1,2,3-Trichloropropane; CASRN 96-18-4

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgrd.html.

STATUS OF DATA FOR 1,2,3-Trichloropropane

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/2009
Inhalation RfC (I.B.)	yes	09/30/2009
Carcinogenicity Assessment (II.)	yes	09/30/2009

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 1,2,3-Trichloropropane
CASRN — 96-18-4
Section I.A. Last Revised — 09/30/2009

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

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

This RfD replaces the previous RfD of 0.006 mg/kg-day. The IRIS database contained an IRIS Summary for 1,2,3-trichloropropane that was posted in 1987. The previous RfD value of 0.006 mg/kg-day was based on a subchronic oral gavage study in rats (NTP, 1983). In the previous assessment, the low-dose group in the principal study (8 mg/kg-day) was identified as the no-observed-adverse-effect level (NOAEL) and a NOAEL-LOAEL approach was adjusted for continuous exposure to identify the point of departure (POD = 8 mg/kg-day x 5/7 = 5.71 mg/kg-day). The previous RfD was derived by dividing the POD by a composite uncertainty factor (UF) of 1,000 (10 to account for interspecies variability, 10 for intraspecies extrapolation, and 10 to extrapolate from subchronic to chronic data).

I.A.1. Chronic Oral RfD Summary

Critical Effect	Point of Departure*	UF	Chronic RfD
Increased absolute liver weight in male rats **2-year bioassay** **NTP, 1993**	BMD_{10}: 3.8 mg/kg-day $BMDL_{10}$: 1.6 mg/kg-day $BMDL_{ADJ}$: 1.1 mg/kg-day	300	0.004 mg/kg-day

*Conversion Factors and Assumptions — The $BMDL_{10}$ was adjusted to a continuous daily exposure ($BMDL_{ADJ}$ = 1.6 mg/kg-day x 5/7 = 1.1 mg/kg-day).

I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (1993) conducted a 2-year study of the toxicity and carcinogenicity of 1,2,3-trichloropropane in F344/N rats. The chemical was administered by corn oil gavage to 60 rats/sex/group. The rats were approximately 6 weeks old when the study was initiated. Rats received doses of 0, 3, 10, or 30 mg/kg-day, and after 15 months (65–67 weeks), 8–10 rats per group were sacrificed to allow an interim evaluation of all toxicological parameters and histopathology. Due to high mortality in rats receiving 30 mg/kg at the interim evaluation, the remaining survivors in that group were sacrificed at week 67 (females) and week 77 (males).

Due to the early termination of this treatment group, organ weights and hematology data were only obtained at the 15-month interim sacrifices.

In rats, the mean body weights of the high-dose males and females appeared lower than control rat body weights. Statistically significant increases in absolute liver weights were observed in male and female rats exposed for 15 months to doses of ≥3 mg/kg-day 1,2,3-trichloropropane. Mean relative liver weights were significantly increased in male rats that received doses of 10 or 30 mg/kg-day when compared with controls. Mean relative liver weights in female rats that received doses of 10 or 30 mg/kg-day were increased. Statistically significant increases in absolute right kidney weights were observed in male rats exposed for 15 months to doses of ≥3 mg/kg-day 1,2,3-trichloropropane and female rats exposed to doses of ≥10 mg/kg-day. Mean relative kidney weights in males from these treatment groups were increased. Mean relative kidney weights of females in the 10 and 30 mg/kg-day treatment groups were increased. In addition, ALT and 5'-nucleotidase levels were statistically significantly decreased in males that received 30 mg/kg-day. Hepatocellular necrosis was observed in 1/49 and 4/52 female rats at 3 and 30 mg/kg-day, respectively. Hepatocellular necrosis was not observed in male rats. In addition, a dose-dependent increase in bile duct hyperplasia was observed in male rats at 30 mg/kg-day. Nonneoplastic effects were also observed in the forestomach, kidney, and pancreas of male and female rats at the 2-year evaluation.

NTP (1993) conducted a 2-year study of the toxicity and carcinogenicity of 1,2,3-trichloropropane in B6C3F1 mice. The chemical was administered by corn oil gavage to 60 mice/sex/group, and the mice were approximately 6 weeks old when the study began. Mice were treated with 0, 6, 20, or 60 mg/kg-day, and after 15 months (65–67 weeks), 8–10 mice per group were sacrificed to allow an interim evaluation of all toxicological parameters and histopathology. Due to high mortality in the mice receiving 60 mg/kg-day, surviving mice were evaluated at week 73 (females) and week 79 (males). Due to the early termination of this treatment group, organ weights and hematology data were only obtained at the 15-month interim sacrifices.

In mice, final mean body weights were significantly decreased in males and females after a dose of 60 mg/kg-day when compared to controls. Mean relative liver weights were increased in males and females that received 60 mg/kg-day. Other significant changes in organ weights among mice that received this dose included increased relative kidney weights in females, and increased relative brain weights in males and females. Creatine kinase and SDH levels were statistically significantly elevated in males and females, respectively, that received 60 mg/kg-day. However, clinical chemistry differences between dose groups and control animals were not considered to be directly related to 1,2,3-trichloropropane administration (NTP, 1993). An increase in hepatocellular necrosis was observed in male mice (1/52, 2/51, 11/54, and 8/56)

and female mice (1/50, 6/50, 5/51, and 10/55) in the vehicle control, 3, 10, and 30 mg/kg-day, respectively (NTP, 1993). The incidence of squamous hyperplasia in the forestomach was increased at 3, 10, and 30 mg/kg-day in male (29/51, 27/54, and 34/56) and female mice (15/49, 14/51, and 31/55), respectively (NTP, 1993).

In the subchronic investigation, 1,2,3-trichloropropane was administered to both rats and mice by corn oil gavage 5 days/week for 120 days at doses of 0, 8, 16, 32, 63, 125, or 250 mg/kg-day (NTP, 1993). Treatment groups contained 20 animals/sex and the vehicle control group contained 30 animals/sex. Half of the animals in each group were sacrificed after 8 weeks, and the rest were maintained until week 17.

In rats, mean relative liver weights were statistically significantly increased in males that received 32, 63, or 125 mg/kg-day, while absolute liver weights were statistically significantly increased in males receiving 8 to 125 mg/kg-day. Mean absolute and relative liver weights were statistically significantly increased in female rats receiving 16, 32, 63, or 125 mg/kg-day. Mean absolute and relative right kidney weights were statistically significantly increased in males that received 32, 63, or 125 mg/kg-day and in females that received 63 and 125 mg/kg-day 1,2,3-trichloropropane. Absolute heart weight was statistically significantly decreased in male rats at 63 and 125 mg/kg-day.

The liver lesions in rats were characterized by multifocal, centrilobular hepatocellular necrosis, with karyomegaly, hemorrhage, and bile duct hyperplasia. Hepatic necrosis was observed in female rats (7/9) receiving 125 mg/kg-day and in all of the rats receiving 250 mg/kg-day 1,2,3-trichloropropane (20/20 males and 20/20 females) at the time of their death. In the 17-week evaluation, hepatic necrosis was observed at terminal sacrifice in 1/10 males and 11/11 females treated with a dose of 125 mg/kg-day, with liver necrosis also evident in 1/10 male rats at 32 and 63 mg/kg-day.

The kidney lesions in the rats were characterized by early diffuse acute tubule necrosis or regenerative hyperplasia, karyomegaly of epithelial cells, and multifocal necrosis. Renal tubular necrosis was observed during the 8-week interim evaluation in 14/20 males and 20/20 females treated with 250 mg/kg-day that died at or before the interim sacrifice. At the 17-week evaluation, renal necrosis was observed in 1/10 males and 0/11 females treated with a dose of 125 mg/kg-day.

Lesions of the nasal turbinates included multifocal necrosis and epithelial attenuation, subepithelial fibrosis, and inflammation. Epithelial necrosis of the nasal turbinates was observed during the 8-week interim evaluation in 14/20 males and 19/20 females treated with 250 mg/kg-day that died at or before the interim sacrifice. At the time of death or at the 17-

week evaluation, epithelial necrosis of the nasal turbinates was observed in 3/9 males and 2/11 females treated with 125 mg/kg-day.

A number of clinical chemistry parameters in rats were statistically significantly affected upon exposure to 1,2,3-trichloropropane. Effects observed were predominantly biomarkers for liver damage. At the 8-week interim evaluation, the activities of alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), and aspartate aminotransferase (AST), were all statistically significantly elevated over controls in females that received 125 mg/kg-day. Total bilirubin levels in female rats at the 8-week evaluation increased at the doses of 63 and 125 mg/kg-day. At the 17-week evaluation, ALT and SDH activities were statistically significantly elevated over controls in females treated with 125 mg/kg-day.

The activity of ALT was statistically significantly elevated in males treated with 125 mg/kg-day at week 8 but not at week 17, while the activity of SDH in males at 17 weeks was statistically significantly increased at 63 and 125 mg/kg-day, respectively. NTP (1993) stated that the increase in ALT and SDH was indicative of hepatocellular damage with subsequent enzyme leakage. The only clinical chemistry parameter that was consistently impacted in both males and females at both time points was pseudocholinesterase (serum carboxylesterase). Activity of this hepatic enzyme decreased in both species with increasing dose and NTP (1993) suggested that the depressed synthesis of pseudocholinesterase was due to hepatocellular damage. A statistically significant decrease was observed at both time points (8 and 17 weeks) evaluated in females at the lowest dose tested at 8 mg/kg-day and in males that received 32 mg/kg-day. The authors observed a dose-dependent decrease in pseudocholinesterase at 8 through 125 mg/kg-day in female rats and at 32 through 125 mg/kg-day in male rats at 17-weeks.

In mice, a statistically significant increase in absolute and relative liver weights was observed in male and female mice that received a dose of ≥125 mg/kg-day, with absolute liver weights in males increasing statistically significantly at ≥32 mg/kg-day. Mean relative right kidney weights in female mice were statistically significantly decreased at ≥16 mg/kg-day, while absolute right kidney weights were statistically significantly decreased at 250 mg/kg-day. The changes in relative and absolute right kidney weights in male mice did not follow a clear dose-response pattern. Mean relative heart weights in males were statistically significantly decreased at ≥8 mg/kg-day and in females at ≥16 mg/kg-day. Absolute heart weights in males were statistically significantly reduced at ≥63 mg/kg-day and in females at 250 mg/kg-day. Relative brain weights in male and female mice were statistically significantly decreased at 16–125 mg/kg-day.

Regenerative lung lesions were observed in 9/12 male mice and 10/12 female mice, and hyperkeratosis of the forestomach in 7/12 male mice and 9/12 female mice receiving 125

mg/kg-day 1,2,3-trichloropropane at the 17-week evaluation. Lung lesions in male and female mice at 250 mg/kg-day 1,2,3-trichloropropane were observed in 14/19 males and 7/14 females, while forestomach lesions in the same dose group were observed in 4/19 males and 8/14 females. At 63 mg/kg-day, female mice displayed lung lesions (7/9) and forestomach lesions (7/9).

Liver lesions were observed at both the 8-week interim and 17-week terminal sacrifice. At the 8-week evaluation, liver lesions were not observed in the only examined male mouse that received 250 mg/kg-day 1,2,3-trichloropropane, but hepatic necrosis was observed in 4/6 females that received this dose. Hepatic necrosis at the 8-week evaluation was observed in 6/8 males and 0/8 females that received 125 mg/kg-day. At the 17-week evaluation, liver necrosis was observed in 14/19 males, most of which died prior to 8-week evaluation, and 5/14 females that received 250 mg/kg-day, and 1/10 male and 0/10 female controls. Hepatocelluar degeneration associated with fatty change and karyomegaly was also observed in 11/19 males and 1/14 females of the high-dose group. Also at the 17-week evaluation, liver lesions in mice at the 125 mg/kg-day dose occurred in 1/12 males and 1/12 females.

There is evidence of hepatocellular damage, including increased incidence of hepatocellular necrosis and decreased synthesis of pseudocholinesterase, from the subchronic NTP (1993) studies, and increased serum concentrations of hepatocellular enzymes (ALT and SDH), decreased concentration of 5'-nucleotidase, and increased incidence of histopathologic liver lesions, including hepatocellular necrosis, from the chronic NTP (1993) studies. Increased liver weight was selected as the critical effect because it represents the most sensitive effect observed in the liver and occurs early in the process of liver toxicity associated with oral exposure to 1,2,3-trichloropropane.

Benchmark dose (BMD) modeling was conducted using EPA's Benchmark Dose Software (BMDS, version 1.4.1) to analyze the changes in liver and kidney weight, fertility, and pups/litter associated with chronic exposure to 1,2,3-trichloropropane (See Section 5.1.2. and Appendix B of the Toxicological Review). The BMD_{10} estimated from the Hill model using absolute liver weight change in male F344/N rats is 3.8 mg/kg-day and the corresponding $BMDL_{10}$ is 1.6 mg/kg-day. The BMDL corresponds to the 95% lower bound on dose associated with a 10% increase in mean absolute liver weight. A benchmark response (BMR) of a 10% change in the mean was used in the modeling of absolute and relative liver and kidney weight because the *Benchmark Dose Technical Guidance Document* (US EPA, 2000) recommends using the minimal amount of change in the endpoint that is considered to be biologically significant to define the BMR.

I.A.3. Uncertainty Factors

UF = 300

A total UF of 300 was applied to this effect level: uncertainty associated with interspecies differences (UF_A: animal to human), consideration of intraspecies variation (UF_H: human variability), and database deficiencies (UF_D: database deficiency).

A 10-fold UF_A was used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability) because information was unavailable to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans.

A 10-fold UF_H was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability) because information is unavailable to predict potential variability in human susceptibility.

An UF_S was not needed to account for extrapolation from subchronic-to-chronic exposure because a chronic study was used to derive the chronic RfD.

An UF_L for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of a 10% change in absolute liver weight was selected under an assumption that it represents a minimal biologically significant change.

A 3-fold UF_D was selected to account for database deficiencies. The database of chronic and subchronic animal studies includes a 2-year gavage study in F344/N rats and B6C3F1 mice (Irwin et al., 1995; NTP, 1993), a 90-day gavage study in Sprague-Dawley rats (Merrick et al., 1991), a 90-day drinking water study in Sprague-Dawley rats (Villeneuve et al., 1985), a 17-week gavage study in F344/N rats (NTP, 1993; Hazleton Laboratories, 1983a), a 17-week gavage study in B6C3F1 mice (NTP 1993; Hazleton Laboratories, 1983b;), and a two-generation reproductive/fertility assessment in Swiss CD-1 mice (NTP, 1990). A threefold UF_D for database deficiencies was applied because the database lacks information on developmental toxicity associated with 1,2,3-trichloropropane. In addition, the two-generation reproductive toxicity study indicates that the developing fetus may be a target of toxicity. The lack of a reproductive toxicity study that extends beyond two generations and the absence of a developmental toxicity study are of particular concern due to the genotoxicity of 1,2,3-trichloropropane, which may mean that any resulting genetic damage to the germ cells of the F1 generation may not be detected until the F2 generation.

I.A.4. Additional Studies/Comments

Merrick et al. (1991) administered 1,2,3-trichloropropane in corn oil to Sprague-Dawley rats by gavage for 90 days at 0, 1.5, 7.4, 15, or 60 mg/kg-day. Animals that received 60 mg/kg-day exhibited a reduction in mean body weight gain when compared to controls. Relative liver weights were statistically significantly increased in animals that received 15 or 60 mg/kg-day, relative kidney weights were increased in the high-dose group animals, and relative brain and testes weights were statistically significantly increased in males from the high dose group. Female rats that received 60 mg/kg-day 1,2,3-trichloropropane exhibited elevated ALT and AST levels. An increased incidence of inflammation-associated myocardial necrosis was observed in males and females that received 60 mg/kg-day 1,2,3-trichloropropane. Bile duct hyperplasia was observed in the livers of one control male and males and females in the high dose group. Other proliferative and neoplastic lesions observed in high-dose animals included a forestomach squamous cell papilloma, forestomach squamous cell hyperplasia, a hepatocellular adenoma, and plasma cell hyperplasia in the mandibular lymph node.

Villeneuve et al. (1985) administered 1,2,3-trichloropropane in drinking water to Sprague-Dawley rats 7 days/week for 90 days at 0, 1, 10, 100, or 1,000 mg/L. Mean body weight gain was reduced in male and female rats that were exposed to 1,000 mg/L 1,2,3-trichloropropane. Relative liver and kidney weights were reportedly increased in males and females. Mean serum cholesterol levels were increased 55% in female rats exposed to 1,000 mg/L and no effect on cholesterol was observed in males. Hepatic aminopyrine demethylase activity was reportedly significantly increased in males and females that were exposed to 1,000 mg/L. Aniline hydroxylase activity was significantly increased in males that received 1,000 mg/L. Mean relative brain weights for the 1000 mg/L exposure groups were reportedly increased in males and females. Mild, but significant, histomorphological changes were reported in the liver, including anisokaryosis, accentuated zonation, and fatty vacuolation; kidney, including eosinophilic inclusions, pyknosis, nuclear displacement, fine glomerular adhesions and interstitial reactions and histologic proteinuria; and thyroid, including angular collapse of follicles, reduction in colloid density, and increased epithelial height, of both sexes of rats in the highest exposure group, although the number of affected animals was not reported.

NTP (1990) conducted a reproduction and fertility assessment of 1,2,3-trichloropropane in CD-1 mice, consisting of four tasks/studies: (1) a range-finding study, (2) a continuous breeding study, (3) a determination of the affected sex, and (4) an offspring assessment. All treatments were administered by corn oil gavage. In Task 1, mice (eight/sex/group) received 0, 12.5, 25, 50, 100, and 200 mg/kg-day for 14 days. No effect on weight gain or clinical signs of toxicity was observed.

Task 2 was a continuous breeding study in which 20 breeding pairs received 30, 60, or 120 mg/kg-day for 126 days. A statistically significant reduction in fertility was evident at the 4th and 5th breedings, from the decrease in the number of pregnancies per fertile mouse pair at the fourth breeding at 60 mg/kg-day group and the fourth and fifth breedings at 120 mg/kg-day. A statistically significant reduction in the number of live mouse pups/litter was observed in the second through the fifth breedings from breeding pairs at the highest dose (120 mg/kg-day) and at the fifth breeding at 60 mg/kg-day. The cumulative days to litter were statistically significantly longer than control values for the third breeding at 60 mg/kg-day and the fourth and fifth breedings at 120 mg/kg-day. The proportion of male pups born alive in the fifth breedings decrease in a dose-dependent manner.

Task 3, a 1-week crossover mating trial, was conducted with the same adult mice from the control and 120 mg/kg-day treatment groups from Task 2. The weights of the right epididymis and cauda epididymis in treated F_0 males were statistically significantly reduced. Treated females delivered fewer live pups than untreated females, with decreased body weight in male offspring and fewer live male pups per litter than controls.

In Task 4, members of the last set of litters (F_1) to be born in Task 2 were reared, weaned, and allowed to reach sexual maturity before being paired individually with a member of the opposite sex from a separate litter but within the same treatment group. There were statistically significant decreases in the indices for mating (# of females with plug/# of cohabiting pairs) and fertility (# of fertile pairs/# of females with plug) for the 120 mg/kg-day group. The estrous cycles for F_1 females of all treatment groups was statistically significantly prolonged. A statistically significant decrease in absolute right ovary weight was evident at the highest dose level, with a statistically significant decrease in relative ovary weight at 60 and 120 mg/kg-day.

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

I.A.5. Confidence in the Chronic Oral RfD

Study — High
Database — Medium-to-High
RfD — Medium-to-High

The overall confidence in this chronic RfD assessment is medium-to-high. Confidence in the principal study (NTP, 1993) is high. Confidence in the database is medium-to-high because the database lacks a multigenerational developmental toxicity study. The lack of a multigenerational study is of particular concern due to the genotoxicity of 1,2,3-

trichloropropane, because genetic damage to the germ cells of the F1 generation may not be detected until the F2 generation. Reflecting high confidence in the principal study and medium-to-high confidence in the database, confidence in the RfD is medium-to-high.

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

I.A.6. EPA Documentation and Review of the Chronic Oral RfD

Source Document — U.S. EPA. (2009)

This document has been reviewed by EPA scientistis, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 1,2,3-trichloropropane* (U.S. EPA, 2009) ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

I.A.7. EPA Contacts

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

I.B. Reference Concentration (RfC) for Chronic Inhalation Exposure

Substance Name — 1,2,3-Trichloropropane
CASRN — 96-18-4
Section I.B. Last Revised — 09/30/2009

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

risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

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

An RfC assessment for 1,2,3-trichloropropane was not previously available on IRIS.

I.B.1. Chronic Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Chronic RfC
peribronchial lymphoid hyperplasia in male rats **13-week inhalation Study** **Johannsen et al., 1988**	BMC_{10}: 1.6 ppm $BMCL_{10}$: 0.84 ppm $BMCL_{ADJ}$: 0.90 mg/m^3 $BMCL_{HEC}$: 0.90 mg/m^3	3000	0.0003 mg/m^3

*Conversion Factors and Assumptions — Assuming 25°C and 760 mmHg, and MW = 147.45, $BMCL_{10}$ (mg/m^3) = 0.84 ppm × 147.45/24.45 = 5.07 mg/m^3. $BMCL_{ADJ}$ = $BMCL_{10}$ (mg/m^3) × 6 hours/ 24 hours × 5 days/ 7 days = 0.90 mg/m^3. Following the U.S. EPA (1994) guidance, the $BMCL_{HEC}$ was calculated to account for a gas:extrarespiratory effect in rats, and because the human and rat blood partition coefficients for 1,2,3-trichloropropane are unknown, a default value of 1 was used for this ratio: $BMCL_{HEC}$ = 0.90 mg/m^3.

I.B.2. Principal and Supporting Studies

Johannsen et al. (1988) conducted a series of short-term and subchronic inhalation studies in 7-week-old CD rats. In a range-finding study, five CD rats/sex/group were exposed to nominal concentrations of 0, 100, 300, 600, or 900 ppm 1,2,3- trichloropropane vapor (0, 600, 1,800, 3,600, and 5,400 mg/m^3) 6 hours/day, 5 days/week, for up to 4 weeks. In the highest concentration group, all but one of the rats died after a single exposure. Three animals exposed to 600 ppm and one exposed to 300 ppm died prior to study termination.

The results of the 4-week range finding study were used to establish target concentrations 0, 5, 15, or 50 ppm (0, 30, 90, or 300 mg/m^3) as the exposure concentrations for a 13-week study. Each exposure group contained 15 CD rats/sex. There were no treatment-related deaths in the 13-week study. Daily observation of treated animals revealed a general, dose-dependent pattern of respiratory tract and conjunctival irritation, including red nasal discharge and excessive lacrimation. An increased incidence of yellow staining of the anogenital fur was also observed.

A number of statistically significant changes were reported for whole body and organ weights; (Johannsen et al., 1988; Biodynamics, Inc., 1979). Statistically significant reductions in terminal body weight were observed in females exposed to 15 and 50 ppm. Mean absolute and relative liver weights were statistically significantly elevated in the male rat exposure groups. Mean absolute liver weights were statistically significantly elevated in females exposed to 50 ppm, and relative liver weights were statistically significantly increased in females at 15 and 50 ppm. Relative lung weights were also statistically significantly increased in female rats at doses of 15 and 50 ppm, although no effect was evident in male rats. The mean relative kidney weight of males exposed to 50 ppm was significantly increased. There were no significant dose-related changes in any of the hematological or clinical chemistry parameters evaluated (Johannsen et al., 1988).

A number of histopathologic lesions were observed, including an increased incidence of mild to marked peribronchial lymphoid hyperplasia at 5, 15, and 50 ppm. The peribronchial lymphoid hyperplasia in the 15-ppm male rats was of equal severity to the 50-ppm group, but the hyperplasia in the 15-ppm female rats and that evident in the 5-ppm males and females were less severe. Hepatocellular hypertrophy in males at 5, 15, and 50 ppm was observed in centrilobular to midzonal levels, but was not evident in the highest dose group females. Treated females showed a dose-dependent increase in extramedullary hematopoiesis of the spleen.

In the second 13-week study, the investigators employed a similar experimental protocol with exposure concentrations of 0, 0.5, or 1.5 ppm (0, 3, or 9 mg/m^3). The presence of lesions in animals of all exposure groups of the first 13-week study prompted the initiation of a follow-up study with lower exposure concentrations (Johannsen et al., 1988). Small increases in mean absolute and relative ovarian weights were observed in females in the 1.5 ppm dose group. Treatment-related histopathological findings at 0.5 or 1.5 ppm were not observed in any tissue examined. Sporadic changes were observed in some hematological and clinical chemistry parameters. In the absence of an apparent dose-response pattern these changes were considered by the investigators to be unrelated to the 1,2,3-trichloropropane exposures.

The critical effect selected for the derivation of the chronic RfC is the development of peribronchial lymphoid hyperplasia in the lungs of CD rats, which is supported by the occurrence of this effect in both male and female rats and the possible correlation between the hyperplasia and the observed increased lung weight. Peribronchial lymphoid hyperplasia, also defined as lymphoid hyperplasia of the bronchus-associated lymphoid tissue, is histologically characterized by the presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along the bronchioles and bronchi (Howling et al., 1999; Myers and Kurtin, 1995; Fortoul et al., 1985; Yousem et al., 1985).

Benchmark dose (BMD) modeling was conducted using EPA's BMDS (version 1.4.1.) to analyze the increased incidence of peribronchial lymphoid hyperplasia in CD rats and, for purposes of comparison, the decreased mating performance in female CD rats (See Section 5.2.2. and Appendix C of the Toxicological Review). For the analysis of increased incidence of peribronchial lymphoid hyperplasia and decreased mating performance, a BMR of 10% was selected, in accordance with the *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000).

I.B.3. Uncertainty Factors

UF = 3000

A 3-fold UF_A was selected to account for uncertainties in extrapolating from rats to humans. This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ has been incorporated. A full UF of 10 is comprised of two components of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component is mostly addressed through the application of a human equivalent concentration as described in the RfC methodology (U.S. EPA, 1994b). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method. However, a threefold UF is retained to fully address this component.

A 10-fold UF_H was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability) because insufficient information is available to predict potential variability in susceptibility among the population.

A 10-fold UF_S was used to account for uncertainty in extrapolating from a subchronic to chronic exposure duration.

A 10-fold UF_D was used to account for deficiencies in the database. The database of 1,2,3-trichloropropane inhalation studies, which included two 2-week studies submitted to EPA by Miller et al. (1987a, b), a 4-week range finding study, two 13-week studies, and a single-

generation reproductive toxicity study (Johannsen et al., 1988; Biodynamics, Inc., 1979), provides reliable dose-response data from subchronic studies in two species and from a single-generation reproductive toxicity study. However, the database is lacking a multigenerational reproductive toxicity study and a developmental toxicity study. The database deficiencies are of particular concern due to the genotoxicity of 1,2,3-trichloropropane, because genetic damage to the germ cells of the F1 generation may not be detected until the F2 generation.

UF for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% change in the incidence of peribronchial lyphoid hyperplasia was selected as the

I.B.4. Additional Studies/Comments

Miller et al. (1987a, b) conducted two inhalation studies of male and female F344/N rats and B6C3F1 mice. These unpublished studies were submitted to the EPA under TSCA. In the first rat and mouse study (Miller et al., 1987a), five animals/sex/group were exposed to an analytical concentration of 0, 13 ± 0.5, 40 ± 0.4, or 132 ± 0.6 ppm (0, 78, 241, and 796 mg/m^3) for 9 days. Effects observed in rats included: increased absolute and relative liver weights, slight hepatocellular necrosis in males, slight depletion of lymphoid elements in the spleen in males, and increased incidence and severity of degeneration and decreased thickness, as well as inflammation with exudation of inflammatory cells into the nasal cavity lumen, of the olfactory epithelium in the nasal turbinates. Effects observed in mice included: increased absolute and relative liver weight, decreased absolute and relative testes weight, moderate increase in hepatocyte size, slight depletion of lymphoid elements in the spleen, and increased incidence of decreased thickness and degeneration, as well as inflammation with exudation of inflammatory cells into the nasal cavity lumen, of the olfactory epithelium in the nasal turbinates.

A follow-up study (Miller et al., 1987b) was initiated using the previous study protocol and analytical concentrations of 0, 1.0 ± 0.0, 2.9 ± 0.2, or 9.7 ± 0.3 ppm (0, 6, 18, or 60 mg/m^3). Effects observed in rats included a slight decreased thickness and degeneration, as well as inflammation with exudation of inflammatory cells into the nasal cavity lumen, of the olfactory epithelium in the nasal turbinates. Effects observed in mice included a slight decrease in thickness, as well as inflammation with exudation of inflammatory cells into the nasal cavity lumen, of the olfactory epithelium in the nasal turbinates.

Johannsen et al. (1988) reported the results of two single-generation reproductive studies using 10 male and 20 female CD rats/group. In the first study, rats were exposed to analytical concentrations of 0, 4.6, and 15 ppm 1,2,3-trichloropropane 6 hours/day, 5 days/week, for a

10-week pre-mating period, a mating period (not to exceed 40 days), and for gestation days 0-14 for females. Male and female rats were housed in a ratio of 1:2, respectively, nightly during the mating period. In the second study, the same numbers of rats were exposed to target concentrations of 0, 0.5, or 1.5 ppm using a similar protocol (mating period not to exceed 30 days).

In the first study, females exposed to 15 ppm had lower body weights during gestation and lactation, although weight gains were consistent with the controls. Both sexes exposed to 15 ppm exhibited decreases in weight and weight gain during the premating period of exposure. All groups of female rats exhibited low mating performance, 16 females out of 20 mated at 5 ppm and 10 females out of 20 mated at 15 ppm, compared with 37 females out of 40 mated in the control group. Fertility indices were unaffected by trichloropropane exposure. There was no treatment-related effect on litter and pup data. Histopathological evaluation of the testes, epididymis, and ovaries did not identify any treatment-related changes. In the second study, adverse effects on mating performance and fertility indices due to 1,2,3-trichloropropane were not observed. Lesions of the testes, epididymides, and ovaries were not evident. Consistent or obviously treatment-related reproductive effects were not observed in any of the experimental groups in either generation.

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

I.B.5. Confidence in the Chronic Inhalation RfC

Study — Low-to-medium
Data Base — Low
RfC — Low

The overall confidence in this RfC assessment is low. Confidence in the principal study (Johannsen et al., 1988) is low-to-medium. Confidence in the database is low as the database lacks a chronic inhalation bioassay and multigenerational reproductive and developmental toxicity studies. The lack of a chronic inhalation bioassay is of concern because the critical effect, peribronchial lymphoid hyperplasia, may be more severe at lower doses with a prolonged exposure, and additional critical effects not observed following subchronic exposure may arise following chronic exposure. The lack of a multigenerational developmental study is of particular concern due to the genotoxicity of 1,2,3-trichloropropane, because genetic damage to the germ cells of the F1 generation may not be detected until the F2 generation. Reflecting low-to-medium confidence in the principal study and low confidence in the database, confidence in the chronic RfC is low.

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

I.B.6. EPA Documentation and Review of the Chronic Inhalation RfC

Source Document — U.S. EPA, 2009

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 1,2,3-Trichloropropane* (U.S. EPA, 2009). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

I.B.7. EPA Contacts

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

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,2,3-Trichloropropane
CASRN — 96-18-4
Section II. Last Revised — 09/30/2009

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

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-

dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A cancer assessment for 1,2,3-trichloropropane was not previously available on IRIS.

II.A. Evidence for Human Carcinogenicity

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

Under the *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a), 1,2,3-trichloropropane is "likely to be carcinogenic to humans", based on a statistically significant and dose-related increase in the formation of multiple tumors in both sexes of two species from an NTP (1993) chronic oral bioassay. Statistically significant increases in incidences of tumors of the oral cavity, forestomach, pancreas, kidney, preputial gland, clitoral gland, mammary gland, and Zymbal's gland in rats, and the oral cavity, forestomach, liver, Harderian gland, and uterus in mice, were reported.

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.A.2. Human Carcinogenicity Data

There are no available studies that examine the potential carcinogenicity of 1,2,3-trichloropropane in humans.

II.A.3. Animal Carcinogenicity Data

NTP (1993) conducted a 2-year study of the toxicity and carcinogenicity of 1,2,3-trichloropropane in F344/N rats. The chemical was administered by corn oil gavage to 60 rats/sex/group. The rats were approximately 6 weeks old when the study was initiated. Rats received doses of 0, 3, 10, or 30 mg/kg-day, and after 15 months (65-67 weeks), 8-10 rats per group were sacrificed to allow an interim evaluation of all toxicological parameters and histopathology. Due to high mortality in rats receiving 30 mg/kg at the interim evaluation, the remaining survivors in that group were sacrificed at week 67 (females) and week 77 (males).

An increase in the incidence of forestomach tumors was observed in all rat treatment groups, regardless of sex. However, the incidences of forestomach neoplasms were generally higher in males than in females at the same dose levels. All male treatment groups also had increased incidence of pancreatic tumors. Male and female rats that received doses of 10 mg/kg-day 1,2,3-trichloropropane or higher had an increase in the incidence of oral cavity tumors. In each male group that received doses of 10 mg/kg-day or higher, an increased incidence of renal tumors was observed. An increase was observed in females at both 10 mg/kg-day and 30 mg/kg-day for the clitoral gland tumors and at the 10 and 30 mg/kg-day for mammary gland tumors. In the 30 mg/kg-day treatment group an increased incidence of Zymbal's gland tumors was observed in females and an increased incidence of preputial gland tumors was observed in males at 30 mg/kg-day. For more information on the tumor incidences observed in F344/N rats, see Section 4.2.1.2 of the *Toxicological Review of 1,2,3-Trichloropropane* (U.S. EPA, 2009).

NTP (1993) conducted a 2-year study of the toxicity and carcinogenicity of 1,2,3-trichloropropane in B6C3F1 mice. The chemical was administered by corn oil gavage to 60 mice/sex/group, and the mice were approximately 6 weeks old when the study began. Mice were treated with 0, 6, 20, or 60 mg/kg-day, and after 15 months (65-67 weeks), 8-10 mice per group were sacrificed to allow an interim evaluation of all toxicological parameters and histopathology. Due to high mortality in the mice receiving 60 mg/kg-day, surviving mice were evaluated at week 73 (females) and week 79 (males).

In mice, the sites of statistically significant neoplasm formation for both sexes were the forestomach and liver. Incidences of Harderian gland tumors were increased in males at 20 and 60 mg/kg-day, and the increase in incidence of oral cavity tumors was statistically significant in females at the highest dose. The incidence of uterine/cervical tumors in female mice was increased at 20 and 60 mg/kg-day. The highest incidence of neoplasms and most marked dose-response effect for both species was in the forestomach. A 97% incidence of tumors of the forestomach was evident in male mice at the lowest dose tested (90% in females). These data suggest that an elevated incidence of tumors in the forestomach might

occur at doses lower than those employed in this study. For more information on the tumor incidences observed in B6C3F1 mice, see Section 4.2.1.2 of the *Toxicological Review of 1,2,3-Trichloropropane* (U.S. EPA, 2009).

II.A.4. Supporting Data for Carcinogenicity

II.A.4.1. Genotoxicity studies

The mutagenic activity of 1,2,3-trichloropropane has been demonstrated in bacterial and mammalian cell systems treated with 1,2,3-trichloropropane and activated with an S9 fraction (Doherty et al., 1996; Tafazoli and Kirsch-Volders, 1996; Lag et al., 1994; NTP, 1993; Ratpan and Plaumann, 1988; von der Hude et al., 1987; Haworth et al., 1983; Kier, 1982; Shell Oil Co., 1982, 1979; Stolzenberg and Hine, 1980). In the absence of the enzyme-rich S9 fraction mutagenic activity is typically not observed. 1,2,3-Trichloropropane was positive in primarily S. typhimuium strains that detect base pair mutations (TA1535 and TA100) and frame shift mutations (TA1537 [one assay] and TA98) in the presence of S9 fraction (Lag et al., 1994; NTP, 1993; Ratpan and Plaumann, 1988; Haworth et al., 1983; Kier, 1982; Stolzenberg and Hine, 1980; Shell Oil Co., 1979). Mutagenicity was also evident in E. coli WP2 uvr A, in the presence of S9 fraction, after exposure to 1,2,3-trichloropropane (Shell Oil Co., 1979). Chromosomal aberrations and sister chromatid exchanges were evident in CHO cells or V79 assays (NTP, 1993; von der Hude et al., 1987), and trifluorothymidine resistance was induced in mouse lymphoma assays, after 1,2,3-trichloropropane exposure and in the presence of S9 fraction (NTP, 1993; Shell Oil Co., 1982). DNA strand breakage caused by 1,2,3-trichloropropane was measured by the Comet assay in isolated human lymphocytes (Tafazoli and Kirsch-Volders, 1996), and 1,2,3-trichloropropane induced micronucleus formation in the mammalian cell lines, AHH-1, MCL-5, and h2E1 (Doherty et al., 1996).

In an in vivo bioassay in D. melanogaster, Chroust et al. (2007) investigated the genotoxic effects of 1,2,3-trichloropropane in the SMART. 1,2,3-Trichloropropane caused a statistically significant (compared with control) increase in the number of total wing spots, which is evidence for genotoxic effects such as somatic mutation, chromosomal rearrangement, or nondisjunction. Belyaeva et al. (1977, 1974) observed an increase in the number of mononuclear hepatocytes with a nucleus of high ploidy and a decrease in the number of binuclear cells following exposure to 1,2,3-trichloropropane. 1,2,3-Trichloropropane also caused DNA breaks in the DNA from isolated kidney nuclei of rats exposed to 1,2,3-trichloropropane (Lag et al., 1991).

1,2,3-Trichloropropane tested nonpositive in bacterial systems not activated with S9 fraction (NTP, 1993; Ratpan and Plaumann, 1988), in the SOS chromotest in E. coli (von der Hude et al., 1988), in the DNA-repair proficient E. coli WP2 (Shell Oil Co., 1979), and in the *A.*

nidulans diploid strain P1 assay for aberrant mitotic segregation (Crebelli et al., 1992). Mammalian cell in vitro assays in which 1,2,3-trichloropropane tested nonpositive for genotoxicity included: the induction of trifluorothymidine resistance in mouse lymphoma cells not activated with S9 fraction (NTP, 1993; Shell Oil Co., 1982); the induction of chromosomal damage in Carworth Farm E rat liver epithelial cells (Shell Oil Co., 1979); the micronucleus formation assay in human lymphocytes, although numerous chlorinated aliphatics failed to induce a clear dose-dependent increase (Tafazoli and Kirsch-Volders, 1996); the unscheduled DNA synthesis assay in rat hepatocytes (Williams et al., 1989); and the induction of DNA strand breaks in Wistar rat hepatocytes (Holme et al., 1991). The in vivo assays in which 1,2,3-trichloropropane tested non-positive included the bone marrow micronucleus formation assay in CD-1 mice (Crebelli et al., 1999) and the dominant lethal induction assay in male Sprague-Dawley rats (Saito-Suzuki et al., 1982).

II.A.4.2. Carcinogenicity of Structurally-Similar Compounds

Halogenated propanes as a class of compounds are generally found to be positive in assays which indicate mutagenicity (Lag et al., 1994; Ratpan and Plaumann, 1988), and there is clear evidence that members of this group, including 1,2-dibromo-3-chloropropane (DBCP) (NTP, 1982a; NCI, 1978) and 1,2-dibromoethane (NTP, 1982b), are carcinogenic in whole animal models. DBCP also forms the same major DNA adduct, S-[1-(hydroxymethyl)-2-(N^7-guanyl)ethyl]-glutathione, as 1,2,3-trichloropropane (Humphreys et al., 1991).

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

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor

EPA has concluded, by a weight of evidence evaluation, that 1,2,3-trichloropropane is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance)* (U.S. EPA, 2005b) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for 1,2,3-trichloropropane are not sufficient to develop separate risk estimates for childhood exposure. The oral slope factor of 30 per mg/kg-day, calculated from data from adult exposure, does not reflect presumed early-life susceptibility for this chemical and age dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance*.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). The 10 fold and 3 fold adjustments in slope factor are to be combined with age specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to 1,2,3-trichloropropane. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for 1,2,3-trichloropropane, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*).

The recommended upper bound estimate on human extra cancer risk from continuous lifetime oral exposure to 1,2,3-trichloropropane is **30 per mg/kg-day**. The value based on female mice is recommended because female mice are the most sensitive to tumor induction following exposure to 1,2,3-trichloropropane. The recommended estimate reflects the time-to-tumor dimension of the responses as well as the exposure-response relationships for the multiple tumor sites. This slope factor should not be used with exposures greater than 0.6 mg/kg-day, the human equivalent dose corresponding to the point of departure for the female mouse alimentary system tumors, because the observed dose-response relationships do not continue linearly above this level and the fitted dose-response models better characterize what is known about the carcinogenicity of 1,2,3-trichloropropane.

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

Drinking water unit risk and concentrations at specified risk levels are not provided for 1,2,3-trichloropropane. Since 1,2,3-trichloropropane is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the unit risk and concentrations at a specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should use the oral slope factor and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.B.1.3. Extrapolation Method

Multistage-Weibull model with linear extrapolation from the point of departure ($BMDL_{10}$). A linear-low-dose extrapolation approach was used to estimate human carcinogenic risk

associated with 1,2,3-trichloropropane exposure due to the mutagenic mode of carcinogenic action.

II.B.2. Dose-Response Data

Tumor Type — alimentary system squamous cell neoplasms; liver hepatocellular adenomas or carcinomas, Harderian gland adenomas, uterine/cervix adenomas or carcinomas
Test Species — B6C3F1 mice (female)
Route — Oral gavage

Site	0 mg/kg-d	6 mg/kg-d	20 mg/kg-d	60 mg/kg-d	Trend test *p*-value[a]
Alimentary system, total squamous neoplasms[b]	0/59[c] (0%) -[d]	54/60[c] (90%) 59	59/60[c] (98%) 45	59/60[c] (98%) 42	<0.001
Liver: adenoma or carcinoma	8/59 (13%) 66	11/60 (18%) 77	9/60 (15%) 65	36/58 (60%) 60	<0.001
Harderian gland adenoma	3/59 (5%) 66	6/59 (10%) 80	7/60 (12%) 78	10/60 (17%) 64	0.04
Uterus: adenoma or adenocarcinoma	0/59 (0%) –	5/59 (8%) 100	3/59 (5%) 83	11/57 (19%) 66	<0.001

[a]By life table test and logistic regression.
[b]Squamous papillomas or squamous cell carcinomas of the pharynx/palate, tongue, or forestomach.
[c]Numbers of animals at risk (denominators) vary due to missing tissues or due to deaths occurring before the first incidence of tumor in that group, or before wk 52, whichever was earlier.
[d]Wk of first incidence.

Source: NTP (1993).

II.B.3. Additional Comments

Due to the occurrence of multiple tumor types, earlier occurrence with increasing exposure, and early termination of at least one dose group, dose-response methods that can reflect the influence of competing risks and intercurrent mortality on site-specific tumor incidence rates are preferred. EPA has generally used the multistage-Weibull model in this type of situation, because it incorporates the time at which death-with-tumor occurred and can account for differences in mortality observed between the exposure groups in the mouse bioassay. Additionally, etiologically different tumor types were not combined across sites prior to modeling, in order to allow for the possibility that different tumor types can have different dose-response relationships because of varying time courses or other underlying mechanisms or factors.

Points of departure for estimating low-dose risk were identified at doses at the lower end of the observed data, generally corresponding to 10% extra risk, defined as the extra risk over the background tumor rate. The lifetime oral cancer slope factor for humans is defined as the slope of the line from the lower 95% bound on the exposure at the point of departure. This 95% upper confidence limit (UCL) represents a plausible upper bound on the true risk.

Tumor type and context[a]		Multistage-Weibull model coefficients (MLE)[b]	Human equivalent continuous POD[c], mg/kg-d		Slope factor[d], $(mg/kg\text{-}d)^{-1}$	Overall slope factor, $(mg/kg\text{-}d)^{-1}$
			BMD_{10}	$BMDL_{10}$		
Female mice						
Alimentary system, total squamous neoplasms	Incidental	$q_1 = 3.3 \times 10^{-12}$ $z = 6.0$	0.0032	0.00065	150	28 (160)
	Fatal	$q_1 = 7.3 \times 10^{-16}$ $q_2 = 9.6 \times 10^{-17}$ $z = 7.5$ $t_0 = 24$	0.0095	0.0039	26	
Liver: adenoma or carcinoma		$q_0 = 5.6 \times 10^{-18}$ $q_1 = 9.2 \times 10^{-19}$ $q_3 = 5.5 \times 10^{-21}$	0.30	0.14	0.73	

Tumor type and context[a]	Multistage-Weibull model coefficients (MLE)[b]	Human equivalent continuous POD[c], mg/kg-d		Slope factor[d], $(mg/kg-d)^{-1}$	Overall slope factor, $(mg/kg-d)^{-1}$
	$z = 8.2$				
Harderian gland adenoma	$q_0 = 6.9 \times 10^{-12}$ $q_1 = 3.0 \times 10^{-12}$ $z = 4.9$	0.42	0.20	0.50	
Uterus: adenoma or carcinoma	$q_1 = 6.0 \times 10^{-23}$ $q_2 = 2.4 \times 10^{-23}$ $z = 10$	0.42	0.21	0.47	

[a]"Incidental" denotes models treating all tumors of the type listed as incidental to the death of the animal. "Fatal" denotes models treating the tumors (among the type listed) present at unscheduled deaths as causing the death, with the remaining tumors considered incidental. If no context is listed, all tumors were considered incidental.
[b]Multistage-Weibull model: $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) \times (t \pm t_0)^z]$, with coefficients estimated in terms of mg/kg-d as administered in bioassay; lower or intermediate stage q_i not listed were estimated to be zero.
[c]POD adjusted to estimate human equivalent continuous exposure, using $BW^{3/4}$ cross-species scaling and by multiplying by (5 d)/(7 d).
[d]Slope factors estimated by dividing the BMR (10% unless specified otherwise) by the BMDL.
[e]Overall slope factor including fatal context for tumors considered under both possibilities. Overall slope factor in parentheses represents incidental context for all tumor types.
[f]BMR = 5%.

BMD_{10} = Concentration at 10% extra risk; $BMDL_{10}$ = 95% lower bound on concentration at 10% extra risk.

Source: NTP (1993).

Adjustments for approximating human equivalent slope factors applicable for continuous exposure were calculated. Following EPA's cross-species scaling methodology, the time-weighted daily average doses were converted to human equivalent doses on the basis of $(body\ weight)^{3/4}$ (U.S. EPA, 1992).

II.B.4. Discussion of Confidence

The NTP (1993) study was well-designed and investigated the carcinogenic effects in both rats and mice; however, there were no other candidate human or animal studies. The number of test animals allocated among three dose levels and an untreated control group was adequate, with examination of appropriate toxicological endpoints in both sexes of rats and mice. Tumor incidences were elevated with increasing exposure level at numerous sites across all sex/species combinations, involving point of contact in the alimentary system and more distant locations.

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

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data

Not applicable.

II.C.3. Additional Comments

Not applicable.

II.C.4. Discussion of Confidence

Not applicable.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2009

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 1,2,3-Trichloropropane* (U.S. EPA, 2009). ***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

II.D.3. EPA Contacts

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

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

VI. Bibliography

Substance Name — 1,2,3-Trichloropropane
CASRN — 96-18-4

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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VII. Revision History

Substance Name — 1,2,3-Trichloropropane
CASRN — 96-18-4
File First On-Line — 03/31/1987

Date	Section	Description
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.
09/30/2009	I.A., I.B., II.	Revised RfD, added RfC and carcinogenicity assessments.

VIII. Synonyms

Substance Name — 1,2,3-Trichloropropane
CASRN — 96-18-4
Section VIII. Last Revised — 09/30/2009

- 96-18-4
- ALLYL TRICHLORIDE
- GLYCEROL TRICHLOROHYDRIN
- GLYCERYL TRICHLOROHYDRIN
- NCI-C60220
- PROPANE, 1,2,3-TRICHLORO-
- TRICHLOROHYDRIN
- 1,2,3-Trichloropropane
- Trichloropropane, 1,2,3-