical effect is based on human data.

A default 10-fold UF for extrapolation from a LOAEL to a NOAEL was used because the lowest exposure concentration examined in the principal study was associated with a measurable deficit in a neurobehavioral test.

A PBPK model was used to predict the exposure concentration that would produce 1,1,1-trichloroethane levels associated with biologically significant changes in neurobehavioral performance when steady state had been achieved (14 days). Therefore, a UF for duration extrapolation was not considered necessary.

A database UF was not applied because the short-term inhalation database was considered relatively complete. The database includes inhalation developmental toxicity studies in three species as well as several studies that investigated neurobehavioral effects of 1,1,1-trichloroethane following short-term exposure. The short-term RfC is based on a study of human neuropsychomotor performance (Mackay et al., 1987) extrapolated to short-term steady-state conditions. The acute literature suggests that the human model is a more sensitive model of neurobehavioral toxicity than the animal models tested, and thus Mackay et al. (1987) is an appropriate and sensitive data set for derivation of the short-term RfC. Further, the available data suggest that repeated exposure to 1,1,1-trichloroethane should not result in an appreciable reduction in the threshold for neurobehavioral effects. This is supported by

chronic animal studies, in which no overt neurobehavioral effects were observed, even after 2 years of exposure of rats and mice to concentrations as high as 8190 mg/m^3 for 6 hours/day, 5 days/week.

I.B.2.4. Additional Comments/Studies

No useful short-term inhalation studies in humans were located. Short-term studies in animals included investigations of neurological and developmental effects. The most sensitive effects in the animal studies were neurological: (1) development of withdrawal symptoms (handling-induced convulsions mitigated by reexposure to 1,1,1-trichloroethane or exposure to some other known depressants) in mice exposed to 2730 mg/m^3 1,1,1-trichloroethane or more continuously for 4 days and abruptly removed from exposure (Balster et al., 1997; Evans and Balster, 1993) and (2) neurophysiological changes in rats following exposure to 5460 mg/m^3 for 6 hours/day for 4 days (adjusted concentration of 1360 mg/m^3) (Albee et al., 1990). Developmental effects were found only at higher concentrations (adjusted concentrations ≥4780 mg/m^3) (Coleman et al., 1999; Jones et al., 1996; BRRC, 1987a,b).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.2.5. Confidence in the Short-Term Inhalation RfC

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

The overall confidence in the short-term reference value is medium. As discussed above (Section I.B.1.5), confidence in the principal study, Mackay et al. (1987), is medium. Confidence in the short-term database is medium. Several animal studies of short-term duration are available. Although most are limited in the scope of the endpoints investigated, they focus on effects expected to be the most sensitive following acute/short-term exposure.

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

I.B.3. Subchronic Inhalation RfC

The subchronic RfC applies to exposures for more than 30 days, up to approximately 10% of the life span in humans (more than 30 days up to approximately 90 days in typically used laboratory animal species).

I.B.3.1. Subchronic Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Subchronic RfC**
Liver histopathologic changes 2-Year inhalation rat study Quast et al. (1988, 1984) 14-Week inhalation mouse study McNutt et al. (1975)	NOAEL(HEC) = 1553 mg/m^3	100	5 mg/m^3

*Conversion Factors and Assumptions -- The human equivalent concentration (HEC) was estimated from the rat NOAEL of 8190 mg/m^3, 6 hours/day, 5 days/week (concentration adjusted to continuous exposure = 1460 mg/m^3) and application of PBPK modeling for interspecies extrapolation.

**Because the subchronic RfC based on liver histopathologic changes following repeated exposure (16 mg/m^3) was higher than the short-term RfC (5 mg/m^3), the subchronic RfC was set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure.

I.B.3.2. Principal and Supporting Studies

Two inhalation studies in rodents, Quast et al. (1988, 1984) and McNutt et al. (1975), were used to establish a NOAEL and LOAEL for effects on the liver in rodents.

Quast et al. (1988, 1984)
Quast et al. (1988, 1984) exposed groups of 80 male and 80 female F344 rats and B6C3F1 mice to 0, 150, 500, or 1500 ppm (0, 820, 2730, or 8190 mg/m^3) production-grade (94%) 1,1,1-trichloroethane vapor for 6 hours/day, 5 days/week for 2 years. Ten rats and 10 mice of each sex from each exposure group were scheduled for interim sacrifices after 6, 12, and 18 months of exposure, and the remaining 50 rats and 50 mice/sex/group were scheduled for sacrifice after 24 months of exposure. Because interim sacrifice groups were included in this 2-year study, the study provides information useful to evaluations of both subchronic and chronic exposures.

There was no statistically significant reduction in survival of treated rats or mice compared with their respective controls, and survival at the end of the study ranged from 40—70% (Quast et al., 1988, 1984). Female rats in both the 2730 and 8190 mg/m^3 groups showed slight, statistically significant deficits in body weight throughout much of the study ($\leq$7% less than controls, estimated from growth curves); the researchers considered the effect to be exposure-related at 8190 mg/m^3. In rats, no exposure-related histopathologic changes were observed, with the exception of histopathologic changes in the liver. Very slight microscopic hepatic changes ("accentuation of the normal hepatic lobular pattern," "altered cytoplasmic staining in the cells surrounding the central vein," and "hepatocytes in the portal region that appeared smaller in the exposed rats when compared with their respective controls") were described in both male and female rats of the 8190 mg/m^3 exposure group necropsied at 6 months (10/10 males and 10/10 females), 12 months (10/10 males and 10/10 females), and 18 months (7/10 males and 5/10 females); no difference from controls was seen in the animals after 2 years of exposure because of confounding geriatric changes. These histopathologic changes were not seen in any control or lower-dose animals at any time point. The histopathologic findings at 8190 mg/m^3 are consistent with a minimal hepatocellular hypertrophy, which is considered an adaptive physiologic response (i.e., stimulation of the drug-metabolizing enzyme system) and not a measure of toxicity. No effects were observed in mice. In light of the adaptive physiologic nature of the liver findings in rats at the highest exposure concentration, this study identified a NOAEL of 8190 mg/m^3, 6 hours/day, 5 day/week in rats and mice; the NOAEL is equivalent to 1460 mg/m^3 when adjusted to continuous exposure. A LOAEL was not identified.

McNutt et al. (1975)
Male CF-1 mice were chamber-exposed to 0, 250, or 1000 ppm (0, 1370, or 5460 mg/m^3) technical grade 1,1,1-trichloroethane (94—97% pure, 2.4—3.0% dioxane, 0.12—0.30% butanol) continuously for up to 14 weeks (McNutt et al., 1975). Serial sacrifices were performed on 10 mice/concentration at weekly intervals during the exposure period and at postexposure weeks 2 and 4. Endpoints included clinical observations, food and water intake, liver weight, liver fat content (determined by oil red O staining in three mice/concentration and triglyceride analysis in remaining seven mice/concentration), liver ultrastructure (three mice/concentration), and histology (liver, kidney, pancreas, intestine, heart, lung, and brain). Minimal changes, consisting of occasional mild liver ultrastructural variations after 10 weeks of exposure, were observed at 1370 mg/m^3. At 5460 mg/m^3, hepatic ultrastructural changes were more pronounced and accompanied by increases in relative liver weight, triglycerides, and lesions visible by light microscopy. Relative liver weight and liver triglyceride values were 22% ($p < 0.01$) and 237% ($p < 0.01$) higher at 5460 mg/m^3 compared with controls at exposure week 14. Histopathological changes included centrilobular hepatocyte swelling, vacuolation, lipid accumulation, and, after 10 weeks, single-cell necrosis. By 12 weeks of exposure, necrosis of individual hepatocytes (associated with acute inflammatory infiltrate and

hypertrophy of Kupffer cells) occurred in 40% of the mice exposed to 5460 mg/m^3. Exposure-related effects in tissues other than liver were not found. The minimal ultrastructural changes observed at 1370 mg/m^3 do not constitute clear evidence of an adverse effect. This study, therefore, identified a NOAEL of 1370 mg/m^3 and a LOAEL of 5460 mg/m^3 for liver effects in mice continuously exposed to 1,1,1-trichloroethane.

Thus, the experimental literature suggests that subchronic exposure to 1,1,1-trichloroethane induces hepatocellular hypertrophy at concentrations (adjusted for continuous exposure) of 1370 to 1460 mg/m^3 (Quast et al., 1988, 1984; McNutt et al., 1975); these effects do not appear to progress in severity or incidence with exposure duration (Quast et al., 1988, 1984) and are considered a physiologic rather than adverse response. At an exposure concentration of 5460 mg/m^3 (about fourfold higher than the NOAELs from McNutt et al. [1975] and Quast et al. [1988, 1984]), clear hepatotoxicity was observed (McNutt et al., 1975), with effects including increased relative liver weight and triglyceride levels, increased lipid content, and necrosis. The highest tested concentration in Quast et al. (1988, 1984) of 1460 mg/m^3 (duration adjusted) is considered a NOAEL, and the concentration in the McNutt et al. (1975) study associated with clear hepatotoxic effects (5460 mg/m^3) is a LOAEL.

Method of Analysis
The use of BMD methods was considered in analyzing the liver histopathology data from Quast et al. (1988, 1984) and McNutt et al. (1975). Because the response at the highest concentration tested in Quast et al. (1988, 1984) was not considered adverse and because McNutt et al. (1975) did not provide incidence data, neither data set was considered amenable to BMD methods. The NOAEL (8190 mg/m^3, 6 hours/day, 5 days/week; duration-adjusted = 1460 mg/m^3) was used as the point of departure.

Yang (2006) used the Reitz et al. (1988) PBPK model to extrapolate from the animal NOAEL from Quast et al. (1988, 1984) to humans. The model was run for 6 months of exposure (time to first sacrifice). (The time-weighted average [TWA] area under the curve [AUC] did not change with exposures longer than 6 months, indicating steady state had been achieved.) Using this model, the TWA liver 1,1,1-trichloroethane AUC resulting from inhalation exposure at the rat NOAEL was predicted. The modeled human inhalation exposure concentration (assuming continuous exposure) corresponding to the TWA AUC was determined to be 1553 mg/m^3. This modeling is more fully described in the *Toxicological Review of 1,1,1-Trichloroethane*, Section 5.2.3.2 (U.S. EPA, 2007).

Comparison to Shorter Duration RfCs and Final Subchronic RfC Derivation
As described below in Section I.B.3.3, Uncertainty Factors, a composite UF of 100 was applied to the point of departure of 1553 mg/m^3 derived from Quast et al. (1988, 1984), and a PBPK model was applied to obtain a subchronic RfC of 16 mg/m^3. This value of the

subchronic RfC turns out to be larger than the acute and short-term RfCs for 1,1,1-trichloroethane (see Sections I.B.1.1 and I.B.2.1), which range from 5 to 9 mg/m^3. This outcome is not surprising in light of the minimal subchronic/chronic toxicity associated with inhaled 1,1,1-trichloroethane, the differences in target organs and modes of action associated with acute and repeat-dose exposure durations, the availability of sensitive neurobehavioral testing in humans for evaluating 1,1,1-trichloroethane acute toxicity, and comparison of acute/short-term reference values based on analysis of peak exposure vs a subchronic reference value based on AUC exposure.

It is generally anticipated, however, that acute (or short-term) RfCs would be higher in absolute value than the subchronic or chronic RfC for that chemical since the acute (or short-term) exposure durations are greatly reduced compared with exposures of subchronic or chronic duration. In the case of 1,1,1-trichloroethane, clearly the short-term RfC of 5 mg/m^3 is protective of hepatotoxicity and other health effects associated with subchronic exposure. Accordingly, the subchronic RfC is set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure.

I.B.3.3. Uncertainty Factors

UF = 100.

A threefold UF was used to account for pharmacodynamic uncertainty in extrapolating from laboratory animals to humans. Use of a PBPK model accounts for differences in the toxicokinetics between rats and humans.

A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

A UF to extrapolate from a LOAEL to a NOAEL was not necessary because a NOAEL was used to determine the point of departure.

A UF to extrapolate from a shorter to a longer duration was not necessary because the NOAEL came from a 2-year chronic study with interim sacrifices at 6, 12, and 18 months; no progression in liver histopathological findings were observed after 6 months.

A database UF of 3 was applied to account for deficiencies in the subchronic database for 1,1,1-trichloroethane. Although the database for 1,1,1-trichloroethane following subchronic durations is relatively complete, there exists some uncertainty related to the potential neurotoxicity of 1,1,1-trichloroethane following repeated exposure. The inhalation database

includes several multi-dose studies that examined a range of endpoints, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study of 1,1,1-trichloroethane by the oral route (Lane et al., 1982), which found no evidence of reproductive toxicity, is available. In addition, an oral developmental neurotoxicity study (Maurissen et al., 1994, 1993), sponsored by the Halogenated Solvents Industry Alliance under a 1,1,1-trichloroethane Testing Consent Order with EPA, is available. Because pharmacokinetic data for 1,1,1-trichloroethane do not suggest route-specific differences in target organs, the findings from these oral studies can inform an evaluation of reproductive and neurodevelopmental toxicity following inhalation exposures. Limited information exists regarding the immunotoxicity of 1,1,1-trichloroethane by any route of exposure, although the limited information provides no clear evidence of immunotoxic potential. Aranyi et al. (1986) found no evidence of immunotoxicity in an in vivo study in mice involving acute inhalation exposure to 1,1,1-trichloroethane, and in repeat dose studies no effects were reported on spleen weight or histopathology (Calhoun et al., 1981; Prendergast et al., 1967; Torkelson et al., 1958; Adams et al., 1950) or spleen or thymus histopathology (Quast et al., 1988, 1984).

The neurotoxicity of 1,1,1-trichloroethane in humans and animals following acute exposure has been extensively documented; in animal models, acute 1,1,1-trichloroethane exposure has caused CNS depression and effects on motor activity and cognitive function. On balance, the available animal data suggest that repeated exposure to 1,1,1-trichloroethane does not cause overt effects on the CNS. Concern about the potential for 1,1,1-trichloroethane to affect the nervous system following prolonged exposure is raised by epidemiological findings and the findings of Rosengren et al. (1985) in gerbils. In a study of 28 workers exposed occupationally to 1,1,1-trichloroethane, Kelafant et al. (1994) reported increased sway in the Romberg test and statistically significant deficits for memory, intermediate memory, rhythm, and speed in a neuropsychological test battery. Workplace exposures were not measured, the number of workers in the study was small, and the Kelafant et al. (1994) findings were not confirmed in other limited studies of worker populations (Cherry et al., 1983; Maroni et al., 1977). Nevertheless, the qualitative findings from Kelafant et al. (1994) raise some concern about potential neurotoxic outcomes following prolonged 1,1,1-trichloroethane exposure. A limited number of experimental animal studies examined neurotoxic endpoints following repeated exposure. In a test of schedule-controlled operant behavior (fixed-ratio responding task), Moser et al. (1985) found that mice exposed repeatedly to high levels of 1,1,1-trichloroethane for 20 minutes per day, 4 days per week, over a 4-week period recovered each day after solvent exposure, indicating no residual effect of the chemical with repeated exposures; however, no similar study involving subchronic exposure is available. Mattsson et al. (1993) reported slight but statistically significant deficits in forelimb grip performance in rats exposed for 13 weeks; investigators considered the deficit possibly attributable to the sedative

properties of 1,1,1-trichloroethane. No other deficits indicative of neurotoxicity were observed (the study included a functional observational battery; evaluations of visual, auditory, somatosensory, and caudal nerve-evoked potentials; and histopathologic examination), although evaluation for cognitive deficits was not performed. In light of the qualitative findings from the epidemiological literature, additional evaluation of cognitive endpoints for subchronic durations would reduce uncertainty in the database.

Rosengren et al. (1985) reported a small but statistically significant increase in regional brain levels of glial fibrillary acidic protein (GFAP), a biomarker of glial hypertrophy in response to neuronal injury, in gerbils exposed to 1,1,1-trichloroethane for 3 months. Questions were raised about the reliability of these findings, and they were not supported by pathological, physiological, or neurochemical findings from other studies (see further discussion in Section 5.2.3.1 of the Toxicological Review of 1,1,1- Trichloroethane [U.S. EPA, 2007]); however, the findings raise a potential concern for effects on the CNS in the absence of an adequately conducted confirmatory study. On balance, issues raised by neurotoxicity findings for 1,1,1-trichloroethane support a database UF of 3 for the subchronic RfC.

I.B.3.4. Additional Comments/Studies

No useful subchronic studies in humans were located. Rosengren et al. (1985) reported increased GFAP, potentially indicating formation of astroglial fibrils in response to brain injury, in the sensorimotor cerebral cortex of gerbils exposed continuously to 1150 mg/m^3 for 3 months and evaluated 4 months after the end of exposure. There is some uncertainty, however, regarding the toxicological significance of this finding. Furthermore, comprehensive neurohistopathology assessment found no evidence of brain injury in rats exposed to 10,920 mg/m^3 of 1,1,1-trichloroethane intermittently for 3 months (duration adjusted concentration of 1950 mg/m^3) (Mattsson et al., 1993). Studies using standard techniques also failed to detect histological evidence of brain damage in rats or mice, most notably following intermittent exposure to 8190 mg/m^3 (duration adjusted concentration of 1440 mg/m^3) for 2 years (Quast et al., 1988, 1984).

Other subchronic studies in animals found ambiguous evidence for impaired forelimb grip strength and minimal lesions in the liver and nasal turbinates with exposure to 10,920 mg/m^3 (duration adjusted concentration of 1939 mg/m^3) for 13 weeks (Mattsson et al., 1993; Calhoun et al., 1981).

For more detail on Susceptible Populations, exit to the [toxicological review, Section 4.8 (PDF)](#).

I.B.3.5. Confidence in the Subchronic Inhalation RfC

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

The overall confidence in the subchronic RfC assessment is medium. Confidence in Quast et al. (1988, 1984), one of the coprincipal studies, is high. This study was well conducted, using two species, adequate numbers of animals, and interim sacrifices. Failure to use an exposure concentration high enough to produce treatment-related effects in this study was offset by the McNutt et al. (1975) study, which included an exposure concentration that resulted in clearly adverse hepatotoxic effects. Confidence in the database is medium. The database includes a 2-year chronic inhalation bioassay in rats and mice, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study by the oral route is available. While the available repeat-dose studies do not provide evidence of overt neurobehavioral effects, most repeat-dose studies did not include examination of subtle CNS toxicity.

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

I.B.4. Chronic Inhalation RfC

The chronic RfC applies to exposures for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).

The previous IRIS file did not include a chronic inhalation RfC for 1,1,1-trichloroethane.

I.B.4.1. Chronic Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Chronic RfC**
Liver histopathologic changes **2-Year inhalation rat study** **Quast et al. (1988, 1984)** **14-Week inhalation mouse study** **McNutt et al. (1975)**	NOAEL(HEC) = 1553 mg/m^3	100	5 mg/m^3

*Conversion Factors and Assumptions -- The human equivalent concentration (HEC) was estimated from the rat NOAEL of 8190 mg/m^3, 6 hours/day, 5 days/week (concentration adjusted to continuous exposure = 1460 mg/m^3) and application of PBPK modeling for interspecies extrapolation.

**Because the chronic RfC based on liver histopathologic changes following repeated exposure (16 mg/m^3) was higher than the short-term RfC (5 mg/m^3), the chronic RfC was set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure.

I.B.4.2. Principal and Supporting Studies

Two inhalation studies in rodents, Quast et al. (1988, 1984) and McNutt et al. (1975), were used to establish a NOAEL and LOAEL for effects on the liver in rodents.

Quast et al. (1988, 1984)

Quast et al. (1988, 1984) exposed groups of 80 male and 80 female F344 rats and B6C3F1 mice to 0, 150, 500, or 1500 ppm (0, 820, 2730, or 8190 mg/m^3) production-grade (94%) 1,1,1-trichloroethane vapor for 6 hours/day, 5 days/week for 2 years. Ten rats and 10 mice of each sex from each exposure group were scheduled for interim sacrifices after 6, 12, and 18 months of exposure, and the remaining 50 rats and 50 mice/sex/group were scheduled for sacrifice after 24 months of exposure.

There was no statistically significant reduction in survival of treated rats or mice compared with their respective controls, and survival at the end of the study ranged from 40—70% (Quast et al., 1988, 1984). Female rats in both the 2730 and 8190 mg/m^3 groups showed slight,

statistically significant deficits in body weight throughout much of the study ($\leq$7% less than controls, estimated from growth curves); the researchers considered the effect to be exposure related at 8190 mg/m^3. In rats, no exposure-related histopathologic changes were observed with the exception of histopathologic changes in the liver. Very slight microscopic hepatic changes ("accentuation of the normal hepatic lobular pattern," "altered cytoplasmic staining in the cells surrounding the central vein," and "hepatocytes in the portal region that appeared smaller in the exposed rats when compared with their respective controls") were described in both male and female rats of the 8190 mg/m^3 exposure group necropsied at 6 months (10/10 males and 10/10 females), 12 months (10/10 males and 10/10 females), and 18 months (7/10 males and 5/10 females); no difference from controls was seen in the animals after 2 years of exposure because of confounding geriatric changes. These histopathologic changes were not seen in any control or lower-dose animals at any time point. The histopathologic findings at 8190 mg/m^3 are consistent with a minimal hepatocellular hypertrophy, which is considered an adaptive physiologic response and not a measure of toxicity. No effects were observed in mice. In light of the adaptive physiologic nature of the liver findings in rats at the highest exposure concentration, this study identified a NOAEL of 8190 mg/m^3, 6 hours/day, 5 days/week in rats and mice; the NOAEL is equivalent to 1460 mg/m^3 when adjusted to continuous exposure. A LOAEL was not identified.

McNutt et al. (1975)

Male CF-1 mice were chamber-exposed to 0, 250, or 1000 ppm (0, 1370, or 5460 mg/m^3) technical grade 1,1,1-trichloroethane (94—97% pure, 2.4—3.0% dioxane, 0.12—0.30% butanol) continuously for up to 14 weeks (McNutt et al., 1975). Serial sacrifices were performed on 10 mice/concentration at weekly intervals during the exposure period and at postexposure weeks 2 and 4. Endpoints included clinical observations, food and water intake, liver weight, liver fat content (determined by oil red O staining in three mice/concentration and triglyceride analysis in remaining seven mice/concentration), liver ultrastructure (three mice/concentration), and histology (liver, kidney, pancreas, intestine, heart, lung, and brain). Minimal changes, consisting of occasional mild liver ultrastructural variations after 10 weeks of exposure, were observed at 1370 mg/m^3. At 5460 mg/m^3, hepatic ultrastructural changes were more pronounced and accompanied by increases in relative liver weight, triglycerides, and lesions visible by light microscopy. Relative liver weight and liver triglyceride values were 22% ($p < 0.01$) and 237% ($p < 0.01$) higher at 5460 mg/m^3 compared with controls at exposure week 14. Histopathological changes included centrilobular hepatocyte swelling, vacuolation, lipid accumulation, and, after 10 weeks, single-cell necrosis. By 12 weeks of exposure, necrosis of individual hepatocytes (associated with acute inflammatory infiltrate and hypertrophy of Kupffer cells) occurred in 40% of the mice exposed to 5460 mg/m^3. Exposure-related effects in tissues other than liver were not found. The minimal ultrastructural changes observed at 1370 mg/m^3 do not constitute clear evidence of an adverse effect. This study,

therefore, identified a NOAEL of 1370 mg/m^3 and a LOAEL of 5460 mg/m^3 for liver effects in mice continuously exposed to 1,1,1-trichloroethane.

Thus, the experimental literature suggests that chronic exposure to 1,1,1-trichloroethane induces hepatocellular hypertrophy at concentrations (adjusted for continuous exposure) of 1370 to 1460 mg/m^3 (Quast et al., 1988, 1984; McNutt et al., 1975); these effects do not appear to progress in severity or incidence with exposure duration (Quast et al., 1988, 1984) and are considered a physiologic rather than adverse response. At an exposure concentration of 5460 mg/m^3 (about fourfold higher than the NOAELs from McNutt et al. [1975] and Quast et al. [1988, 1984]), clear hepatotoxicity was observed (McNutt et al., 1975), with effects including increased relative liver weight and triglyceride levels, increased lipid content, and necrosis.

Quast et al. (1988, 1984) and McNutt et al. (1975) together can be used to establish a NOAEL and LOAEL for effects on the liver in rodents. The highest tested concentration in Quast et al. (1988, 1984) of 1460 mg/m^3 (duration adjusted) is considered a NOAEL, and the concentration in the McNutt et al. (1975) study associated with clear hepatotoxic effects is a LOAEL. Although McNutt et al. (1975) is a subchronic study, the findings from Quast et al. (1988, 1984) suggest a lack of progression of effects, at least at the NOAEL, from subchronic to chronic exposure durations.

Method of Analysis
The use of BMD methods was considered in analyzing the liver histopathology data from Quast et al. (1988, 1984) and McNutt et al. (1975). Because the response at the highest concentration tested in Quast et al. (1988, 1984) was not considered adverse and because McNutt et al. (1975) did not provide incidence data, neither data set was considered amenable to BMD methods. The NOAEL (8190 mg/m^3, 6 hours/day, 5 days/week; duration-adjusted = 1460 mg/m^3) was used as the point of departure.

Yang (2006) used the Reitz et al. (1988) PBPK model to extrapolate from the animal NOAEL from Quast et al. (1988, 1984) to humans. The model was run for 6 months of exposure (time to first sacrifice). (The TWA AUC did not change with exposures longer than 6 months, indicating steady state had been achieved.) Using this model, the TWA liver 1,1,1-trichloroethane AUC resulting from inhalation exposure at the rat NOAEL was predicted. The modeled human inhalation exposure concentration (assuming continuous exposure) corresponding to the TWA AUC was determined to be 1553 mg/m^3. This modeling is more fully described in the *Toxicological Review of 1,1,1-Trichloroethane*, Section 5.2.3.2 (U.S. EPA, 2007).

Comparison with Shorter Duration RfCs and Final Chronic RfC Derivation

As described below (Section I.B.4.3, Uncertainty Factors), a composite uncertainty factor of 100 was applied to the point of departure of 1553 mg/m^3 derived from Quast et al. (1988, 1984), and PBPK modeling was applied to obtain a chronic RfC of 16 mg/m^3. This value of the chronic RfC turns out to be larger than the acute and short-term RfCs for 1,1,1-trichloroethane (see Sections I.B.1.1 and I.B.2.1), which range from 5 to 9 mg/m^3. This outcome is not surprising in light of the minimal chronic toxicity associated with inhaled 1,1,1-trichloroethane, the differences in target organs and modes of action associated with acute and repeat-dose exposure durations, the availability of sensitive neurobehavioral testing in humans for evaluating 1,1,1-trichloroethane acute toxicity, and comparison of acute/short-term reference values based on analysis of peak exposure vs a chronic reference value based on AUC exposure.

While the outcome is not surprising, it is generally anticipated that acute (or short-term) RfCs would be higher in absolute value than the chronic RfC for that chemical since the acute (or short-term) exposure durations are greatly reduced compared with exposures of chronic duration. In the case of 1,1,1-trichloroethane, clearly the short-term RfC of 5 mg/m^3 is protective of hepatotoxicity and other health effects associated with chronic exposure. Accordingly, the chronic RfC is set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure. It should be noted that there are limited data suggesting neurobehavioral effects in chronically (occupationally) exposed humans (see Section I.B.4.4, below).

I.B.4.3. Uncertainty Factors

UF = 100.

A threefold UF was used to account for pharmacodynamic uncertainty in extrapolating from laboratory animals to humans. Use of a PBPK model accounts for differences in the toxicokinetics between rats and humans.

A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

A UF to extrapolate from a LOAEL to a NOAEL was not necessary because a NOAEL was used to determine the point of departure.

A UF to extrapolate from a shorter to a longer duration was not necessary because the NOAEL came from a 2-year chronic study with interim sacrifices at 6, 12, and 18 months; no progression in liver histopathological findings was observed after 6 months.

A database UF of 3 was applied to account for deficiencies in the chronic database for 1,1,1-trichloroethane. Although the database for 1,1,1-trichloroethane is relatively complete, there exists some uncertainty related to the potential neurotoxicity of 1,1,1-trichloroethane following repeated exposure. The inhalation database includes one reasonably comprehensive chronic bioassay in rats and mice, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study of 1,1,1-trichloroethane by the oral route (Lane et al., 1982), which found no evidence of reproductive toxicity, is available. In addition, an oral developmental neurotoxicity study (Maurissen et al., 1994, 1993), sponsored by the Halogenated Solvents Industry Alliance under a 1,1,1-trichloroethane Testing Consent Order with EPA, is available. Because pharmacokinetic data for 1,1,1-trichloroethane do not suggest route-specific differences in target organs, the findings from these oral studies can inform an evaluation of reproductive and neurodevelopmental toxicity following inhalation exposures. Limited information exists regarding the immunotoxicity of 1,1,1-trichloroethane by any route of exposure, although the limited information provides no clear evidence of immunotoxic potential. Aranyi et al. (1986) found no evidence of immunotoxicity in an in vivo study in mice involving acute inhalation exposure to 1,1,1-trichloroethane, and in repeat dose studies no effects were reported on spleen weight or histopathology (Calhoun et al., 1981; Prendergast et al., 1967; Torkelson et al., 1958; Adams et al., 1950) or spleen or thymus histopathology (Quast et al., 1988, 1984).

The neurotoxicity of 1,1,1-trichloroethane in humans and animals following acute exposure has been extensively documented; in animal models, acute 1,1,1-trichloroethane exposure has caused CNS depression and effects on motor activity and cognitive function. On balance, the available animal data suggest that repeated exposure to 1,1,1-trichloroethane does not cause overt effects on the CNS. Concern about the potential for 1,1,1-trichloroethane to affect the nervous system following prolonged exposure is raised by epidemiological findings and the subchronic findings of Rosengren et al. (1985) in gerbils. In a study of 28 workers exposed occupationally to 1,1,1-trichloroethane, Kelafant et al. (1994) reported increased sway in the Romberg test and statistically significant deficits for memory, intermediate memory, rhythm, and speed in a neuropsychological test battery. Workplace exposures were not measured, the number of workers in the study was small, and Kelafant et al. (1994) findings were not confirmed in other limited studies of worker populations (Cherry et al., 1983; Maroni et al., 1977). Nevertheless, the qualitative findings from Kelafant et al. (1994) raise some concern about potential neurotoxic outcomes following prolonged 1,1,1-trichloroethane exposure. A

limited number of experimental animal studies examined neurotoxic endpoints following repeated exposure. In a test of schedule-controlled operant behavior (fixed-ratio responding task), Moser et al. (1985) found that mice exposed repeatedly to high levels of 1,1,1-trichloroethane for 20 minutes per day, 4 days per week, over a 4-week period recovered each day after solvent exposure, indicating no residual effect of the chemical with repeated exposures; however, no similar study involving subchronic or chronic exposure is available. Mattsson et al. (1993) reported slight but statistically significant deficits in forelimb grip performance in rats exposed for 13 weeks; investigators considered the deficit possibly attributable to the sedative properties of 1,1,1-trichloroethane. No other deficits indicative of neurotoxicity were observed (the study included a functional observational battery; evaluations of visual, auditory, somatosensory, and caudal nerve-evoked potentials; and histopathologic examination), although evaluation for cognitive deficits was not performed. In light of the qualitative findings from the epidemiological literature, additional evaluation of cognitive endpoints for subchronic or chronic durations would reduce uncertainty in the database.

Rosengren et al. (1985) reported a small but statistically significant increase in regional brain levels of GFAP, a biomarker of glial hypertrophy in response to neuronal injury, in gerbils exposed to 1,1,1-trichloroethane for 3 months. Questions were raised about the reliability of these findings, and they were not supported by pathological, physiological, or neurochemical findings from other studies (see Section 5.2.3.1 in *Toxicological Review of 1,1,1-Trichloroethane* [U.S.EPA, 2007]); however, the findings raise a potential concern for effects on the CNS in the absence of an adequately conducted confirmatory study. On balance, issues raised by neurotoxicity findings for 1,1,1-trichloroethane support a database UF of 3 for the chronic RfC.

I.B.4.4. Additional Studies/Comments

Studies of workers with chronic occupational exposure to 1,1,1-trichloroethane provide only limited data for use in dose-response assessment. Kelafant et al. (1994) provided evidence of neurobehavioral effects in a group of workers exposed to high concentrations of 1,1,1-trichloroethane over a 10-year period, but the exposures were not quantified. Maroni et al. (1977) did not find neurological effects in another group of workers, but exposures (600 to 1880 mg/m^3 for most workers) were estimated based on very limited data, group sizes were small (7—8 per group), and the neurological tests did not include reaction time, which was found to be the most sensitive endpoint in the controlled exposure studies. In a larger study of textile plant workers, Kramer et al. (1978) found no exposure-related effects on health but included only limited investigation of neurological endpoints (Romberg test).

For more detail on Susceptible Populations, exit to the [toxicological review, Section 4.8 (PDF)](#).

I.B.4.5. Confidence in the Chronic Inhalation RfC

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

The overall confidence in this RfC assessment is medium. Confidence in Quast et al. (1988, 1984), one of the coprincipal studies, is high. This study was well conducted, using two species, adequate numbers of animals, and interim sacrifices. Failure to use an exposure concentration high enough to produce treatment-related effects in this study was offset by the McNutt et al. (1975) study, which included an exposure concentration that resulted in clearly adverse hepatotoxic effects. Confidence in the database is medium. The database includes a 2-year chronic inhalation bioassay in rats and mice, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study by the oral route is available. While the available repeat-dose studies do not provide evidence of overt neurobehavioral effects, most repeat-dose studies did not include examination of subtle CNS toxicity.

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

I.B.5. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2007

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007). *[To review this appendix, exit to the toxicological review, Appendix A Summary of External Peer Review and Public Comments and Disposition (PDF)](#).*

Agency Completion Date -- 09/28/2007

I.B.6. 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 — 1,1,1-Trichloroethane
CASRN — 71-55-6
Section II. Last Revised — 09/28/2007

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 an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is an 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.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for 1,1,1-trichloroethane provides "inadequate information to assess carcinogenic potential." Epidemiologic studies of humans chronically exposed to 1,1,1-trichloroethane are

inconclusive. A 2-year inhalation bioassay showed no treatment-related increase in tumors in rats and mice at an exposure concentration below the maximum tolerated dose. The two available oral cancer bioassays in rats and mice are considered inadequate for evaluation of carcinogenic potential. 1,1,1-Trichloroethane has been tested extensively for genotoxic potential. The chemical has shown little capacity to produce genotoxic effects in bacteria or fungi. Results in mammalian test systems in vitro and in vivo were more mixed but still predominantly negative for assays other than cell transformation. The chemical has been shown to interact weakly with DNA.

The previous IRIS assessment (1987) classified 1,1,1-trichloroethane as Group D ("not classifiable as to human carcinogenicity") under the 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986), based on a lack of data on the carcinogenicity of 1,1,1-trichloroethane in humans and inadequate evidence of carcinogenicity in animals.

II.A.2. Human Carcinogenicity Data

The potential carcinogenicity of 1,1,1-trichloroethane was examined in two occupational cohort studies and several case-control and environmental studies. Finnish workers (cohort consisting of 2050 men and 1924 women) exposed to 1,1,1-trichloroethane had statistically significantly increased standardized incidence ratios (SIRs) for cancer of the nervous system (SIR = 6.05; 95% CI: 1.25—17.7) and multiple myeloma (SIR = 15.98; 95% CI: 1.93—57.7) (Anttila et al., 1995). The results are based on only three cases of nervous system tumors and two cases (both females) of multiple myeloma among 1,1,1-trichloroethane-exposed workers. The large confidence intervals reveal the low statistical power of these findings. An increased risk of multiple myeloma was also observed in female workers exposed to 1,1,1-trichloroethane at an aircraft maintenance facility in Utah (standardized mortality ratio = 56.6; 95% CI: 6.85—204.45) (Spirtas et al., 1991). The cohort consisted of 27,223 person-years (men) and 1215 person-years (women) with 1,1,1-trichloroethane exposure. The multiple myeloma finding was also based on only two observed cases. No cases of multiple myeloma were seen in men. In both studies, workers were exposed to multiple solvents, and in neither case was it possible to isolate the effects of 1,1,1-trichloroethane from those of other solvents. Case-control and environmental studies did not find any associations between tumors of various types (including astrocytic brain cancer) and 1,1,1-trichloroethane exposure (Dosemeci et al., 1999; Kernan et al., 1999; Mulla, 1996; Heineman et al., 1994; Garland, 1987; Garabrant, 1986; Isacson et al., 1985); however, the power of such studies to find an association is low.

II.A.3. Animal Carcinogenicity Data

1,1,1-Trichloroethane has been tested for carcinogenicity in rats and mice by the oral route in two studies (NCI, 1977; Maltoni et al., 1986) and by the inhalation route in one study (Quast et al., 1988, 1984). Maltoni et al. (1986) found a small increase in the incidence of leukemias, primarily pulmonary immunoblastic lymphosarcomas, in rats (male and female combined) treated with 1,1,1-trichloroethane by gavage in oil for 104 weeks. These results were considered inconclusive, however, because of the marginal nature of the findings, inherent limitations of the experimental design (one dose level, one species), and incomplete analysis and reporting of results. Oral studies by NCI (1977) in rats and mice conducted at higher doses did not find tumor increases associated with 1,1,1-trichloroethane exposure but were not adequate tests due to high early mortality in all groups of treated animals (due, at least in part, to intercurrent chronic murine pneumonia) that left few animals at risk for development of late-appearing tumors. Inhalation studies by Quast et al. (1988, 1984) found no evidence of a carcinogenic effect of 1,1,1-trichloroethane in either rats or mice. In these studies, however, it appears that exposure levels were too low. The maximum tolerated dose (MTD) was not reached in mice (no adverse effects were observed in either sex) and may not have been reached in rats, as the only toxic effects noted were a slight reduction in body weight gain in female rats and slight microscopic hepatic changes in male and female rats exposed to the high concentration of 8190 mg/m^3. Therefore, the possibility of tumors occurring at higher inhalation exposures cannot be ruled out.

One of the metabolites of 1,1,1-trichloroethane, trichloroacetic acid, has been reported to cause hepatocellular tumors in mice. Trichloroacetic acid is also a metabolite of trichloroethylene and has been implicated as one of the active agents involved in the production of liver tumors in mice treated with trichloroethylene (Bull, 2000). However, metabolism of 1,1,1-trichloroethane is slight (< 5% of the absorbed dose) and far less extensive than that of trichloroethylene (40—75% of the absorbed dose; ATSDR, 1997). The limited extent of metabolism of 1,1,1-trichloroethane (and resulting low production of trichloroacetic acid) may explain, at least in part, the apparent inability of 1,1,1-trichloroethane to produce liver tumors in mice, despite the production of mouse liver tumors by the metabolite trichloroacetic acid and the qualitatively similarly metabolized compound trichloroethylene.

II.A.4. Supporting Data for Carcinogenicity

Supporting studies provide mixed evidence regarding the carcinogenic potential of 1,1,1-trichloroethane. A rat liver foci assay for tumor-initiating and -promoting activity was negative for both (Story et al., 1986; Milman et al., 1988). In vitro studies for effects associated with carcinogens (inhibition of interferon induction in mouse embryo fibroblasts

and inhibition of the natural tumoricidal activity of human liver immune cells) were also negative (Wright et al., 1994; Sonnenfeld et al., 1983). The genotoxic effects of 1,1,1-trichloroethane have been studied extensively. The chemical has shown little capacity to produce genotoxic effects in bacteria or fungi, regardless of test system, use of metabolic activation, or measures to counter loss due to volatility. Results in mammalian test systems in vitro and in vivo were more mixed, although still predominantly negative for assays other than cell transformation. Positive results were found in six of seven reported cell transformation assays. It has also been shown that 1,1,1-trichloroethane has the ability to bind DNA, at least weakly, in vivo (Milman et al., 1988; Prodi et al. 1988; Turina et al., 1986).

A potential complicating factor in interpreting the results of cancer bioassays of 1,1,1-trichloroethane is the frequent addition of stabilizing chemicals to commercial formulations of this compound (Henschler et al., 1980). Several of these stabilizers have produced positive responses in cancer bioassays with rats and mice (e.g., 1,4-dioxane, 1,2-epoxybutane, and nitromethane). Anttila et al. (1995) reported that small amounts of 1,4-dioxane (< 1—5%) were used as stabilizer in the 1,1,1-trichloroethane to which the workers in their study were exposed but did not consider this small exposure to 1,4-dioxane to be responsible for the increased cancer risks observed in workers exposed to 1,1,1-trichloroethane in their study.

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 4.8 (PDF)](#).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable. Data are inadequate for an assessment of human carcinogenic potential.

II.B.1. Summary of Risk Estimates

Not applicable.

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable. Data are inadequate for an assessment of human carcinogenic potential.

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2007

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of 1,1,1-Trichloroethane* (U.S. EPA, 2007). ***To review this appendix, exit to the toxicological review, Appendix A Summary of External Peer Review and Public Comments and Disposition (PDF).***

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Completion Date -- 09/28/2007

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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 (internet address).

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

VI. Bibliography

Substance Name — 1,1,1-Trichloroethane
CASRN — 71-55-6
Sectopm VI. Last Revised — 09/28/2007

VI.A. Oral RfD References

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VII. Revision History

Substance Name — 1,1,1-Trichloroethane
CASRN — 71-55-6

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
08/01/1991	I.A.	Withdrawn pending further review
12/03/2002	I.A., II.D.2.	Screening-Level Literature Review Findings message has been added.
09/28/2007	I., II., VI.	Reference value and cancer sections updated. Included as a pilot to test recommendations of the RfD/RfC Technical Panel (U.S. EPA, 2002).

VIII. Synonyms

Substance Name — 1,1,1-Trichloroethane
CASRN — 71-55-6
Section VIII. Last Revised — 09/28/2007

- 71-55-6
- Aerothene MM
- Aerothene TT
- Algylen
- Baltana
- CF 2
- Chloroethane-NU
- Chloroethene
- Chloroethene NU
- Chloroform, Methyl-
- Chlorothane NU
- Chlorothene
- Chlorothene NU
- Chlorothene SM
- Chlorothene VG
- Chlortene
- Chlorten
- Chlorylen
- Dowclene LS
- Ethane, 1,1,1-Trichloro-
- Gemalgene
- Genklene LB
- ICI-CF 2
- Inhibisol
- Methylchloroform
- Methyltrichloromethane
- NCI C04626
- RCRA Hazardous Waste Number U226
- Solvent 111
- Alpha-T
- 1,1,1-TCE
- 1,1,1-TCA
- TCEA
- Trichloran
- Trichloroethane, 1,1,1-
- alpha-Trichloroethane
- Trichloromethylmethane
- Tri-ethane
- Trielene
- UN 2831