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1,1,1-Trichloroethane

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
1,1,1-TCA	1,1,1-Trichloroethane
1,1,2-TCA	1,1,2-Trichloroethane
$5HT_3$	5-hydroxytryptamine type 3
AEGL	Acute Exposure Guideline Level
ADAUCL	average daily area under the curve of the liver concentration
AIHA	American Industrial Hygiene Association
AMCV	Air Monitoring Comparison Value
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
AUCLT	total area under the curve of the liver concentration
ºC	degrees centigrade
CNS	central nervous system
CYP	cytochrome P450
EEG	electroencephalogram
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{linear(c)}$	chronic health-based Effects Screening Level for linear dose response cancer effect
$^{chronic}ESL_{linear(nc)}$	chronic health-based Effects Screening Level for linear dose response noncancer effects
$^{chronic}ESL_{nonlinear(c)}$	chronic health-based Effects Screening Level for nonlinear dose response cancer effects
$^{chronic}ESL_{nonlinear(nc)}$	chronic health-based Effects Screening Level for nonlinear dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
F	exposure frequency, days per week

Acronyms and Abbreviations	Definition
h	hour
$GABA_A$	gamma-aminobutyric acid type A
Hg	mercury
HEC	human equivalent concentration
HQ	hazard quotient
IARC	International Agency for Research on Cancer
kg	kilogram
K_{ow}	Octanol-Water Partition Coefficient
LOAEL	lowest-observed-adverse-effect-level
MRL	minimal risk level
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
n	number
NAC	National Advisory Committee
NIOSH	National Institute for Occupational Safety and Health
NMDA	N-methyl-D-aspartate
NOAEL	no-observed-adverse-effect-level
PBPK	physiologically-based pharmacokinetic
OSHA	Occupational Safety and Health Administration
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion

Acronyms and Abbreviations	Definition
ppm	parts per million
RfC	reference concentration
ReV	reference value
SCOB	scheduled-controlled operant behavior
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TWA	time-weighted-average
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	database uncertainty factor
USEPA	United States Environmental Protection Agency

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of 1,1,1-trichloroethane (1,1,1-TCA). Please refer to the Air Monitoring Comparison Values (AMCVs) Document and Fact Sheet available at AMCVs at TCEQ for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on 1,1,1-TCA's physical/chemical data. Figure 1 compares the values in Tables 1 and 2 to values developed by other federal/occupational organizations.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	**Concentration**	**Notes**
acute ReV	9500 µg/m^3 (1700 ppb) **Short-Term Health**	**Critical Effect:** increased reaction time in human volunteers (i.e., impaired psychomotor performance)
$^{acute}ESL_{odor}$	---	Mild, chloroform-like
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
chronic ReV (noncarcinogenic)	5100 µg/m^3 (940 ppb) **Long-Term Health**	**Critical Effect:** slight microscopic hepatic changes in F344 rats
chronic ReV (carcinogenic/nonlinear) or $^{chronic}ESL_{linear(c)}$	---	Data inadequate to assess carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

Abbreviations used: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **HQ**, hazard quotient; **AMCV**, air monitoring comparison value; **ESL**, Effects Screening Level; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effects; **$^{chronic}ESL_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

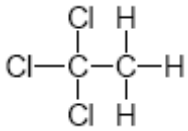
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	2800 µg/m^3 (510 ppb) [a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** increased reaction time in human volunteers (i.e., impaired psychomotor performance)
$^{acute}ESL_{odor}$	---	Mild, chloroform-like
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	1500 µg/m^3 (280 ppb) [b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** slight microscopic hepatic changes in F344 rats
$^{chronic}ESL_{linear(c)}$	---	Data inadequate to assess carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 9500 µg/m^3 (1700 ppb) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV (noncarcinogenic) of 5100 µg/m^3 (940 ppb) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_2H_3Cl_3$ or CCl_3CH_3	(USEPA 2007)
Chemical Structure		(ATSDR 2006)
Molecular Weight	133.4 (g/mole)	(TRRP 2006)
Physical State	Liquid	(TRRP 2006)
Color	Colorless	(USEPA 2007)
Odor	Mild, chloroform-like	(USEPA 2007)
CAS Registry Number	71-55-6	(TRRP 2006)
Synonyms and Trade Names	Synonyms: 1,1,1-TCA; 1,1,1-TCE Methylchloroform; Methyltrichloromethane; Trichloromethylmethane; α-Trichloromethane; Trade Names: Alpha-T; Aerothene MM; Aerothene TT; Algylen; Baltana; CF 2; Chloroethane-NU; Chlorotene; Chlorothane NU; Chlorothene NU; Chlorothene SM; Chlorothene VG; Chlorylen; Dowclene LS; Gemalgene; Genklene LB; ICI-CF 2; Inhibisol; Solvent 111; TCEA; Trichloran; Trielene	(ATSDR 2006) (USEPA 2007)
Solubility in water	1330 mg/L	(TRRP 2006)
Log K_{ow}	2.68	(TRRP 2006)
Vapor Pressure	124 mm Hg at 20°C	(TRRP 2006)
Vapor Density (air = 1)	4.6 g/L	(USEPA 2007)
Density (water = 1)	1.3390 g/ml at 20°C	(USEPA 2007)
Melting Point	-30.4°C	(USEPA 2007)
Boiling Point	74.0°C	(USEPA 2007)
Conversion Factors	1 mg/m^3 = 0.185 ppm @ 20°C 1 ppm = 5.4 mg/m^3	(ATSDR 2006)

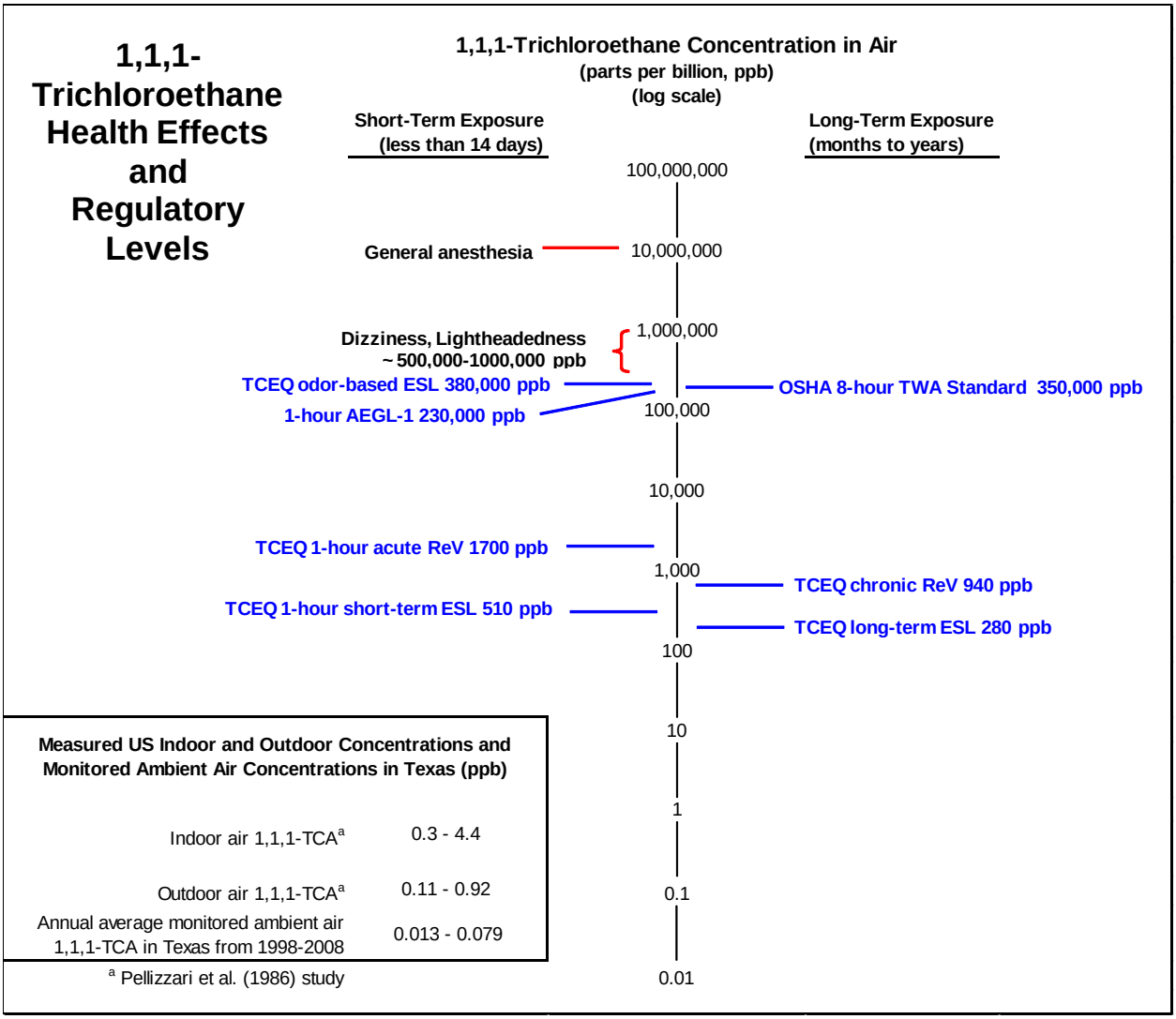


Figure 1: 1,1,1-TCA Health Effects and Regulatory Levels.

This figure compares 1,1,1-TCA's acute toxicity values (acute ReV, odor-based ESL, and health-based, short-term ESL) and chronic toxicity values (chronic ReV and health-based, long-term ESL) found in Table 1 and Table 2 to OSHA's occupational values, and the AEGL-1 value (AEGL 2000). The TCEQ odor-based ESL has been withdrawn (TCEQ 2015)

Abbreviations used: **1,1,1-TCA**, 1,1,1-trichloroethane; **TCEQ**, Texas Commission on Environmental Quality; **TWA**, Time-Weighted Average; **ESL**, Effects Screening Level; **ReV**, Reference Value; **OSHA**, Occupational Safety and Health Administration; and **AEGL-1**, Level 1-Acute Exposure Guideline Levels.

Chapter 2 Major Sources and Use

1,1,1-TCA is a synthetic chemical. It was initially developed as a less toxic solvent to replace other chlorinated and flammable solvents like carbon tetrachloride, and was used extensively in industry and in household products. Although the general population has historically been exposed to 1,1,1-TCA because of its prevalence in common household products, it is no longer used them. Currently, 1,1,1-TCA is primarily used as a precursor chemical for the synthesis of hydrofluorocarbons. According to the Agency for Toxic Substances and Disease Registry (ATSDR 2006), use of 1,1,1-TCA as of 1995 included use as a hydrochlorofluorocarbon intermediate (60%), in vapor degreasing and cold cleaning (25%), as a solvent for adhesives (5%), in coatings and inks (3%), in textiles (2%), and in electronics and miscellaneous (5%). The 2003 Toxics Release Inventory (TRI) indicated that over 100 facilities in Texas produced, processed, or used 1,1,1-TCA that year. The total U.S. production volume of 1,1,1-TCA has fallen from 720 million pounds in 1992 to a estimated 125 million pounds in 2005 (ATSDR 2006).

The majority of 1,1,1-TCA has been released to the environment by process and fugitive emissions during its manufacture and formulation, use in industrial products, and historical use in common consumer products. Small amounts of 1,1,1-TCA are released from coal-fired power plants, from incineration of hospital and industrial wastes, as well as incineration of municipal waste water sludge. The long half-life for 1,1,1-TCA in the troposphere allows it to be carried great distances from its original point of release, and it has been found in remote places far from any known source of release. Therefore, exposure may occur from unknown remote sources.

1,1,1-TCA has been identified in urban, rural, and indoor air throughout the United States at various concentrations. In the 1970s and 1980s, the reported ambient air levels of 1,1,1-TCA in urban areas were in the range of 0.1 - 1 ppb. Indoor air concentrations were determined to be greater than nearby outdoor concentrations (Pellizzari et al. 1986). Representative data taken from five geographic areas throughout the United States, including Deer Park/Pasadena, TX, in the Pellizzari et al. (1986) study indicated indoor concentrations of 0.3 - 4.4 ppb and outdoor concentrations of 0.11 - 0.92 ppb. The reported ambient air levels of 1,1,1-TCA in Texas indicates statewide annual average concentrations in the range of 0.013 to 0.079 ppb based on Texas Commission and Environmental Quality (TCEQ) monitoring data collected from 1998 to 2008 (Figure 1). See ATSDR (2006) and USEPA (2007) for additional source and use information.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

Because of time and resource constraints, the Toxicology Division (TD) utilizes toxicity assessments conducted by other federal, state, and international agencies that have undergone a peer-review process (e.g., USEPA 2007, ATSDR 2006) as initial background information. These toxicity assessments are critically reviewed by the TD and any relevant calculations are confirmed and/or reproduced whenever possible. Additionally, the TD obtains copies of key and

supporting studies and other important studies and critically reviews them. The key study (Mackay et al. 1987) discussed in this section was initially identified through review of ATSDR (2006) and USEPA (2007). A thorough review of the scientific literature since 2006 was conducted by the TD and did not identify any new adequate toxicity studies for development of the acute Reference Value (ReV) and acute Effects Screening Level (^{acute}ESL). ATSDR (2006) and USEPA (2007) selected the Mackay et al. (1987) human study as most appropriate for derivation of the acute inhalation minimal risk level (MRL) and acute reference concentration (RfC), respectively.

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

1,1,1-TCA is a volatile, colorless liquid with a sweet, sharp odor similar to chloroform. It is soluble in alcohol, ether, chloroform, and common organic solvents, and is miscible with other chlorinated solvents. It is moderately soluble in water (TRRP 2006). The main chemical and physical properties of 1,1,1-TCA are summarized in Table 3.

3.1.1.2 Essential Data and Key Studies

Available human and animal data indicate that the central nervous system (CNS) is the most sensitive target for acute inhalation exposure to 1,1,1-TCA. The acute depressive effect of 1,1,1-TCA in both humans and animals progresses from subtle behavioral effects at low-to-moderate concentrations to unconsciousness at high concentrations. In addition to CNS depression effects, the health effects observed in human acute inhalation exposure to sufficiently high concentrations of the chemical include ocular irritation, hypotension, and mild hepatic effects. Cardiac arrhythmia and respiratory arrest may result from exposure to high concentrations of 1,1,1-TCA when severe depression of the CNS occurs. A summary of human and animal studies may be found in ATSDR (2006) and USEPA (2007).

3.1.1.2.1 Human Studies

Studies of controlled exposure to 1,1,1-TCA in humans provide the most sensitive measure of effects for this chemical. The studies of neurobehavioral performance by Mackay et al. (1987), Gamberale and Hultengren (1973), and Muttray et al. (2000) identified the lowest effect levels among the available human studies. Those three human studies were categorized as a within-subjects design in which the same group of subjects was exposed to all experiment conditions and served as their own controls. All the subjects of three studies were healthy adults whom passed similar preliminary medical examinations and screening. Similar to ATSDR (2006) and USEPA (2007), Mackay et al. (1987) was selected by the TD as the key study. The other two studies (Gamberale and Hultengren 1973, Muttray et al. 2000) were selected as supporting studies. Study details are provided below along with why the supporting studies were not selected as the key study.

3.1.1.2.1.1 Key Study - Mackay et al. (1987)

Twelve healthy adult male volunteers were chamber exposed to 0, 175, and 350 ppm of 1,1,1-TCA (purity not reported) for 3.5 hours. Each subject was exposed to all three exposure concentrations in a balanced design, with at least 14 days between the exposures. The concentration in the chamber was monitored continuously and remained constant over a 4-hour period (coefficient of variation was typically 4%). The experiment was conducted double-blind to both subject and experimenter, and 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 neurobehavioral 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). This study also provided blood-level data collected at the time points concurrent with tests of neurobehavioral performance. Measurements of 1,1,1-TCA 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 as soon as 20 minutes after exposure to both 175 and 350 ppm exposure levels, including increased simple reaction time, increased choice reaction time, impaired performance in the tracking test, and improved performance in the Stroop test, suggesting the impairment produced by 1,1,1-TCA may be task-specific. Though not fully understood, 1,1,1-TCA is capable of producing biphasic effects on behavior, i.e., an increase in activity followed by a decrease (Warren et al. 2000). The simple and four-choice 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). Exposure to 1,1,1-TCA (175 and 350 ppm) was reported to produce statistically significant changes in various performance variables (e.g., acquisition time, simple reaction time, four-choice reaction time), although the study did not include pair-wise tests to identify the specific exposure level at which a statistical difference from controls was achieved for each effect. The test results at 20 minutes were different from controls but no significant difference compared the test results at 60, 120 and 180 minutes. When adjusted for both baseline (pre-exposure) and control exposures, performance changes in the more sensitive tests (e.g., simple reaction time) followed the time-course of 1,1,1-TCA levels in blood and correlated with absolute blood levels. Impaired psychomotor performances were reversible within 14 days (Mackay et al. 1987 and USEPA 2007).

Key findings were:

- Impaired psychomotor performance, particularly increased reaction time, was observed 20 minutes after exposure at both 175 and 350 ppm exposure levels;

- Measurements of 1,1,1-TCA 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 at both 175 and 350 ppm exposure levels;
- Observed performance changes correlated with blood level;
- The change in simple reaction time represented a 10 - 15% increase over baseline performance.

Human data from Mackay et al. (1987) will be utilized as the key study for derivation of the acute ReV and ^{acute}ESL. Based on Mackay et al. (1987), TD will utilize 175 ppm (950 mg/m^3) as the lowest-observed-adverse-effect-level (LOAEL) for impaired psychomotor performance, particularly increased reaction time for acute CNS effects. *The LOAEL of 175 ppm (950 mg/m3) will be used as the point-of-departure (POD) for derivation of the acute ReV and ESL.*

3.1.1.2.1.2 Supporting Study - Muttray et al. (2000)

Twelve healthy adult male volunteers (nonsmoking and right-handed students, mean age 27 ± 1.9 years) were exposed to both 20 and 200 ppm of 1,1,1-TCA (99.8%) for 4 hours in two exposure chamber sessions, with one week interval between the two exposures. Twenty ppm was chosen in the study as the control exposure in an attempt to blind subjects and staff to the exposure conditions, but it was described as not effective in the paper. Most subjects and staff identified the exposure concentrations in double-blind rating questionnaires. Electroencephalograms (EEGs) of the volunteers were recorded in the chamber before (reference) and after 3.7 hours of exposure (during the last 15 minutes of exposure), with eyes opened and closed and during a choice reaction time test (color word stress test). The mean blood concentration was 6.38 mg/L (± 4 SD) at 3.7 hours of exposure for subjects exposed to 200 ppm. Blood levels were below the detection limit (50 :g/L) before the experiment and during exposure to 20 ppm 1,1,1-TCA. Statistically significant EEG changes were found in volunteers exposed to 200 ppm when compared with the same volunteers exposed to 20 ppm. The EEG changes were consistent with increased drowsiness, as well as with subjectively reported tiredness, in volunteers performing a choice reaction time test with eyes closed during 3.7 hour exposure to 200 ppm. This study identified a LOAEL of 200 ppm for subtle neurological effects of 1,1,1-TCA (tiredness and EEG changes). A no-observed-adverse-effect-level (NOAEL) was not able to be identified because of the design of the study, as the controls for this study were exposed to 20 ppm. The LOAEL of 200 ppm for 3.7 hours exposure identified from this study was very similar to, but higher than the LOAEL of 175 ppm for 20 - 45 minutes exposure identified from the key study. Muttray et al. (2000) was not a double-blind study and also used 20 ppm as the control exposure concentration (i.e., there were no true controls), therefore this study was not selected as the key study.

3.1.1.2.1.3 Supporting Study - Gamberale and Hultengren (1973)

Twelve healthy adult male volunteers (20 to 30 years old) were both exposed to air (control condition) or to progressively increasing concentrations of 250, 350, 450, and 550 ppm of 1,1,1-TCA (purity not reported) for 30 minutes per concentration for a total of 2 hours (experimental condition) via respiratory valve and mouthpiece. The volunteers were randomly divided into two

groups, one group was exposed to the control condition first and then the experimental condition with seven days between the two exposure conditions. The second group was concurrently exposed but in reverse order. Menthol crystals were introduced into the mouthpiece tubing to mask the presence or absence of the solvent. Tests to measure manual dexterity, perceptual speed, and reaction time were administered at the final 20 minutes of each of the four 30-minute exposures. Mean performance during a 30-minute exposure at 250 ppm was not statistically significantly different from the control for any of the tests. A statistically significant reduction in task performance was observed during the subsequent 30-minute exposure to 350 ppm of 1,1,1-TCA. Performance was impaired in all five tests at ≥ 350 ppm, with deficits that were concentration related. A 30-minute NOAEL of 250 ppm and a 1-h time-weighted-average (TWA) LOAEL of 300 ppm were identified from this study for acute neurobehavioral effects. The NOAEL of 250 ppm identified from this study is higher than the LOAEL of 175 ppm from Mackay et al. key study, and therefore Gamberale and Hultengren (1973) study was not selected as the key study.

3.1.1.2.2 Animal Studies

There is extensive supporting evidence from the laboratory animal scientific literature that the CNS is a sensitive target for 1,1,1-TCA. 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 (≥ 700 ppm for effects of toxicological significance in acute studies). The acute literature suggests that the human model is a more sensitive model of neurobehavioral toxicity than the animal models tested (ATSDR 2006; USEPA 2007). Human data are available and preferred over animal studies for calculation of the acute ReV and ^{acute}ESL (TCEQ 2006). Therefore, this document focuses on relevant human studies (see above). Please refer to ATSDR (2006) and USEPA (2007) for a detailed discussion of short-term animal inhalation studies.

3.1.1.2.2.1 Developmental/Reproductive Effects in Animals

Reproductive/developmental studies were conducted in the rat, mouse, and rabbit (ATSDR 2006; USEPA 2007). These data suggest that 1,1,1-TCA is not a potent developmental toxin. Minor developmental effects characteristic of developmental delay were reported only at high doses (≥ 2000 ppm), were usually accompanied by maternal toxicity, and are not as sensitive as the CNS effects which serve as the basis for the acute ReV and ^{acute}ESL.

3.1.2 Mode-of-Action (MOA) Analysis for CNS Effects

The lipophilicity and volatility of 1,1,1-TCA, along with the low rates at which it is metabolized, appear to be the most important factors influencing distribution within and elimination from the body. 1,1,1-TCA is rapidly absorbed from the respiratory tract, and has been detected in human arterial blood within 10 seconds after initiation of inhalation exposure and approached steady-state concentrations around 2 hours of exposure (Mackay et al. 1987; Nolan et al. 1984; Reitz et al. 1988; Dallas et al. 1989). The compound is widely distributed by the blood among tissues, with higher concentrations found in tissues with higher lipid content such as adipose tissue and

the brain. Up to 90% of the 1,1,1-TCA absorbed by any route is rapidly excreted unchanged in the expired air. Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-TCA is rapidly eliminated from the body; ≥ 99% is eliminated within 50 hours (ATSDR 2006; USEPA 2007).

The mechanism by which 1,1,1-TCA and other organic solvents depress the CNS is not fully understood, but is thought to involve interactions of the parent compound with lipids and/or proteinaceous components of neural membranes (Evans and Balster 1991). In research with animal models of inhalant abuse, N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid type A ($GABA_A$), glycine, and 5-hydroxytryptamine type 3 ($5HT_3$) receptors appear to be important targets of action for several abused solvents with emerging evidence suggesting that other receptor subtypes and nerve membrane ion channels may be involved as well (Bowen et al. 2006; Beckstead, Phelan, and Mihic 2001). 1,1,1-TCA may share discriminate-stimulus properties with a variety of classic CNS depressants; including ethanol and pentobarbital (Bowen 2009; Bowen et al. 2006; Shelton 2009, 2010). Drug discrimination (i.e., an animal model of the abuse-related intoxicating effects of drugs in humans which has been used extensively to examine other classes of abused drugs), has recently been utilized in analysis of the mechanism of neurological effects of volatile chemicals. Using classic CNS depressants as the training drugs, the animals did not discriminate between the neurological effects of moderate to high concentrations of 1,1,1-TCA and a variety of classic CNS depressants or vice verse (Bowen 2009; Bowen et al. 2006; Shelton 2009, 2010).

3.1.3 Dose Metric

If available, the concentration of parent compound at the target tissue (i.e., brain) would arguably be the best dose metric to evaluate neurobehavioral effects of this chemical. However, experimental studies of acute 1,1,1-TCA exposure show blood and brain concentrations of 1,1,1-TCA to be correlated with operant performance in the rat (Warren et al. 1998) and locomotor activity in the mouse (Warren et al. 2000). Studies of operant behavior (food-reinforced lever-pressing) are thought to reflect effects of 1,1,1-TCA in laboratory animals comparable to psychomotor changes in humans. There is a strong correlation between the blood and brain concentration of 1,1,1-TCA in mice (Warren et al. 2000) and rats (Warren et al. 1998) exposed to wide ranges of 1,1,1- TCA levels via inhalation. Similarly, blood concentration is highly correlated linearly ($R^2 = 1$) with the exposure level in the range of 10–5000 ppm up to 336 h (14 days) when steady-state is reached (87% of steady state occurs at 48 h, 94% at 96 h, and 98% at 168 h) (Lu et al. 2008). Thus, exposure concentrations, blood concentrations, and brain concentrations are all strongly correlated over a wide exposure range and can serve as appropriate dose metrics. Although both air and blood concentrations of 1,1,1-TCA are available from the key study (Mackay et al., 1987), the 1,1,1-TCA air exposure concentration (LOAEL of 175 ppm) is an appropriate dose metric and the most straightforward dose metric for deriving the acute ReV and ESL. Use of the air exposure concentration as the dose metric for deriving a 1-h health-protective value is consistent with USEPA (2007).

3.1.4 Point-of-Departure (PODs) for the Key Study

The LOAEL of 175 ppm (analytical concentration) from the Mackay et al. (1987) key study will be used as the human point-of-departure (POD_{HEC}) in calculation of the acute ReV and ^{acute}ESL.

3.1.5 Dosimetric Adjustments

Although the total continuous inhalation exposure duration was 3.5 h in the Mackay et al. (1987) key study, neurobehavioral tests were performed 25 minutes before exposure and four times during exposure, starting at 20, 60, 120, and 180 minutes. Impaired psychomotor performance, particularly increased reaction time, was observed 20 minutes after exposure at 175 ppm. One-hour exposure was evaluated in the experiment and the results of psychomotor performance taken at 20 minutes and 60 minutes were not significantly different. This may suggest that concentration may be the dominant determinant, and that duration plays only a minor role in 1,1,1-TCA-induced acute neurotoxicity. Studies of 1,1,1-TCA and related solvents in animal models demonstrate that Haber's rule is not an accurate predictor of acute CNS toxicity (Boyes et al. 2000; Boyes et al. 2005; Warren et al. 2000; Warren et al. 1998; Boyes et al. 2003). Therefore, adjustment for exposure duration from 20-45 minutes to 1 hour is not appropriate (TCEQ 2006). The 1-h POD_{HEC} is 175 ppm (LOAEL). This is consistent with USEPA's derivation of the 1-h RfC, in which the POD was based on the LOAEL of 175 ppm (950 mg/m^3) and a duration adjustment to a 1-h exposure was not conducted (USEPA 2007).

3.1.6 Critical Effect and Adjustments of the POD_{HEC}

3.1.6.1 Critical Effect

The most sensitive endpoint for human acute inhalation exposure to 1,1,1-TCA is subtle neurobehavioral effects. Impaired psychomotor performance is the specific critical effect of 1,1,1-TCA exposure in the key study (Mackay et al. 1987).

3.1.6.2 Uncertainty Factors (UFs)

Acute impaired psychomotor performance in the key study (Mackay et al. 1987) is primarily concentration-dependent and reversible. CNS depression, as indicated by impaired psychomotor performance, is the critical effect of short-term 1,1,1-TCA exposure and the effects appear to have a threshold (USEPA 1998). For noncarcinogenic effects that exhibit a threshold MOA, a POD_{HEC} is determined and appropriate UFs are applied to derive a ReV (TCEQ 2006).

The LOAEL from Mackay et al. (1987) of 175 ppm was used as the POD_{HEC} and divided by the following uncertainty factors (UFs): 10 for intrahuman variability (UF_H), 10 for extrapolation from a LOAEL to a NOAEL (UF_L), and 1 for the acute database (UF_D) (total UF = 100). An animal-to-human UF (UF_A) is not applicable since the LOAEL is from an experimental human study.

- A UF_H of 10 was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-TCA in the human population.

- A UF_L of 10 was used because the lowest exposure concentration examined in the key study was associated with a measurable deficit in a neurobehavioral test (Chou and Williams-Johnson 1998). A NOAEL was not identified in the key study, and the supporting studies did not help bound what the NOAEL might be expected to be for the key study.
- A UF_D of 1 was applied because the acute database for this chemical was considered 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-TCA, the most sensitive effects following acute inhalation exposure, have been investigated in both animals and humans.

3.1.7 Health-Based Acute ReV and ^{acute}ESL

As discussed in the previous section, UFs are applied to the key study (Mackay et al. 1987) POD_{HEC} to derive the acute ReV:

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 175 \text{ ppm} / (10 \times 10 \times 1)$$
$$= 1.75 \text{ ppm (1750 ppb)}$$

The acute ReV value was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then multiplied by 0.3 to calculate the ^{acute}ESL. Rounding to two significant figures, the 1-h acute ReV for 1,1,1-TCA is 1.7 ppm, or 1700 ppb (9500 µg/m^3). At the target hazard quotient of 0.3, the ^{acute}ESL is 510 ppb (2800 µg/m^3) (Table 4). The acute ReV is the same as the USEPA 1-h reference concentration (1-h RfC of 1700 ppb) (USEPA 2007). For reference, information concerning the USEPA derivation of short-term RfCs for other exposure durations is provided in Appendix A.

Table 4. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Values and Descriptions
Study	Mackay et al. (1987)
Study population	12 adult male volunteers
Study quality	Medium - high
Exposure Method	Inhalation exposure to 0, 175, and 350 ppm for 3.5 hours, impaired psychomotor performance was observed around 20-45 minutes.
LOAEL	175 ppm
NOAEL	Not identified
Critical Effects	Impaired psychomotor performance
POD_{HEC}	175 ppm
Exposure Duration	1 hour, exposure duration adjustment from 20-45 minutes to 1 hour was not conducted
Extrapolation to 1 h	Not Applicable
Extrapolated 1 h concentration	175 ppm
Total Uncertainty Factors (UFs)	100
Interspecies UF	NA
Intraspecies UF	10
LOAEL-to-NOAEL UF	10
Database UF *Database Quality*	1 High
Acute ReV [1 h] (HQ = 1)	**9500 µg/m^3 (1700 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**2800 µg/m^3 (510 ppb)**

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

1,1,1-TCA has a sweet and sharp odor similar to chloroform. One study was located which published odor threshold values for 1,1,1-TCA. May (1966) reported odor detection threshold and 50% odor recognition threshold values of 2,100,000 and 3,900,000 µg/m^3, respectively. Since 1,1,1-TCA does not have a pungent or disagreeable odor and it's odor based values are significantly above health-based value an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015).

3.2.2 Vegetation Effects

No data were found on the potential effects of 1,1,1-TCA on vegetation.

3.3. Short-Term ReV and ^{acute}ESL

The acute evaluation resulted in the derivation of the following values:

- acute ReV = 9500 µg/m^3 (1700 ppb)
- ^{acute}ESL = 2800 µg/m^3 (510 ppb)

The Air Monitoring Comparison Value (AMCV) used for comparison to ambient air monitoring data is the acute health-based ReV of 9500 µg/m^3 (1700 ppb). (Table 1).

The critical short-term ESL applicable to air permit reviews is the health-based ^{acute}ESL of 2800 µg/m^3 (510 ppb). (Table 2). The health-based ^{acute}ESL of 2800 µg/m^3 (510 ppb) is not used in the evaluation of air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of 1,1,1-TCA are discussed in Chapter 3. While human and animal data indicate that the CNS is the most sensitive target for acute inhalation exposure to 1,1,1-TCA, available long-term studies do not provide evidence of overt neurobehavioral effects. However, most long-term studies did not include examination of subtle CNS toxicity (ATDSR 2006; USEPA 2007). Based on available experimental subchronic and long-term animal studies, mild hepatotoxicity is the critical effect for 1,1,1-TCA (ATSDR 2006; Braubar 2002; USEPA 2007). Discussions of human and animal studies relevant for the chronic noncarcinogenic evaluation and the key studies used for derivation of the chronic ReV and noncarcinogenic ESL ($^{chronic}ESL_{nonlinear(nc)}$) are presented below.

4.1.1.1 Human Studies

While human data are preferred for derivation of a chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$, information on the long-term toxicity of inhaled 1,1,1-TCA in humans is limited. Epidemiological studies on occupational workers exposed to 1,1,1-TCA have shown CNS effects and minor changes in liver enzymes. However, either exposure concentrations were not provided or co-exposure to other solvents occurred (ATSDR 2006; Braubar 2002; USEPA 2007). No human study could be identified for derivation of the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$. Refer to ATSDR (2006) and USEPA (2007) for available human study information regarding the potential health effects of long-term 1,1,1-TCA inhalation exposure.

4.1.1.2 Animal Studies

In regard to animal data, important information on the long-term inhalation toxicity of 1,1,1-TCA is available from a well-designed, two-year chronic rat and mouse study (Quast, Calhoun, and Frauson 1988). Animal studies have shown 1,1,1-TCA to be a hepatotoxicant, producing mild effects on the liver at relatively high levels (Quast et al. 1988, McNutt et al. 1975, ATSDR 2006, USEPA 2007). The chronic Quast et al. (1988) study is identified as the key study, and the McNutt et al. (1975) subchronic study is the supporting study, used in the derivation of a chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$. These are the same studies used by USEPA to derive their 2007 chronic RfC, and a review of the scientific literature since 2006 by the TD did not identify any new adequate toxicity studies for development of the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$. Study details are provided below.

4.1.1.2.1 Key Study – Quast et al. (1988)

Quast et al. (1988) exposed groups of 80 male and 80 female F344 rats and $B6C3F_1$ mice to mean analytical concentrations of 0, 150, 500, or 1500 ppm production-grade (94%) 1,1,1-TCA 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 of each sex from each exposure 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 (Quast et al. 1988). Female rats in both the 500 and 1500 ppm groups showed slight, statistically significant deficits in body weight throughout much of the study (≤ 7% of controls, estimated from growth curves); the researchers considered the effect to be exposure-related at the highest concentration of 1500 ppm. 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 1500 ppm 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 1500 ppm are consistent with a minimal hepatocellular hypertrophy, which is considered an adaptive physiologic response and not a measure of toxicity (Chou et al. 2002). 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 technically identified a free-standing NOAEL of 1500 ppm, 6 hours/day, 5 days/week in rats and mice since a LOAEL was not identified in this 2-year study. However, a 90-day subchronic pre-study by the same laboratory for selecting appropriate exposure concentrations for this 2-year study found statistically significant liver effects (liver weight) and other effects (body weight and minimal microscopic changes in the olfactory epithelium) at a LOAEL of 2000 ppm, 6 hours/day, 5

days/week (Calhoun et al. 1981 cited in Quast et al. 1988). Therefore, TD believes 1500 ppm may be appropriately considered as the NOAEL for liver effects from this study, especially considering the liver effects found in the supporting study and a comparison of the study NOAELs on a continuous exposure basis (see the discussion below and Table 5).

4.1.1.2.2 Supporting Study – McNutt et al. (1975)

Male CF-1 mice were chamber-exposed to 0, 250, or 1000 ppm technical grade 1,1,1-TCA (94-97%) continuously for up to 14 weeks (McNutt et al., 1975). Serial sacrifices were performed on 10 mice from each exposure concentration at weekly intervals during the exposure period and at two and four weeks post-exposure. 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 the remaining seven mice/concentration), liver ultrastructure (three mice/concentration), and histology (liver, brain, lung, heart, kidney, pancreas and intestine). Exposure-related effects in tissues other than liver were not found.

In animals exposed to 250 ppm of 1,1,1-TCA, centrilobular hepatocytes frequently were indistinguishable from control animals. Minimal changes with electron microscopic evaluations were observed after 10 weeks of exposure, including occasional mild liver ultrastructural variations. The relative liver weight (liver weight per 100 gm of body weight) and liver triglyceride levels for animals exposed to 250 ppm 1,1,1-TCA were not generally elevated significantly as compared to control animals.

In mice exposed to 1000 ppm 1,1,1-TCA, hepatic ultrastructural changes were more pronounced and accompanied by increases in relative liver weight, triglycerides, and lesions visible by light microscopy. However, there were no obvious correlations between the severity of observed liver effects and duration of exposure. The relative liver weight and liver triglyceride levels for animals exposed to 1000 ppm were elevated significantly ($p < 0.05$ or $P < 0.01$) compared to control animals at all sampling periods during the exposure including following one week of exposure. The triglyceride levels peaked at approximately seven weeks; there was partial recovery after 7 to 14 weeks, and full recovery was observed at two and four weeks post-exposure. Relative liver weight and liver triglyceride values were 22% ($p< 0.01$) and 237% ($p< 0.01$) higher, respectively, at 1000 ppm compared with controls at exposure week 14. The liver fat content determined by oil red O staining showed a close correspondence with the results of triglyceride analysis. Histopathological changes such as centrilobular hepatocyte swelling, vacuolations, and lipid accumulations were also observed at all sampling periods during the exposure. Necrosis of individual hepatocytes in the centrilobular region were the exception, which became evident after 10 weeks of exposure to 1000 ppm of 1,1,1-TCA. 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 1000 ppm.

The minimal ultrastructural changes observed at 250 ppm do not constitute clear evidence of an adverse effect. This subchronic study, therefore, identified a NOAEL of 250 ppm and a LOAEL of 1000 ppm for liver effects (increased relative liver weight and liver triglyceride levels as well as necrosis of individual hepatocytes) in mice continuously exposed to 1,1,1-TCA.

4.1.1.2.2.1 Usefulness of the Supporting Subchronic Study (McNutt et al. 1975) in Chronic ReV Derivation

The key study (Quast et al. 1988) did not technically identify a LOAEL for liver effects, only a free-standing NOAEL of 1500 ppm for discontinuous exposure (6 hours/day, 5 days/week) in rats and mice, although the 90-day pre-study found a LOAEL of 2000 ppm for liver effects.This chronic study NOAEL is equivalent to 268 ppm when adjusted to continuous exposure (i.e.,24 hours/day, 7 days/week, see Section 4.1.5 for the adjustment calculation) and may be used for comparison to the continuous exposure NOAEL of 250 ppm from the supporting subchronic study (Table 5).

Table 5. Comparison of the Key and Supporting Studies

Parameter	Key Study	Supporting Study
Study	Quast et al. 1988	McNutt et al. 1975
Testing Animals	F344 rats and B6C3F1 mice (both males and females)	Male CF-1 mice
Exposure Duration	6 hours/day, 5 days/week for 2 years	Continuously for 14 weeks
NOAEL	1500 ppm discontinuous exposure (268 ppm[a] adjusted to continuous exposure)	250 ppm continuous exposure
LOAEL	Not identify	1000 ppm continuous exposure

[a] see Section 4.1.5 for the calculation.

The results from the supporting subchronic study (McNutt et al. 1975) can be directly compared with those from the chronic study (Quast et al. 1988) based on the following considerations:

- Slight microscopic hepatic changes do not appear to progress in severity or incidence with exposure duration after six months from Quast et al. (1988) study. The analysis of physiologically-based pharmacokinetic (PBPK) modeling demonstrated that internal dose did not change with exposures longer than six months, indicating steady state had been achieved (Yang 2006, Lu 2008). The findings from Quast et al. (1988) study may therefore also apply to the findings from McNutt et al. (1975) study.
- The Reitz et al. (1988) PBPK model was used with data from Mackay et al. (1987) study. The steady state venous blood concentration appears to be reached around 168 hours or soon thereafter (Yang 2006). The steady state was likely already reached at 14 weeks of the McNutt et al. (1975) study.
- The major characteristic favoring accumulation of volatile compounds in blood and systemic tissues is poor whole-body clearance, not lipophilicity (Andersen, Reddy, and Plotzke 2008). Highly cleared 1,1,1-TCA would not be considered to bioaccumulate on repeated exposures.

In addition to supporting the NOAEL from the key chronic study, the supporting subchronic study (McNutt et al. 1975) is useful for purposes of this document because it also identifies a LOAEL for liver effects (1000 ppm for continuous exposure). Due to the comparability of the results and the marked similarity of the continuous exposure NOAELs, use of either of these studies would result in similar chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values. However, a chronic study is typically preferred for use as the key study. The Quast et al. (1988) study is a well-designed, two-year chronic rat and mouse study. The similarity of the continuous exposure NOAELs further supports use of this chronic study. Therefore, the NOAEL of 1500 ppm for 6 hours/day, 5 days/week for 2 years from Quast et al. (1988) was used as the POD for derivation of the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$.

4.1.2 Metabolism and MOA Analysis for Liver Toxicity

Studies in animals and humans demonstrate that only a small fraction of absorbed 1,1,1-TCA (< 10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air. 1,1,1-TCA is metabolized oxidatively to trichloroethanol and trichloroacetic acid by the cytochrome P450 (CYP) mixed function oxidase system. Trichloroethanol (and its glucuronide conjugate) and trichloroacetic acid are excreted in the urine in both humans and experimental animals. A minor metabolite, CO_2, is eliminated in expired air (Johns et al. 2006; Nolan et al. 1984; Reitz et al. 1988; Schumann, Fox, and Watanabe 1982). A general metabolic scheme for 1,1,1-TCA is presented in Figure 2.

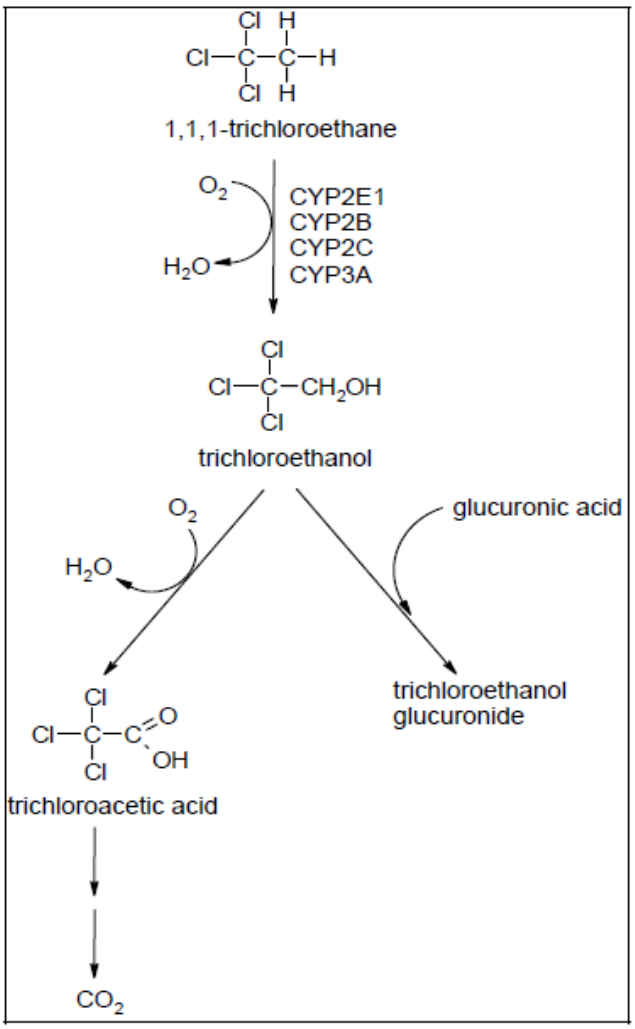


Figure 2: Metabolic Scheme for 1,1,1-TCA (USEPA 2007)

The hepatotoxicity of 1,1,1-TCA is quite low compared to other chlorinated hydrocarbons, including 1,1,2-trichloroethane (1,1,2-TCA). The relatively low toxicity of 1,1,1-TCA may be due to its relatively low metabolism rate, since the more hepatotoxic halocarbons are extensively metabolized. There is evidence that the metabolites of 1,1,1-TCA may induce hepatotoxicity, since pretreatment of rat with the enzyme-inducing agent phenobarbital potentiated the hepatotoxicity of 1,1,1-TCA (Carlson 1973). However, whether the mild effects of repeated 1,1,1-TCA exposure are evoked by the parent compound or the limited quantities of metabolites produced is not known (ATSDR 2006, USEPA 2007). It is possible that the effects of the 1,1,1-TCA parent compound on the liver involve altered function of cellular and mitochondrial membranes. Additionally, liver damage may be caused by reactive (free radical) intermediates generated during the oxidative and/or reductive metabolism by microsomal CYP, although much weaker than that of 1,1,2-TCA (Xia and Yu 1992). The liver is a target organ following repeated exposure and 1,1,1-TCA is metabolized, albeit to a limited extent, in the liver (Lu et al. 2008).

See ATSDR (2006), USEPA (2007), for additional information regarding the metabolism of 1,1,1-TCA and MOA of hepatotoxicity.

4.1.3 Dose Metric

For the Quast et al. (1988) key study, only the exposure concentration of the parent chemical is available. However, Yang (2006) and Lu et al. (2008) used the Reitz et al. (1988) PBPK model to estimate internal dose metrics from the Quast et al. (1988) rat inhalation study. Liver effects observed with 1,1,1-TCA may arise from the parent chemical or metabolites. However, due to the limited metabolism of 1,1,1-TCA and uncertainty associated with the estimates of dose metrics of metabolites, metabolite dose metrics were not calculated (Lu et. al. 2008). Yang (2006) and Lu et al. (2008) calculated the total area under the curve of the liver concentration (AUCLT) of 1,1,1-TCA over the entire duration. The AUCLT was then divided by days that gave the average daily area under the curve of the liver concentration (ADAUCL). The ADAUCL is considered the most appropriate dose metric by TCEQ (and USEPA) because the liver is the target organ for repeated exposure of 1,1,1-TCA (TCEQ 2006; USEPA 2007; Lu et al. 2008; Thompson et al. 2008).

4.1.4 POD for Key Study

The NOAEL of 1500 ppm (analytical concentration) for 6 hours/day, 5 days/week for 2 years from key study (Quast et al. 1988) was used as the POD for derivation of the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$.

4.1.5 Dosimetric Adjustments

4.1.5.1 Default Exposure Duration Adjustments

The POD_{ADJ} for Quast et al. (1988) key study in this section is calculated only for comparison to the NOAEL of 250 ppm and LOAEL of 1000 ppm from the McNutt et al. (1975) supporting study since the key study is a discontinuous exposure animal study, while the supporting study is a continuous exposure study. The adjustment of animal exposure regimen to a continuous exposure is shown below. The final dosimetric adjustment for the key study (Quast et al. 1988) used PBPK modeling to directly adjust from the intermittent NOAEL POD (i.e., 1500 ppm for 6 hours/day, 5 days/week for 2 years) to a continuous POD_{HEC} (see Section 4.1.5.2).

$$POD_{ADJ} = POD \times (D/24\ h) \times (F/7\ days)$$

where:

POD = POD from animal study based on discontinuous exposure regimen
D = exposure duration (hours per day)
F = exposure frequency (days per week)

Quast et al. (1988):

$$POD_{ADJ} = 1500\ ppm \times (6/24) \times (5/7) = 268\ ppm$$

4.1.5.2 Dosimetry Adjustments from Animal-to-Human Exposure

PBPK modeling was used for dosimetric adjustment from the POD of the intermittent exposure rat key study to a continuous exposure human POD_{HEC}.

In a PBPK model, several compartments represent the anatomical organs or groups of tissues/organs of an organism connected by the circulating blood. The disposition of a chemical in each compartment is determined by physiological (e.g., tissue volume, blood flow rate), physicochemical (e.g., partition coefficient), and biochemical (e.g., metabolism rate) parameters (Lu et al. 2008). The amounts and/or concentrations of the chemical in each compartment, including the target organ, can be calculated by solving a group of mass balance differential and algebraic equations.

Yang (2006) and Lu et al. (2008) evaluated 15 published PBPK models for 1,1,1,-TCA in rats and humans, and identified the Reitz et al. (1988) PBPK model as the most suitable for deriving toxicity reference values for 1,1,1-TCA. The Reitz model included liver, fat, rapidly and slowly perfused compartments, and contained a saturable process for 1,1,1-TCA hepatic metabolism. The structure of the Reitz model is shown in Figure 3, and the parameters for both the rat and human models are provided in Table 6.

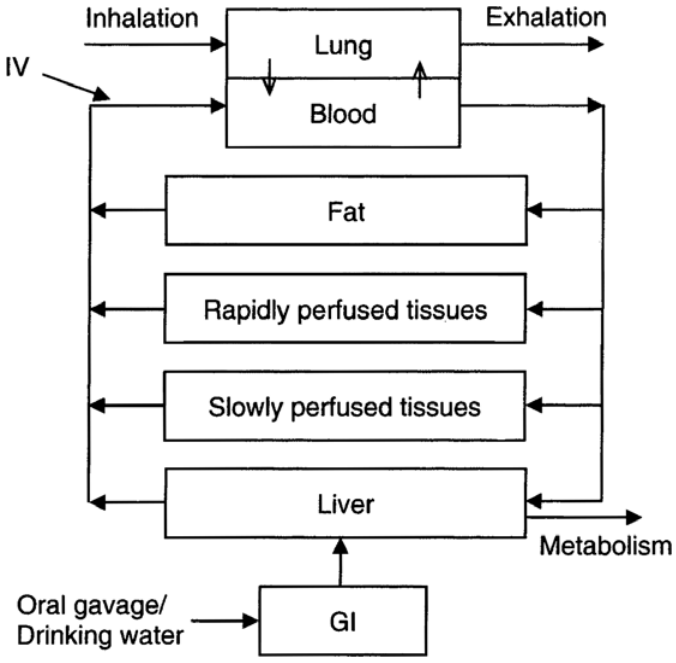


Figure 3: Structure of the Reitz et al. (1988) PBPK Model for 1,1,1-TCA

Table 6. Rat and Human Parameters for Simulations Using Reitz PBPK Model

Parameter		**Rat**	**Human**
Body Weight (kg)		Experiment specific	70 kg (reference default)
Tissue Volume Fractions	Fat	0.07	0.231
	Liver	0.04	0.031
	Rapidly Perfused	0.05	0.037
	Slowly Perfused	0.75	0.611
Cardiac Output Constant (L/h/kg $^{0.74}$)		15	15
Tissue Blood Flow Fractions	Fat	0.05	0.09
	Liver	0.24	0.24
	Rapidly Perfused	0.53	0.49
	Slowly Perfused	0.18	0.18
Pulmonary Ventilation Constant (L/h/kg $^{0.74}$)		15	15
Partition Coefficients	Blood: Air	5.76	2.53
	Blood: Fat	45.66	103.95
	Blood: Liver	1.49	3.4
	Blood: Rapidly Perfused	0.55	1.25
	Blood: Slowly Perfused	1.49	3.4
Metabolism	$V_{max}C$ (mg/h/kg $^{0.7}$)	0.419	0.419
	K_m (mg/L)	5.75	5.75

The Reitz et al. (1988) PBPK model was used to extrapolate from the animal NOAEL from Quast et al. (1988) to humans. More specifically, it was used to calculate a human continuous inhalation exposure concentration (POD_{HEC}) that would yield an internal dose equivalent to that resulting from the intermittent exposure of rats at the NOAEL from the key Quast et al. (1988) study (i.e., 1500 ppm, 6 h/day, 5 days/week for 2 years). The model was run to simulate six months of exposure (time to first sacrifice) because the internal dose did not change with exposures longer than six months, indicating steady state had been achieved.

The internal dose metric was ADAUCL. The predicted ADAUCL at steady state derived from the PBPK analysis of Lu et al. (2008) is shown in Table 6. The calculated POD_{HEC} corresponding to the ADAUCL is also shown in Table 7. The POD_{HEC} is 283.1 ppm.

Table 7. Calculation of POD_{HEC} using PBPK modeling based on liver concentration of 1,1,1-TCA as the dose metric

Parameter	Values and Descriptions
NOAEL from Quast et al. (1988)	1500 ppm, 6 hour/day, 5 days/week for 6 months[a]
Predicted AUCLT [b] in the rat	57,140.4 (mg x h/L)
Predicted ADAUCL[c] in the rat	313.1 (mg x h/L)
POD_{HEC}	283.1 ppm

[a] The model was run to simulate 6 months not 2 years since the internal dose did not change with exposures longer than 6 months.

[b] Total area under the curve of the liver concentration.

[c] Average daily area under the curve of the liver concentration.

4.1.6 Critical Effect and Adjustments of the POD_{HEC}

4.1.6.1 Critical Effect

Slight microscopic hepatic changes (slight morphological changes in the liver) in both male and female rats were the critical effects identified in the Quast et al. (1988) key study for long-term exposure to 1,1,1-TCA.

4.1.6.2 UFs

The critical effects from the key study (Quast et al. 1988) were slight microscopic hepatic changes, which were only observed in animals exposed to the highest exposure concentration of 1500 ppm. These effects were not seen in any control or lower-dose animals at any time point. The hepatotoxicity of 1,1,1-TCA from the key study demonstrated a threshold/nonlinear MOA. Therefore, UFs were applied to the POD_{HEC} value from the key study to derive the chronic noncarcinogenic ReV. The UF_L and Subchronic-to-Chronic UF (UF_{Sub}) are not applicable since the POD_{HEC} is based on a NOAEL from a 2-year chronic study. The POD_{HEC} of 283.1 ppm from Quast et al. (1988) was divided by a UF_A of 3, a UF_H of 10, and a UF_D of 10. The total UF for Quast et al. (1988) is 300.

- A UF_A of 3 was used for potential toxicodynamic differences between laboratory animals and humans. A higher UF_A was not considered necessary because PBPK modeling was used to account for the toxicokinetic (PK) differences between rats and humans.
- A UF_H of 10 was used since data regarding potential intrahuman sensitivity are lacking.
- A UF_D of 10 was used in consideration of important deficiencies in the chronic database for 1,1,1-TCA. Uncertainty exists related to the potential neurotoxicity of 1,1,1-TCA following long-term exposure. Sensitive testing for subtle neurobehavioral effects in either humans or animals is unavailable following long-term exposure despite short-term studies indicating that CNS effects are of concern (i.e., the most sensitive effects). Due to

this database concern, ATSDR (2006) did not derive a chronic duration inhalation MRL for 1,1,1-TCA. Lastly, long-term health-protective air concentrations should also protect against short-term effects if the most sensitive effects of long-term exposure are adequately identified. Use of a lower UF_D (e.g., 3) would not sufficiently account for uncertainty in the chronic study database or result in a chronic ReV as protective of acute subtle neurological effects as the acute ReV. Based on these considerations, it is reasonable to use a UF_D of 10 to account for an incomplete database (e.g., lack of adequate human studies of subtle CNS effects due to long-term exposure).

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

As discussed in the previous section, UFs are applied to the POD_{HEC} values from the key study in deriving the chronic ReV:

$$\text{chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 283.1 \text{ ppm} / (10 \times 3 \times 10)$$
$$= 0.9437 \text{ ppm (943.7 ppb)}$$

Rounding to two significant figures at the end of all calculations for the Quast et al. (1988) key study yields a chronic ReV of 940 ppb (5100 µg/m^3). At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 280 ppb (1500 µg/m^3).

Table 8. Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Values and Descriptions**
Study	Quast et al. (1988)
Study Population	80 male and 80 female F344 rats and B6C3F1 mice per exposure group
Study Quality	High
Exposure Levels	0, 150, 500, and 1500 ppm (mean analytical concentrations)
Critical Effects	slight microscopic hepatic changes
POD (free-standing NOAEL)	1500 ppm
Exposure Duration	6 hours per day, 5 days per week, for 2 years
Extrapolation to continuous exposure (POD_{ADJ}) Extrapolation to humans (POD_{HEC})	The Reitz PBPK model was used for dosimetry adjustment from POD NOAEL (discontinuous) to POD_{HEC} 283.1 ppm
Total Uncertainty Factors (UFs)	300
Interspecies UF	3
Intraspecies UF	10
LOAEL-to-NOAEL UF	Not applicable
Subchronic-to-Chronic UF	Not applicable
Database UF *Database Quality*	10[a] Low[a]
Chronic ReV (HQ = 1)	**5100 µg/m^3(940 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**1500 µg/m^3(280 ppb)**

[a]see Section 4.1.6.2 for explanations

4.1.8 Comparison of Chronic ReV to other Acute and Chronic Values

Table 9 provides a comparison of the derivation of the chronic ReV of 940 ppb versus the calculated chronic RfC of 2800 ppb (USEPA 2007). The only difference in derivation of the chronic values is the application of database UF (i.e., UF_D of 10 by TCEQ versus 3 by USEPA).

Table 9. Comparison of Chronic ReV and Chronic RfC

Chronic Toxicity Value	POD_{HEC}	UF_H	UF_A	UF_{Sub}	UF_D	Total UFs	Chronic Toxicity Value
ReV based on slight microscopic hepatic changes (TCEQ)	283.1 ppm	10	3	NA	10	300	940 ppb
RfC based on slight microscopic hepatic changes (USEPA)	283.1 ppm	10	3	NA	3	100	2800 ppb[a]

[a] The final USEPA chronic RfC value was set at 960 ppb.

The USEPA calculated chronic RfC of 2800 ppb derived from Quast et al. (1988) was higher than the USEPA short-term RfCs of 960 to 1700 ppb (5 to 9 mg/m^3) for various exposure durations (information concerning the USEPA derivation of short-term RfCs is provided in Appendix A). However, USEPA set the final chronic RfC at 960 ppb so as not to exceed the 14-day RfC for the following reasons quoted from USEPA (2007):

> "The point of departure for the acute (and short-term) exposure duration is based on CNS effects in humans, whereas the point of departure for subchronic and chronic exposure durations is based on liver effects in rats and mice. Thus, the target organ for acute/short-term exposure durations differs from that for subchronic/chronic exposure durations. Although the modes of action for the CNS and liver effects of 1,1,1-trichloroethane have not been established, it is likely that the modes of action at the two sites of toxicity are different.
>
> The endpoints examined following acute exposure to 1,1,1-trichloroethane differ from those examined following subchronic or chronic exposure. In particular, sensitive neurobehavioral testing in humans is available for evaluating 1,1,1-trichloroethane acute toxicity. In fact, human test batteries proved to be more sensitive than animal models of acute neurobehavioral toxicity. Sensitive testing for neurobehavioral effects in either humans or animals is unavailable following repeated exposure.
>
> The acute/short-term RfCs are based on analysis of peak exposure, whereas subchronic/chronic RfCs are based on AUC exposure."

For selection of the UF_D for the chronic ReV, the TD is concerned that the critical chronic effects identified for the liver may not be the most sensitive when considering important data on sensitive neurological effects are unavailable for humans from well-conducted long-term (i.e., chronic) studies. Only limited repeat exposure animal studies are available which examined neurotoxicological endpoints, and based on acute studies it appears that humans are more

sensitive to such effects than animals. In other words, based on what is known about the most sensitive effects of 1,1,1-TCA exposure from acute studies, the chronic database has a significant gap. TCEQ's selection of a UF_D adequately accounts for this important data gap, thereby alleviating a need to account for this consideration outside of the ReV derivation process (unlike USEPA's chronic RfC derivation). Consequently, TCEQ's chronic ReV of 940 ppb is below the acute ReV (1700 ppb) and is slightly below the most conservative USEPA short-term (14-day) RfC (960 ppb). For reference, the summary of USEPA derivation of short-term RfCs for various exposure durations including 14 days is provided in Appendix A. The chronic ReV is similar to ATSDR's intermediate MRL (700 ppb) based on neurological effects in a subchronic study (Rosengren et al. 1985), and the $^{chronic}ESL_{nonlinear(nc)}$ (280 ppb) is 2.5 times lower that the intermediate MRL. [The study results serving as the basis for the intermediate MRL (from Rosengren et al. 1985), however, are actually considered by the TD to be equivocal, of uncertain toxicological significance (e.g., apparently not dose dependent and unsupported by other relevant studies), and inadequate to establish a critical effect, consistent with USEPA (2007).] Therefore, the chronic ReV of 940 ppb and the $^{chronic}ESL_{nonlinear(nc)}$ of 280 ppb should protect against sensitive neurobehavioral effects as well as the most sensitive chronic hepatic effects identified to date.

4.2 Carcinogenic Potential

Under the Guidelines for Carcinogen Risk Assessment (USEPA 2005), the database for 1,1,1-TCA provides "inadequate information to assess carcinogenic potential". Epidemiologic studies of humans chronically exposed to 1,1,1-TCA are inconclusive. The key 2-year chronic study (Quast et al. 1988) was originally designed for both chronic inhalation toxicity and oncogenicity, but showed no treatment-related increase in tumors in rats and mice below the maximum tolerated dose. 1,1,1-TCA 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 mixed but still predominantly negative for assays other than cell transformation. The chemical has been shown to interact weakly with DNA (USEPA 2007).

The International Agency for Research on Cancer (IARC 1999) has classified 1,1,1-TCA as Group 3, the agent is unclassifiable as to carcinogenicity in humans. The National Institute for Occupational Safety and Health (NIOSH) has classified 1,1,1-TCA as A4, not classifiable as a human carcinogen. The TD has concluded that the data are inadequate for an assessment of human carcinogenic potential by the inhalation pathway.

4.3. Welfare-Based Chronic ESL

No data were found on the potential effects of 1,1,1-TCA on vegetation.

4.4 Long-Term ReV and ESL

The chronic evaluation resulted in the derivation of the following values:

chronic ReV = 5100 µg/m^3 (940 ppb)
$^{chronic}ESL_{nonlinear(nc)}$ = 1500 µg/m^3 (280 ppb)

The AMCV used for comparison to ambient air monitoring data is the chronic health-based ReV of 5100 µg/m^3 (940 ppb) (Table 1).

The critical long-term ESL applicable to air permit reviews is the health-based $^{chronic}ESL_{nonlinear(nc)}$ of 1500 µg/m^3 (280 ppb) (Table 2). The health-based $^{chronic}ESL_{nonlinear(nc)}$ of 1500 µg/m^3 (280 ppb) is not used in the evaluation of air monitoring data.

Chapter 5. References

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DocumentAppendix A. Summary of USEPA derivation of short-term RfCs for various exposure durations

USEPA (2007) used various PODHEC values to calculate short-term RfCs for several exposure durations based on sensitive neurobehavioral effects in humans from the Mackay et al. (1987) study. A LOAEL of 175 ppm (950 mg/m3) was used as the PODHEC for deriving a 1-h RfC. PBPK modeling was used for duration extrapolation of PODHEC values for durations longer than 1 hour. Based on the assumption that CNS effects are correlated with blood 1,1,1-TCA levels, the 1,1,1-TCA level in blood associated with a 1-h exposure to 175 ppm (950 mg/m3) was determined (USEPA 2007). Then, the Reitz et al. (1988) PBPK model was used with data from Mackay et al. (1987) to estimate exposure concentrations at different exposure durations (greater than 1 hour) which would result in the same target internal dose as resulting from 1-h exposure (Lu et al. 2008, Yang 2006).

More specifically, Yang (2006) estimated the internal dose (concentration in venous blood) in humans exposed to 175 ppm (950 mg/m3) 1,1,1-TCA for 1 hour to be 1.33 mg/L. The Reitz PBPK model was then used to predict the exposure concentration required to achieve the same target internal dose (1.33 mg/L) after 4, 8, 24, and 366 hours of exposure using continuous exposure assumptions. These exposure concentrations are provided in column 2 of Table 10 below and are considered PODHEC values for various exposure durations. USEPA short-term RfCs for different exposure durations were derived by applying a total UF of 100 to the PODHEC (USEPA 2007), and are shown in Table 10.

Table 10. Summary of Derivation of USEPA Short-Term RfC values for 1,1,1-TCA (USEPA 2007)

Exposure Duration (hours)	**POD_{HEC} ppm (mg/m^3)**	**Total UFs**	**RfC ppb ($\mu g/m^3$)**
1	175 (950)[a]	100	1700 (9000)
4	131 (715.3)	100	1300 (7000)
8	127 (693.4)	100	1300 (7000)
24	119 (649.8)	100	1200 (6000)
336 (14 days)	96 (526)	100	960 (5000)

[a] A LOAEL of 175 ppm (950 mg/m^3) was identified from the Mackay et al. (1987) study and used as the POD_{HEC} for deriving a 1-h RfC, duration adjustment was not conducted for 1-h exposure (USEPA 2007).