INTERIM 1_modified without modeling results: 12/2009

TETRACHLOROETHYLENE
(CAS Reg. No. 127-18-4)

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For
NAS/COT Subcommitte for AEGLs

INTERIM 1 PRESENTED ON JULY 2001

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

TETRACHLOROETHYLENE (CAS Reg. No. 127-18-4)

Oak Ridge National Laboratory, Managed and Operated by UT-Battelle, LLC, for the U.S. Department of Energy under contract number DE-AC05-00OR22725.

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL

TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

Tetrachloroethylene (PCE) [CAS Reg. No. 127-18-4], also commonly known as perchloroethylene or Perc, is a colorless, nonflammable liquid. It has an ethereal odor, with a reported odor threshold ranging from 2-71 ppm. PCE is commonly used as a dry-cleaning solvent and as a degreaser, and is also used as a chemical intermediate and as a veterinary antithelmintic.

Following exposure to PCE, humans experience primarily central nervous system (CNS) effects and irritation, with some cases of reversible liver effects reported. CNS effects also predominate in animals, although liver effects are noted in mice, and nephrotoxicity is observed in rats. However, both hepatotoxicity and nephrotoxicity are commonly associated with repeated or chronic exposures. Tetrachloroethylene was carcinogenic in both mice and rats.

The AEGL-1 derivation is based on the exposure of 6 volunteers to 106 ppm for 1 hour (Rowe et al., 1952). At this level, an apparent non-objectionable odor and eye irritation were noted, and one subject experienced a slight fullness in the head. An interspecies uncertainty factor was not applicable. An intraspecies uncertainty factor of 3 was applied because mucous membrane irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect which should not vary over time, the AEGL-1 value was not scaled across time, but rather the same value was applied to all times.

The AEGL-2 values are based upon the no-effect level for ataxia in rats following exposure to 1150 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (the time period of 4 hours was used for the derivation) (Goldberg et al., 1964). Exposure to the next higher concentration of 2300 ppm resulted in reversible ataxia. The endpoint of 1150 ppm is supported by the Rowe et al. (1952) study in which rats inhaling 1600 ppm for 7 hours daily over 25 days appeared drowsy or stuporous. A total uncertainty factor of 3 is applied to the no-effect level for ataxia of 1150 ppm. An intraspecies uncertainty factor of 3 is applied because the MAC for volatile anesthetics does not vary by more than a factor of 2-3-fold. An interspecies uncertainty factor of 1 would normally be applied based on the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants, giving a total uncertainty factor of 3. However, a total uncertainty factor of 3 would result in AEGL-2 values of 1100, 1100, 770, 380, and 270 ppm for the 10- and 30-minute and 1-, 4-, and 8-hour exposure durations, respectively. These concentrations seem too high when placed in the context of available human data reported by Rowe et al. (1952): exposure of subjects to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort), and exposure to 280 ppm for up to 2 hours resulted in eye irritation, lightheadedness, and impaired motor coordination, with recovery generally occurring within 1 hour. Therefore, the interspecies uncertainty was assigned a factor of 3, resulting in a total uncertainty factor of 10.

The experimentally derived exposure value was scaled to AEGL-2 time frames using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and *n* generally ranges from 1 to 3.5 (ten Berge et al., 1986). The value of *n* used for PCE was the calculated and published value of $n = 2$ based upon the Rowe et al. (1952) rat mortality data for PCE (ten Berge et al., 1986). The 10- and 30-minute AEGL-2 values were set equal to the 1-hour value of 230

ppm because a human study demonstrated an exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort; Rowe et al., 1952). The AEGL-2 values are supported by the Carpenter (1937) inhalation study in which volunteers exposed to 475 ppm for 2 hours and 10 minutes reported salivation, slight eye irritation, tightness in the frontal sinuses, increased hand perspiration, and increased nasal irritation. These effects are milder than those defined by AEGL-2. An AEGL derivation based on these exposure parameters, a total uncertainty factor of 3 (3 to account for intraspecies variability; an interspecies uncertainty factor is not needed because the derivation is based on human data), and an *n* of 2 result in identical AEGL-2 values.

The AEGL-3 derivation is based on one-third of the 4-hour mouse LC_{50} value of 5200 ppm, resulting in a point of departure of 1733 ppm (Friberg et al., 1953). An interspecies uncertainty factor of 1 was applied based on similar exposure effects in humans compared with animals, and pharmacokinetic data indicating an interspecies uncertainty factor for toxicokinetic differences of less than 1 when using rat data to derive exposure values for humans. An intraspecies uncertainty factor of 3 is applied because the MAC for volatile anesthetics should not vary by more than a factor of 2-3-fold. The AEGL-3 values are supported by a human study in which the effects noted were milder than those defined by the AEGL-3 definition (humans exposed to 934 ppm for 95 min experienced tightness of the frontal sinuses, increased hand perspiration, nostril irritation, congestion of eustachian tubes, lassitude, slight mental fogginess, stinging eyes, exhilaration, and/or the tip of nose and lips anesthetized; Carpenter, 1937), and an animal study in which rats exposed to 2300 ppm for 4 hours/day, 5 days/week for 2 weeks exhibited overt ataxia only following the first 4 hour exposure (Goldberg et al., 1964).

The experimentally derived exposure values were scaled to AEGL time frames using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and *n* generally ranges from 1 to 3.5 (ten Berge et al., 1986). The value of *n* used for PCE was the calculated and published value of $n = 2$ based upon the Rowe et al. (1952) rat mortality data for PCE (ten Berge et al., 1986). The 10-minute AEGL-3 was set equal to the 30-minute value of 1600 ppm because of the uncertainty in extrapolating from an exposure duration of 4 hours to 10 minutes.

A carcinogenic risk assessment of tetrachloroethylene resulted in values that exceed the values based on acute toxicity. Therefore, they are not proposed for AEGL-3.

The derived AEGL values are listed in the table.

TABLE S 1. Summary of AEGL Values for PCE [ppm (mg/m^3)]

Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	35 (240)	35 (240)	35 (240)	35 (240)	35 (240)	Mild eye irritation in 6 subjects exposed to 106 ppm for 1 hr (Rowe et al., 1952)
AEGL-2 (Disabling)	230 (1600)	230 (1600)	230 (1600)	120 (810)	81 (550)	No-effect level for ataxia in rats following exposure to 1150 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (4 hr time period used for the derivation) (Goldberg et al., 1964).
AEGL-3 (Lethal)	1600 (11,000)	1600 (11,000)	1200 (8100)	580 (3900)	410 (2800)	1/3 of the mice 4 hour LC_{50} of 5200 ppm (1733 ppm) (Friberg et al., 1953; NTP, 1986)

I. INTRODUCTION

Tetrachloroethylene (PCE), also commonly known as perchloroethylene or Perc, is a colorless, nonflammable liquid. The chemical has limited solubility in water but is miscible with a number of organic solvents (Budavari et al., 1996; Lide and Frederikse, 1993). PCE has an ethereal odor, with a reported odor threshold ranging from 2-71 ppm (ACGIH, 1996; U.S. EPA, 1992). The physicochemical data on tetrachloroethylene (PCE) are presented in Table 1.

PCE is commonly used as a dry-cleaning solvent and as a degreaser, and is also used as a chemical intermediate and a veterinary antithelmintic (ACGIH, 1996; ATSDR, 1997). Previously, PCE was used as an antithelmintic in humans because it was found to be less toxic than carbon tetrachloride.

Following exposure to PCE, humans primarily experience central nervous system (CNS) effects and mucous membrane irritation, with some cases of reversible liver effects reported. CNS effects also predominate in animals, although liver effects are noted in mice, and nephrotoxicity is observed in rats. The hepatotoxicity and nephrotoxicity are commonly associated with repeated or chronic exposures, however. Data addressing effects consistent with the definitions for AEGL endpoints were limited. The odor threshold for tetrachloroethylene has been reported to range between 2-71 ppm (U.S. EPA, 1992).

TABLE 1. Chemical And Physical Data

Parameter	Value	Reference
Synonyms	Perchloroethylene, ethylene tetrachloride, tetrachloroethene	Budavari et al., 1996
Molecular formula	C_2Cl_4	Budavari et al., 1996
Molecular weight	165.83	Budavari et al., 1996
CAS Registry Number	127-18-4	
Physical state	Liquid	Budavari et al., 1996
Color	Colorless	Budavari et al., 1996
Solubility	0.15 g/L at 25°C Miscible with alcohol, ether, chloroform, benzene	Lide and Frederikse, 1993 Budavari et al., 1996
Vapor pressure	20 torr at 26 3°C (saturates in air at 25,000 ppm) 2.5 kPa at 25°C	ACGIH, 1996 Lide and Frederikse, 1993
Specific gravity (water = 1)	1.6230 at 20°C	Budavari et al., 1996
Vapor density (air = 1)	5.83	Sax and Lewis, 1989
Melting point	~ -22°C	Budavari et al., 1996
Boiling point	121°C	Budavari et al., 1996
Conversion factors	1 ppm = 6.79 mg/m^3 1 mg/m^3 = 0.15 ppm	ACGIH, 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

A 2-year-old boy was found dead after napping in a room containing curtains that were recently cleaned improperly at a dry cleaner's self-service establishment (Gaillard et al., 1995). Analysis of blood and tissues confirmed the fatal exposure to PCE. Other fatal cases involved a

53-year-old male dry cleaner exposed to PCE in a poorly ventilated room while cleaning and recycling PCE by distillation (Levine et al., 1981), a 33-year-old male found dead after being left alone for 20 minutes to repair a plugged line in a commercial dry-cleaning establishment (Lukaszewski, 1979), and a 26-year-old male found dead following inhalation of the contents of a can of Fix-A-Flat (Isenschmid et al., 1998). In all cases, analysis of blood and tissues during autopsy confirmed the fatal exposure to PCE.

2.2. Nonlethal Toxicity

2.2.1. Controlled Exposures

Four volunteers (presumably males: the study author and 3 of his colleagues) exposed themselves to 475, 934, 1500, 2000, and 5000 ppm PCE vapors in a chamber (210 ft^3) (Carpenter, 1937). No control exposures were conducted. A Zeiss interference refractometer (interferometer) was used to measure PCE vapor concentrations at "close intervals." The chamber was equilibrated to 50 ppm before entry for the first exposure. All of the subjects noted an odor upon entry. The chamber concentration was brought up to an average of 475 ppm (peak concentration of 678 ppm), and subjects were exposed for 2 hours and 10 minutes. Symptoms reported by the volunteers included salivation, sweetish metallic taste, slight eye irritation, tightness in the frontal sinuses, increased hand perspiration, and increased nasal secretions. One man additionally felt nauseous after leaving the room, while another reported a feeling of elation. After eating a meal, the subjects were exposed to an average of 934 ppm (peak concentration of 1140 ppm) for 1 hour and 35 minutes. Tightness of the frontal sinuses and increased hand perspiration were again noted, as were nostril irritation, congestion of eustachian tubes, lassitude, slight mental fogginess, stinging eyes, and exhilaration. The tip of the nose and lips were also anesthetized in one subject. The chamber concentration was then increased to 1500 ppm. The subjects experienced slight inebriation, followed by a feeling of faintness and dizziness that caused them to leave the chamber. Dyspnea was observed following slight exertion. Mental sluggishness, slight inebriation, and a slight effect on physical balance were still felt 30 minutes post exposure. Following a 45-minute reprieve in the fresh air, the original four subjects plus a previously unexposed fifth subject were exposed to 2000 ppm. All left the chamber within 7.5 minutes because of faintness. The effects were noted first by the fifth subject. Nausea, ringing in the ears, vertigo, and dyspnea following slight exertion were reported post exposure. One subject reported fatigue the entire evening, while the others reported no effects following a meal. Two days later, the original four subjects were again exposed to 2000 ppm. All volunteers left after 5.5 minutes. When exposed to a concentration built up to approximately 5000 ppm, everyone again left the chamber. Eye irritation, nasal congestion, salivation, vertigo, nausea, and retarded mental activity were noted. No changes were noted in any of the 24-hour urine samples taken from the subjects, and blood pressure readings taken during the exposures indicated a drop in blood pressure or pulse in one individual during the 943 ppm exposure or 475 ppm exposure, respectively.

Human volunteers were exposed to 106, 216, 280, 600, or 1060 ppm PCE vapor for various time periods in a sealed room (12,860 L) serving as an exposure chamber (Rowe et al., 1952; see Table 2). "The concentration of the vapor in the room was established by volatilizing the theoretical amounts of liquid PCE with thorough mixing by means of two electric fans." Subjects entered the room once the proper concentration had been obtained. The room concentration of PCE was continuously monitored by use of a Davis Micro Gas Analyzer and was checked by analyzing air samples taken simultaneously by silica gel. Small amounts of

liquid PCE were added as needed to maintain the desired concentration. No information was provided regarding the human test subjects, if some subjects participated in more than one exposure, or the time between exposures. Results of the single exposures in the human test subjects are presented in Table 2. In summary, exposure to 100 ppm for approximately 1 hour generally resulted in slight eye irritation and detection of an odor; exposure to 200 ppm or greater generally resulted in more severe eye irritation and nasal irritation and central nervous system effects; exposure to greater than 1000 ppm was intolerable to the test subjects.

TABLE 2. Results of Single Exposures in Human Subjects

Concentration (ppm) [range]	Approximate exposure time	No. of subjects	Response
106 [83-130]	1 hr	6	Non-objectionable odor upon entry; desensitized in few min.; Very slight eye irritation -correlated with addition of PCE for concentration maintenance 1/6 - slight fullness in head ~ 30 min into exp, disappeared by end of exp.
216 [206-235]	45 min- 2 hr	4	Non-objectionable odor upon entry; desensitized in few min.; Persistent eye irritation (stinging) 20-30 min. into exposure; Congestion of frontal sinus with slight nasal discharge 2/4 slight dizziness; 3/4 felt sleepy Complete recovery in 1 hour
280 [206-356]	Up to 2 hr	4	Eye irritation (burning); lightheadedness, congestion of frontal sinuses, thickness of tongue, tightness about mouth, irresponsibility; 1/4 - nauseous 30 min. into exposure - disappeared by end of exposure Impaired motor coordination - coordination required great effort Recovery generally within 1 hr of exposure, but didn't feel well for several hrs.
600 [513-690]	10 min.	2	Eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, motor coordination required great effort
1060 [930-1185]	1 min. 2 min.	3 1	Marked eye and upper respiratory tract irritation - left room Marked eye and upper respiratory tract irritation; dizziness - left room

Data taken from Rowe et al., 1952.

Groups of six, healthy male workers (ages 30-59) from the Dow Chemical Company were exposed to PCE vapor at mean measured concentrations of 194 ppm for 187 minutes, 194 ppm for 83 minutes, or 101 ppm for 183 minutes (Stewart et al., 1961b). The exposures were four weeks apart, and several subjects participated in all three exposures. It was not stated if the volunteers were subjected to solvent exposure in their occupation. No control exposures were conducted. An interior room (11 x 12 x 7 ft. 2 in) served as the exposure chamber. PCE vapors were generated by pouring an amount of PCE into a partially covered dish, with a pedestal fan blowing across the dish to circulate the vapors throughout the room. Air samples were taken using probes of Saran tubing suspended from ceiling to head height at the center of the room, and the probes were passed outside of the room to continuous monitoring devices. After three different monitoring methods showed agreement for the first monitoring exposure period

(200, 202, and 200 ppm for 187 minutes using a Davis Halide Meter coupled to a recorder providing continuous measurements, silica gel followed by combustion and analysis of Volhard titration for samples measured every 32 minutes, and an infrared spectrometer measuring samples taken every 20 minutes, respectively), the remaining two exposures were measured using the Davis Halide Meter.

The subjective and physiological responses to rising concentrations during exposures to mean concentrations of 194 ppm for 187 minutes and 194 ppm for 83 minutes were recorded and are presented in Table 3 (Stewart et al., 1961b). Eye irritation was noted one to four minutes into the exposure at concentrations of 75-80 ppm, followed by soft palate irritation and dryness four to six minutes into the exposure at 100-120 ppm. Exposure to 200 ppm for 6-30 minutes did not elicit any remarkable response, but 30 minutes and longer into the exposure to 210 - 244 ppm resulted in lightheadedness and difficulties in performing the Romberg test (subject balancing on one foot with his eyes closed and with both arms at his side). No exposure-related changes occurred in blood pressure, expirogram (time vital capacity), serum glutamic oxaloacetic transaminase, urinary urobilinogen, or serum glutamic pyruvate transaminase measurements following exposure to PCE, and PCE was not detected in the urine during or post exposure. Although blood concentrations of PCE rose slowly during the 187 minute exposure to 194 ppm, PCE was no longer detected in the blood 30 minutes post exposure, suggesting that it is rapidly removed from the blood. However, PCE had a prolonged exponential decay in post exposure expired air (as measured by an infrared spectrophotometer following collection of a one-minute sample of expired air), being present in the expired air 94 hours following the 83-minute exposure to 194 ppm.

TABLE 3. Subjective and Physiologic Responses of 6 Volunteers to Rising Concentrations of PCE (Exposures to Mean Concentrations of 194 ppm for 187 Minutes or 194 ppm for 83 Minutes)

Concentration (ppm)	Time after start of exposure (min)	Response
75 - 80	1-4	Very slight eye irritation - a mild burning sensation; subjects became aware of irritation after a few minutes of exposure
100-120	4-6	Slight soft palate irritation and dryness noticeable
200	6-30	Odor not unpleasant; Romberg's sign and heel-to-toe tests normal
210-244	30+	Slight light-headedness noted; increased effort necessary to maintain a normal Romberg test

Table taken from Stewart et al. (1961b), p. 43.

To obtain additional data regarding the human response following inhalation of PCE vapor, Stewart et al. (1970) exposed 17 healthy male workers (age 24-64 years) to a mean concentration of 101 ppm of PCE for 7 hours; five of the workers were repeatedly exposed to this concentration for 7 hours/day for 5 consecutive days. It was not stated if the volunteers were subjected to solvent exposure in their occupation, and no controls were included. An interior room (41 x 6 x 72 ft) served as the exposure chamber, and the solvent was introduced into the room's recirculation system by the means of a dual action syringe pump. The concentration of PCE in the chamber was recorded continuously by an infrared spectrometer, and a Dow-modified Davis Halide meter with a continuous recorder served as a backup monitor. All of the subjects reported the odor of the solvent to be moderately strong during the first 5 minutes of the exposure and "faint" after the first hour of exposure. After that, the ability to detect the odor

continued to decline throughout the exposure, so that only 40% could detect the odor after 7 hours of exposure. The ability to detect the odor progressively diminished in the repeated-exposure group with successive days. Subjective responses noted by subjects during the acute 7-hour exposure (not stated if just the 12 subjects or all 17 subjects) included the following: 25% reported a mild frontal headache; 60% had mild eye, nose or throat irritation within the first 2 hours of exposure that subsided by the end of the 7-hour exposure; 25% noted a flushing sensation in the "blush area;" 40% felt "slightly sleepy;" 25% reported some difficulty in speaking in a manner similar to that experienced with ethanol intoxication. Those who were repeatedly exposed had fewer subjective complaints, with only 2/5 experiencing mild eye and throat irritation, and a mild frontal headache noted by a subject with chronic sinusitis. The only "objective" response was an abnormal modified Romberg test (balancing on one foot with eyes closed and both arms at side) in three subjects during the first 3 hours of exposure. One individual with a known sensitivity to chlorinated solvents complained of dizziness and reduced mental faculties one-hour into the exposure; he exhibited an abnormal modified Romberg test at that time and after the second hour of exposure. He was removed from the chamber, and exhibited a normal modified Romberg test thirty minutes later. All other tests in the subjects were normal, including hematology and blood chemistry tests, urinalysis, pulmonary function tests, and other behavioral/neurological tests.

Six volunteers/sex were involved in a double-blind experiment to determine the potential interaction of alcohol or diazepam with inhalation exposure to PCE vapor (Stewart et al., 1977). Subjects were exposed to 0, 25, or 100 ppm PCE vapors for 5.5 hours alone or in combination with 0, 0.75, or 1.5 mL vodka/kg body weight or 0, 6, or 10 mg diazepam/day. Subjects exercised (on bicycle ergometers) for 30 minutes early into each PCE exposure to more rapidly increase the body burden of PCE. Alcohol was administered in juice to produce two drinks, with each drink being consumed over a 15-minute time period. Diazepam or the placebo prescriptions were filled the Friday before the week of diazepam exposure and were to be taken during the week of exposure. Blood and breath analysis confirmed body burdens of PCE and/or alcohol, while blood analysis measured diazepam burdens. Chamber concentrations of PCE vapors were continuously monitored at 30-second intervals using an infrared spectrometer, with a backup analysis using gas chromatography to measure air samples taken every 3 minutes. The effects of the 3 compounds alone or in combination were assessed using a battery of neurological and behavioral tests (including an EEG for spectral density analysis), subjective response forms filled out by the subjects reporting symptoms and mood, and subjective response forms filled out by the staff assessing the subjects' moods and behavior. Exposure to 100 ppm PCE alone resulted in occasionally statistically significant decreased Flanagan coordination scores (test requires the subject to rapidly follow a spiral pathway with a pencil). The decreased scores in this study were supported by decreases observed in another study, in which male volunteers were exposed to 150 ppm for 7.5 hours (Stewart et al., 1981; described in next paragraph). No additive effects or clear interactions between alcohol or diazapem with PCE were noted. The significant but inconsistent increase noted in the beta activity of the EEG in subjects exposed to diazepam and PCE concurrently was ascribed to treatment with diazepam. The authors stated that this effect had previously been noted for diazepam alone, but had not been associated with PCE exposure. An altered EEG was not observed in subjects exposed to PCE alone.

In 1981, Stewart et al. published the results of a study that established the relationship between exposure magnitude and PCE body burden as measured by urine, blood, and breath (results presented in Section 4.1) and evaluated the effects of repeated PCE vapor exposure on

human health. A total of 10 Caucasian male workers and 11 Caucasian females (students or housewives) were exposed to PCE vapors. The subjects were subdivided into three groups for 7 1/2 hours, 3 hours, or 1 hour of daily exposures. Males and females were exposed the first week (5 consecutive days) to 100 ppm PCE. Males were additionally exposed to 20 ppm for four consecutive days, fluctuating concentrations of 50 to 150 ppm (for a time weighted average of 100 ppm) for five consecutive days, and 150 ppm for five consecutive days, with exposure to 0 ppm both before and at the end of the PCE exposures. Males exercised on bicycle ergometers at specified times during the exposures; females did not exercise. Exposures were conducted in a controlled environment chamber (20 x 20 x 8 ft). Appropriate vapor concentrations of PCE were maintained using a reciprocal dual-piston pump to maintain a steady flow of liquid into a flask, which was then introduced into the chamber's circulating air by a stream of air sweeping the vapor from the flask. PCE chamber vapor concentrations were continuously monitored and an infrared spectrometer with a gas chromatograph serving as a back-up monitor.

All the subjects could detect an odor upon entering the chamber with PCE concentrations of 20, 100, and 150 ppm, but the response thereafter became varied. Subjects generally became less sensitive to the odor of PCE during the study period, some even losing the ability to detect the odor by the end of the first exposure. Although some claimed to detect the odor throughout the study, none of the subjects could detect the 50 ppm fluctuations during the week in which PCE concentrations fluctuated from 50 to 150 ppm. Other subjective responses were also recorded, although the individual data were not provided in the published study. The greatest number of responses was reported on day 1 of exposure and decreased with subsequent exposures. However, an almost equal number of subjective responses were recorded on 0 ppm exposure days (Stewart et al., 1981).

In the above study (Stewart et al., 1981), other endpoints selected to evaluate PCE toxicity included neurological, blood chemistry, and cardio-pulmonary function tests. Changes in the EEG (reduction in overall wave amplitude and frequency; delta or theta wave activity replaced alpha wave activity) were recorded in 3/4 males and 4/5 females exposed for 7.5 hours daily. The altered pattern in the EEG was consistent with cortical depression, similar to that seen in adults "during drowsiness, light sleep, and the first stages of anesthesia." The changes were generally noted during the first day of exposure (100 ppm PCE), with one male responding 10 minutes into the exposure, and the other subjects generally responding about 5 hours into the exposure. The EEG changes were similarly altered (but to a lesser extent) during remaining exposures, with changes still evident during the 0 ppm exposure conducted after the final PCE exposure. Other neurological studies were within normal parameters except for a significantly lowered score on the Flanagan coordination test in Group I males exposed to 150 ppm for 7.5 hours/day. No changes in the visual evoked response (VER), blood chemistry, or cardio-pulmonary function tests could be attributed to PCE exposure (Stewart et al., 1981).

To assess effects of PCE on the sensory system, Altmann et al. (1990) exposed groups of 12 or 10 healthy male volunteers for 4 days to measured concentrations of 10 or 50 ppm, respectively. The 10 ppm group served as the blind control group, as 10 ppm is above the odor threshold of 5 ppm (this controls for any psychological effect of being able to smell the chemical, and therefore know that exposure to the chemical is occurring). Additionally, each of the 50 ppm subjects served as their own control because measurements were also made the day before exposure. Exposure to 50 ppm PCE resulted in an increased latency of pattern reversal visual evoked potentials (VEPs). Linear regression revealed an association between increased blood

PCE concentrations and the increased latency of VEPs ($p<0.03$), both increasing with successive exposure days. No differences in brainstem auditory evoked potentials (BAEPs), indicating peripheral hearing loss, were measured between the 10 and 50 ppm groups. Visual contrast sensitivity assessed in a few of the test subjects revealed a loss at low and intermediate spatial frequencies following exposure to 50 ppm.

Altmann et al. (1992) published another paper on the results of a study in which groups of 16 and 12 healthy male volunteers were exposed for 4 hours to 50 or 10 ppm (controls) PCE, respectively. In addition to measuring changes in VEPs and BAEPs, a neurological evaluation system was used to assess cognitive and psychomotor performance and mood. Baseline values were determined 72 hours before the first exposure. Odor was detected on the first day of testing by 33% and 29% of the 10 and 50 ppm group subjects, respectively, with 17% and 36%, respectively, reporting odor on day 4. Blood analysis for PCE concentration revealed cumulative increases. Analysis of co-variance, with pre-exposure baseline values as co-variates, revealed significant performance deficits for vigilance ($p<0.04$) and eye-hand coordination ($p<0.05$) and borderline prolongation of simple reaction time ($p<0.09$) in the 50 ppm group compared with controls. Increases in mean peak latencies of pattern reversal VEPs were again reported for 10 subjects exposed to 50 ppm compared with the 12 subjects exposed to 10 ppm. It is likely that this part of the study is the same as that reported in the Altmann et al. (1990) paper: the number of the subjects evaluated for changes in VEPs and BAEPs is the same, and the values of the VEP latency differences reported in a study table are identical to the previous paper. The study authors conclude that the increased peak latencies of the VEPs suggest interference with nerve cell conduction, and could be due to a variation in the arousal level or to a direct solvent-induced cortical depression.

2.2.2. Case Reports

A 57-year-old woman who worked as a dry cleaner for 20 years developed an abrupt onset of optic neuritis with residual tunnel vision following a 9-hour day ironing clothes and fabrics (Onofrj et al., 1999). High levels of PCE and chloroform (a product of decomposition of trichloroacetic acid when heated at 80°C for 20 min.) were found in the blood and urine, respectively. A recreation of the exposure found PCE concentrations of 64 ppm near the basket filled with dry-cleaned fabrics, and up to 252 ppm in steam during ironing. The optic neuritis was attributed to acute PCE toxicity. No explanation for the presence of chloroform was provided.

A worker was alternately cleaning stairs with a mixture of 50% PCE: 50% Stoddard solvent and mixing cement to then resurface the stairs (Stewart et al., 1961a). An auxiliary air hose supplied one air change per hour in an otherwise poorly ventilated area. The worker initially noted eye irritation and lightheadedness, and became “too woozy” and had to leave the area on three separate occasions. He would return to work when his lightheadedness had sufficiently abated, generally within 3 to 5 minutes. The worker turned the auxiliary hose off the last 30 minutes of exposure because of the noise it produced. He was then found unconscious by a fellow worker and taken to the hospital. Oxygen was administered for 15 minutes, by which time he had regained consciousness and appeared recovered. No abnormalities were noted during neurological examination one hour after the exposure. Although still asymptomatic, follow-up examinations revealed that the patient developed a mild case of hepatitis two to three weeks following the exposure as evidenced by elevated urinary urobilinogen, total serum

bilirubin, alkaline phosphatase activity, and serum glutamic pyruvate transaminase activity. Analysis of samples of expired air taken from the worker over various periods of time confirmed that the worker indeed had been exposed to high concentrations of PCE, with traces in the expired air up to 21 days post exposure. Simulation of the exposure revealed an average exposure concentration of 393 ppm for the 3.5 hour long exposure period, with a range of 25 to 1470 ppm. The simulated concentration for the last 30 minutes of exposure when the air hose was turned off was 1100 ppm. The exposure to Stoddard solvent was not believed to have adversely impacted the health of the worker.

Stewart (1969) also reported the case of a worker exposed to PCE when using the solvent to clean a polymer from a tank car. He was found unconscious in the bottom of the tank after approximately 15 minutes of exposure. Thirty minutes after removal from the tank, he was drowsy and displayed an abnormal Romberg test, although all other neurological findings were normal. Analysis of his expired breath confirmed overexposure to PCE. He stated he felt completely recovered by the next day. He returned to work two days after the exposure, complaining of fatigue which diminished over the next two days. Clinical evaluation revealed mild liver injury, as evidenced by slightly elevated SGOT activity on the third and fourth days post exposure, and elevated urinary urobilinogen on the ninth day.

A number of case reports concerning PCE overexposure coincided with the transition from carbon tetrachloride to PCE in the dry cleaning industry; particularly with the advent of self-service dry cleaning establishments. A 21-year-old male was admitted to the hospital in a coma with acute pulmonary edema following accidental exposure to PCE (Patel et al., 1973). The patient had been working in a laundry facility when the system overheated, resulting in the release of PCE fumes. The patient became dizzy and lay down, and was found seven hours later unconscious. Upon examination, bubbling rales were heard over the entire lung fields. The patient was treated with oxygen, bronchodilators, diuretics, and anti-inflammatory agents. His pulmonary edema and level of consciousness improved within six hours of admittance. No abnormalities in liver or kidney function were noted upon admittance or during bi-weekly check-ups for several weeks.

A 29-year-old man was admitted to the hospital after being found unconscious on the floor of his laundry facility (Ling and Lindsay, 1971). A faulty machine had released PCE onto the floor. The vapors caused the worker to lose consciousness and fall to floor, leading to direct skin contact with the chemical. Consequently, he also suffered extensive erythema and blistering on approximately 30% of his body. He was treated with oxygen and given plasma. He regained consciousness over the next 24 hours, and his burns healed over 3 weeks.

Nine fireman were exposed to PCE vapors when responding to a call reporting a leak of fumes from a self-service dry cleaning establishment (Saland, 1967). The fireman located a PCE leak from an open drain pipe in the cellar. The nine men were exposed to the high concentration of vapors for 2-3 minutes without gas masks. All the firemen complained of feeling “woozy” upon emergence from the cellar, but did not note eye, mucous, or upper respiratory tract irritation. The men recovered after going out into the fresh air. Examination by the Fire Department medical office staff did not find any abnormalities except moderate hypertension in two firemen. Twelve days after the exposure, the men were admitted to a hospital for a period of six days for observation. At this time, mild liver damage, indicated by increases in serum glutamic oxaloacetic transaminase activity, was noted in 8/9 firemen. One man additionally

developed hepatomegaly and splenomegaly 12 days post exposure. All men had returned to normal by approximately two months post-exposure.

A 47-year-old woman was admitted to a hospital with an acute case of hepatitis assumed to be caused by exposure to high concentrations of PCE at her workplace (dry-cleaners) two weeks prior (Meckler and Phelps, 1966). Following the exposure in question, she had noted transient dizziness, headache, and malaise, and experienced generalized weakness and decreased appetite that did not dissipate. Clinical signs worsened two days prior to admission, and she presented with an acute stage of hepatitis upon admission to the hospital. She was released two weeks after admission; her liver function tests returned to normal two months later. Liver enlargement and the initial finding of spider nevi were still present six months after discharge, but there was no evidence of jaundice.

A 24-year-old white male was admitted to a hospital with a history of premature ventricular beats, dizziness, and headaches, correlating with his employment at a dry-cleaning facility (Abedin et al., 1980). Following the 5-day stay in the hospital, the patient was asymptomatic, and his plasma PCE levels were 0.15 ppm. He returned to work shortly after his release, and soon developed the same symptoms. During his checkup 2 weeks after discharge, physical examination revealed ventricular premature beats, and a plasma PCE concentration of 3.8 ppm. The patient changed jobs, and a month later was free from symptoms and cardiac arrhythmias.

2.2.3. Chronic Studies

Although AEGLs are for acute exposures, some of the studies investigating potential health effects of chronic exposure to PCE in humans are included here because they report nonlethal exposure concentrations. The exposure concentrations reported in the studies were generally measured by the investigators at the time of the study to provide a representative exposure value.

Several researchers have investigated behavioral effects of long-term exposure to PCE. Seeber (1989) found decrements in perceptual and intellectual function and attention in dry cleaners (n = 101) exposed to low (12 ppm) and high (54 ppm) TWAs (time-weighted averages) compared with controls, but no differences in function were observed between exposure groups. Decrements in a behavioral evaluation were also reported by Echeverria et al. (1995) in 65 dry cleaners exposed to estimated PCE concentrations of 11-41 ppm. Altmann et al. (1995) found that subjects living in the neighborhood of dry cleaning shops (median air concentration 0.2 ppm [1.36 mg/m^3]; mean residential time of 10.6 years) had statistically impaired performance on tests assessing vigilance, simple reaction time, and visual memory compared with controls. No effects were noted in exposed individuals compared with controls in a finger tapping test, eye-hand coordination, or in pattern-reversal visual-evoked potentials (VEPs). In a cross-sectional survey of female dry cleaners matched with unexposed controls, Ferroni et al. (1992) found females exposed to PCE (median concentration of 15 ppm for 4-hour random sampling periods) had statistically increased prolonged reaction times and statistically increased serum prolactin levels during the proliferative phase of the menstrual cycle. However, the impaired performance of the exposed workers was not statistically correlated with duration of exposure or air or blood PCE levels, nor were exposure variables associated with the increased prolactin levels. Cai et al. (1991) reported an increased prevalence of subjective symptoms in dry cleaners (n = 56) exposed

to an 8-hour TWA of 20 ppm (range of 3.8 to 94.4 ppm), but no differences in hematology, serum biochemistry, or clinical signs compared with unexposed controls were noted.

When investigating hepatic effects of chronic PCE exposure, Brodkin et al. (1995) found only minimal changes in serum hepatic transaminase activity, but reported diffuse parenchymal changes in echogenicity during hepatic ultrasonagraphy in dry cleaners exposed to an 8-hour TWA of up to 20 ppm compared with controls. Dry cleaning workers exposed to an average 8-hour concentration of 11 ppm exhibited variations in the gamma-glutamyltransferase isozyme activity pattern in the absence of any other evidence of liver injury (Gennari et al., 1992). Lauwerys et al. (1983) did not find any measurable effects on the CNS, liver, or kidneys of workers exposed 6 years to PCE concentrations under 50 ppm.

To determine renal effects in dry cleaning workers exposed to PCE, Franchini et al. (1983) conducted a cross-sectional study of workers exposed to PCE for an average exposure time of 13.9 years and an approximated TWA of 10 ppm PCE. Exposed workers had increased levels of the urinary enzymes β-glucuronidase and lysozyme compared with controls, indicating mild, tubular renal damage. Mutti et al. (1992) reported findings of early renal changes consistent with diffuse abnormalities along the nephron as measured in the urine of dry cleaners exposed to a median of 15 ppm PCE with an average 10-year working history compared with controls. Solet and Robins (1991), however, did not find any renal effects in dry cleaning workers exposed chronically (tenure years: 11.6 years) to an estimated mean air concentration of 14 ppm. Examination of renal function in 16 female dry cleaners exposed to an 8-hour TWA of 23 ppm (2 workers were exposed to a mean of 47 ppm) did not reveal any renal damage compared with 13 control females (Vyskoćil et al., 1990).

Slight measurable immunological changes were found in dry cleaners exposed to PCE concentrations ranging from 2-111 ppm (measured in the breathing zone of workers during an 8-hour shift; the geometric mean of PCE concentrations measured in workers from 2/6 shops was 49 ppm) (Andrýs et al., 1997). The changes were suggestive of a slight response of the respiratory system, mainly of the alveolar macrophages. Cavalleri et al. (1994) reported a dose-related color vision loss, primarily in the blue-yellow range, in a group of 35 dry cleaners exposed to an 8-hour TWA of 6 ppm (range of 0.4-31 ppm), while Nakatsuka et al. (1992) was not able to detect color loss in a group of 30 men and 34 women dry cleaners exposed to a geometric mean of 13 ppm PCE.

2.3. Developmental/Reproductive Effects

For a comprehensive review of the epidemiologic studies addressing the potential of PCE to cause adverse reproductive effects, the reader is referred to ATSDR, 1997; IARC, 1995; van der Gulden and Zielhius, 1989. In summary, published studies investigating the reproductive hazards of exposure to PCE are not conclusive. Some studies point to an increased risk of spontaneous abortions (Ahlborg, 1990; Doyle et al., 1997; Hemminki et al., 1980a, 1980b; Kyyrönen et al., 1989; Olsen et al., 1990; Windham et al., 1991), while others have not found any association (Bosco et al., 1987; McDonald et al., 1986). Bosco et al. (1987) and McDonald et al. (1986) did not observe any increased risk of stillbirths, low birth weights, or malformations in children of exposed mothers. It should be noted that the studies have a number of limitations, one of the primary ones being that data addressing exposure concentrations are not available other than categorization of “low” and “high” exposure concentrations based on job category.

Many of the studies also had small sample sizes, thereby not permitting any definitive conclusions to be made.

A study addressing the effect of PCE exposure on semen quality in dry cleaning workers found a similar sperm concentration and a similar percentage of abnormal forms of sperm between exposed (dry cleaners) and nonexposed (laundry) workers (Eskenazi et al., 1991b). However, dry cleaners had sperm that were more likely to be round and less likely to be narrow, and tended to swim with more lateral head displacement. These effects appeared to be related to the levels of PCE exposure as measured in expired air and/or estimated by an index of exposure based on job tasks. The reproductive outcomes of wives of 17 of the dry-cleaning workers and 32 of the laundry workers was then evaluated (Eskenazi et al., 1991a). Although the number of pregnancies and the standardized fertility ratios were similar between both groups, wives of the dry cleaners were twice as likely to take longer to get pregnant or to seek help for infertility.

2.4. Genotoxicity

Ikeda et al. (1980) analyzed lymphocytes from workers exposed to 92 ppm or 10-40 ppm PCE for 3 months to 8 years for signs of cytogenic damage. No significant, dose-related changes were observed in chromosomal aberrations, sister chromatid exchange (SCE) frequencies, or the proportion of $M_2 + M_3$ metaphase or mitotic index compared with concurrent controls. Peripheral lymphocytes from workers exposed to a geometric mean of 10 ppm PCE for an 8-hour shift did not exhibit a measurable increase in the frequency of SCEs compared with controls (Seiji et al., 1990).

2.5. Carcinogenicity

No studies were found in the literature addressing cancer risk following acute inhalation exposure to PCE; rather, studies were limited to chronic exposure. Cohort studies investigating the potential for PCE to increase the risk of cancer following chronic inhalation exposure have indicated elevated relative risks or standardized mortality ratios (SMR) for esophageal cancer (2.1 and 2.6: Blair et al., 1990; Ruder et al., 1994), non-Hodgkin's lymphoma (3.8, 1.7, and 3.2: Anttila et al., 1995; Blair et al., 1990; Spirtas et al., 1991), and cervical cancer (3.2, 1.7, and 1.6: Anttila et al., 1995; Blair et al., 1990; Ruder et al., 1994)(summarized in IARC 1995). It should be noted that the increase observed in esophageal cancer in the Blair et al. (1990) study was due to the excess observed in black males (3.5). The cohort studies by Anttila et al. and Ruder et al. included subcohorts of workers exposed predominantly to PCE, while the studies by Blair et al. and Spirtas et al. are confounded by exposure to multiple halogenated hydrocarbons. Other factors to be considered are the low total numbers of subjects in the cohort studies, the lack of direct measurements of solvent concentration, and the general confounding factors of tobacco or alcohol use or socioeconomic status. A case-control study by Vaughan et al. (1997), in which alcohol and tobacco use were controlled for, found elevated adjusted odds ratios for esophageal (3.6) and laryngeal (2.7) cancer among dry cleaning workers. Cohort and case-control studies investigating the incidence of renal, liver, or brain cancer in relation to PCE exposure have not demonstrated a consistent increase in risk (summarized in IARC, 1995 and McLaughlin and Blot, 1997).

IARC (1995) concluded that there is limited evidence in humans for the carcinogenicity of PCE, with an overall classification that PCE is probably carcinogenic to humans (Group 2A)

based partly on the "consistently positive associations between exposure to PCE and the risks for esophageal and cervical cancer and non-Hodgkin's lymphoma." A cancer assessment by the U.S. EPA is currently not available on the IRIS database.

2.6. Summary

Exposure to PCE vapor has been reported to cause eye and nasal irritation and central nervous system depression, with symptoms including headaches, dizziness, mental sluggishness, nauseousness, feelings of exhilaration or inebriation, faintness, sleepiness, vertigo, tinnitus, and reduced motor coordination. Case reports of high-level exposure have described one or more cases of unconsciousness, reversible liver damage, pulmonary edema, cardiac arrhythmia, and optic neuritis. Scientists investigating the effects of chronic exposure to PCE have reported decrements in perceptual and intellectual function, minimal hepatic effects, slight immunological changes, and color vision loss. Epidemiological studies investigating the potential for PCE exposure to induce developmental or reproductive toxicity are generally confounded by a lack of exposure information and small sample sizes. At this point, it is unclear if PCE exposure results in an increased risk of spontaneous abortion. IARC has classified PCE as being probably carcinogenic to humans (Group 2A). Epidemiology studies indicate an increased risk of esophageal cancer, non-Hodgkin's lymphoma, and cervical cancer in exposed individuals. However, increases in the risk of renal, liver, or brain cancer in relation to PCE exposure have not yet been consistently demonstrated.

3. ANIMAL TOXICITY DATA

Lethal and nonlethal toxicity data for PCE inhalation exposure were available for monkeys, dogs, rats, mice, rabbits, and guinea pigs. Although only acute toxicity studies are generally included in the evaluation of toxicity data for consideration of AEGL derivation, repeated exposure studies are also included to provide backup of the acute toxicity data. The repeated exposure studies are included after the evaluations of the acute toxicity data in the respective sections.

3.1. Acute Lethality

3.1.1. Rats

Bonnet et al. (1980) reported a 6-hour LC_{50} of 4100 ppm [95% CL: 3899-4387 ppm] in rats. Although exposure concentrations were measured, they were not reported. Other information not reported included the strain and sex of rats, number of animals per group, and mortality rate. Animals were observed for 14 days for mortality and signs of toxicity. Signs noted during the exposure included hypotonia, tremors, and narcosis (unconsciousness). Typically, excitement was followed by hypoactivity and narcosis. The authors stated that most deaths occurred within 6 hours and all occurred within 24 hours of exposure.

In a single inhalation exposure study by NTP (1986), groups of five F344/N rats of each sex were exposed to air containing 2445, 3786, 4092, 4513, or 5163 ppm measured PCE vapor for 4 hours, and then observed for 14 days for signs of toxicity and mortality. Hypoactivity, ataxia, and anesthesia were noted in all exposure groups; the severity of each sign in each of the exposure groups was not provided. Mortality occurred in groups exposed to 3786 ppm or higher (Table 4).

TABLE 4. Mortality of F344/N Rats Exposed to PCE for 4 Hours			
Concentration (ppm)	Mortality (%)		Other Effects
	Males	Females	
2445	0/5 (0)	0/5 (0)	Hypoactivity, ataxia, anesthesia
3786	1/5 (20)	4/5 (80)	Hypoactivity, ataxia, anesthesia
4092	2/5 (40)	3/5 (60)	Hypoactivity, ataxia, anesthesia
4513	2/5 (40)	3/5 (60)	Hypoactivity, ataxia, anesthesia
5163	5/5 (100)	5/5 (100)	Hypoactivity, ataxia, anesthesia

Taken from NTP, 1986

Rowe et al. (1952) exposed groups of five to twelve albino rats (approximately equal number of males and females) to nominal concentrations of 2000, 3000, 6000, 12,000, or 20,000 ppm PCE vapor for periods of time ranging from 0.08 hours to 14 hours (see Table 5). Periodic analysis of chamber concentrations revealed measured concentrations at least 90% of the nominal, although the method of analysis was not provided. Animals were observed for 2-weeks post exposure for behavior and body weight changes and the time of death. Additional groups of rats were necropsied one day post exposure to assess any pathological changes in the animals. Mortalities (see Table 5) generally occurred during the exposure or immediately following removal of the animals from the chamber. The predominant clinical manifestation of exposure was central nervous system depression as evidenced by "drunkenness," stupor, unconsciousness, and respiratory or cardiac arrest. Unconsciousness was noted within a few minutes of exposure to 6000 ppm, after several hours of exposure to 3000 ppm, but was not noted in rats exposed to 2000 ppm. Other information about the severity of the signs at the various exposure concentrations and durations was not provided. Necropsy of surviving animals from groups with high mortality revealed mild liver changes including slight increases in liver weight, total lipid content, and cloudy swelling. A small increase in liver weight and total lipid content was noted in animals from exposure groups with no mortalities, but only after exposure for at least 5-7 hours. Rowe et al. then exposed groups of 3-5 rats to determine the maximum concentrations not producing hepatic damage. The results were as follows (given as exposure concentration: exposure hours without effect and exposure hours with effect): 12,000 ppm: 0.2 hour and 0.6 hour; 6000 ppm: 0.4 hour and 0.6 hour; 2500 ppm: 3.0 hours and 5.0 hours; 1600 ppm: 5.0 hours and 7.0 hours. Although some of these levels did not result in measurable hepatic damage, central nervous system effects were still present.

TABLE 5. Mortality of Albino Rats Exposed to PCE		
Concentration (ppm)	**Duration (h)**	**Mortality**
2000	10.0	0/20
	14.0	0/10
3000	4.0	0/30
	5.0	2/15
	6.0	3/10
	8.0	2/5
6000	0.6	0/20
	0.8	1/11
	1.0	1/15
	5.0	4/5
	6.0	8/10
	8.0	17/20
16,000	0.2	0/20
	0.3	4/20
	0.4	1/20
	0.6	5/20
	1.0	16/20
	2.0	19/20
	2.5	4/5
	3.0	20/20
20,000	0.08	0/30
	1.2	30/30

Data taken from Rowe et al., 1952.

In a repeated-exposure study by NTP (1986), five male and five female F344/N rats were exposed to target concentrations of 0, 100, 200, 425, 875, or 1750 ppm PCE vapor for 6 hours/day, 5 days/week for 2 weeks. Mortality was observed only at 1750 ppm: 2/5 males died on days 7 and 8, and 3/5 females died on days 7, 8, and 13. Toxic signs observed at the highest concentration included dyspnea, hypoactivity, and ataxia. In addition, 1750 ppm males had a final mean body weight that was 72% of controls. No mortality, clinical signs, or changes in body weight were noted in male or female rats exposed to 875 ppm or less.

Groups of ten male and ten female F344/N rats were exposed to target concentrations of 0, 100, 200, 400, 800, or 1600 ppm PCE vapor for 6 hours/day, 5 days/week, for 13 weeks (NTP, 1986). In the 1600 ppm group, 4/10 males and 7/10 females died before the end of the study. Final mean body weight in the 1600 ppm group was 20% lower in 1600 ppm males and 11% lower in 1600 ppm females compared with controls. No clinical signs were reported. Pathological evaluation revealed lung congestion in 1600 ppm rats and dose-related increases in hepatic congestion.

Rowe et al. (1952) exposed five male and five female albino rats to 2500 ppm PCE vapor for 7 hours/day for a total of 13 exposures in 18 days. Only one rat/sex survived. Central nervous system depression with a frequent loss of consciousness was noted in all rats. Necropsy of these animals and others killed after 1, 2, 3, or 4 exposures (no further experimental details provided) revealed hepatic effects, including slight to moderate cloudy swelling and a few, small diffusely distributed fat vacuoles.

In an effort to determine the highest concentration of PCE that did not result in anesthesia of the animal, groups of albino rats were exposed to 2750, 4500, 9000, 19,000, or 31,000 ppm PCE for 8 hours (Carpenter, 1937). Mortality occurred in the groups exposed to 19,000 or 31,000 ppm PCE. Clinical signs in animals that died included normal movement around the cage initially, "then they seemed content to remain prone, after which they passed from light anesthesia to insensibility... followed rapidly by death." Necropsy of animals surviving exposure to 19,000 ppm revealed hepatic congestion and granular swelling; animals exposed to 9000 ppm had similar hepatic effects and marked granular swelling of the kidney.

3.1.2. Mice

Bonnet et al. (1980) reported a 6-hour LC_{50} of 2978 ppm [95% CI: 2758-3215 ppm] in mice. Although exposure concentrations were measured, they were not reported. Other information not available included the strain and sex, number of animals per group, and mortality rate. Animals were observed for 14 days for mortality and signs of toxicity. Signs noted during the exposure included hypotonia, tremors, and narcosis (unconsciousness). Typically, there was excitement followed by hypoactivity and narcosis. The authors stated that most deaths occurred within 6 hours, and all occurred within 24 hours of exposure.

In a single inhalation exposure study by NTP (1986), groups of five $B6C3F_1$ mice of each sex were exposed to air containing 2328, 2445, 2613, 2971, or 3786 ppm measured PCE vapor for 4 hours, and then observed for 14 days for signs of toxicity and mortality. Hypoactivity and anesthesia were noted in all exposure groups; the severity of each sign in each of the exposure groups was not provided. No changes in body weights were noted. Mortality occurred in males and females exposed to 2613 ppm or higher (Table 6); additionally, 2 females in the lowest exposure group died. The NTP study authors did not specifically ascribe the deaths in the 2328 ppm group to treatment as it did the mortalities at the higher concentrations. No mortalities occurred at the next highest exposure concentration of 2445 ppm.

TABLE 6. Mortality of B6C3F1 Mice Exposed to PCE for 4 Hours

Concentration (ppm)	Mortality (%)		Other Effects
	Males	Females	
2328	0/5 (0)	2/5 (40)	Hypoactivity and anesthesia
2445	0/5 (20)	0/5 (0)	Hypoactivity and anesthesia
2613	4/5 (80)	2/5 (40)	Hypoactivity and anesthesia
2971	5/5 (100)	5/5 (100)	Hypoactivity and anesthesia
3786	5/5 (100)	5/5 (100)	Hypoactivity and anesthesia

Taken from NTP, 1986

Groups of 8 female white mice were exposed for 4 hours to 2450, 3000, 3950, 5200, 5900, 6750, 7250, or 8900 ppm PCE vapor (not stated if measured or nominal concentrations) to assess mortality (Friberg et al., 1953). Mortality was 0/8, 2/8, 3/8, and 5/8 animals in the 2450, 3000, 3950, 5200 ppm groups, respectively, while all mice exposed to 5900 ppm and higher died. Based on these data, a 4-hour LC_{50} was calculated to be 5200 ppm.

Gehring (1968) exposed groups of female Swiss Webster mice to 3700 ppm PCE for various time periods (times not given) to determine the effective exposure duration (ET) required

for PCE to induce anesthesia as determined by immobilization of the animals (single group of 8 mice), hepatotoxicity as measured by serum glutamic-pyruvic transaminase (SGPT) activity 24 hours following exposure (groups of 11-18 mice), and lethality (groups of 20-94 mice) in 50% of the animals. Air chamber PCE concentrations were measured continuously by an infrared spectrophotometer. The ET_{50}s for the onset of anesthesia and hepatotoxicity were 24.0 minutes [95% CL: 20.2-28.6] and 470 minutes [95% CL: 379-583], respectively, while the LT_{50} was 730 minutes [707-752]. This experiment demonstrated that following acute exposure to PCE, central nervous system effects occur well before liver damage.

Groups of ten male and ten female $B6C3F_1$ mice were exposed to target concentrations of 0, 100, 200, 400, 800, or 1600 ppm PCE vapor for 6 hours/day, 5 days/week, for 13 weeks (NTP, 1986). In the 1600 ppm group, 2/10 males and 4/10 females died before the end of the study. Final mean body weight was 8% lower in 1600 ppm males compared with controls. Clinical signs noted only on the second day of exposure included a hunched position and no movement in 400 ppm animals, panting and irritation in 800 ppm animals, and incoordination and unconsciousness in the 1600 ppm group. Pathologic evaluation revealed liver lesions consisting of leukocytic infiltration, centrilobular necrosis, and bile stasis in 400, 800, and 1600 ppm animals, and karyomegaly of the renal tubule epithelial cells in 7/10 males and 7/10 females exposed to 1600 ppm.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

No adverse effects were noted in two male rhesus monkeys exposed 179 times to 400 ppm PCE vapors for 7 hours/day, 5 days/week (Rowe et al., 1952).

3.2.2. Dogs

Groups of male beagles were exposed to air containing 5000 ppm (n = 5) or 10,000 ppm (n = 12) for 10 minutes through a one-way face mask (Reinhardt et al., 1973). Dogs exposed to 10,000 ppm exhibited excitement and struggling, and signs of stage II anesthesia. No effects were reported for dogs exposed to 5000 ppm. Challenge with epinephrine did not result in cardiac arrhythmia, indicating that PCE was not a cardiac sensitizer at the doses of PCE and epinephrine tested.

3.2.3. Rats

Groups of 8-10 female rats approximately 30-40 days old were exposed to nominal concentrations of 0, 1150, or 2300 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (Goldberg et al., 1964). Vapor concentrations determined with a Zeiss interferometer were within 10% of nominal. The animals were trained for the "pole-climb" test (an "avoidance-escape" test) prior to exposure. Overt ataxia was noted following the first 4-hour exposure to 2300 ppm, resulting in an 80% loss of both avoidance and escape responses, but disappeared after subsequent exposures. Decreased growth was observed in the 2300 ppm group starting on day 4 of exposure. No effects were reported for the rats exposed to 1150 ppm PCE.

Respiratory irritating properties of PCE were investigated in 3 groups of 3 male CPB-WU Wistar derived rats exposed by nose only to air containing measured concentrations of

10,520-11,430 ppm PCE for 25 minutes (Janssen, 1990). No decreases in respiratory rate (RR) were noted during or 25 minutes after exposure as measured by plethysmographs. On the contrary, all animals exhibited an increase in respiratory rate during the exposure (ranging from +125% to +277% of pre-exposure RR), and 8/9 animals still had elevated rates 25 minutes post exposure (+123 to +169% of pre-exposure RR). Janssen proposes that the increases in RR are due to a systemic action on the nervous system, based on the fact that the increases were noted during and post exposure and because of the regularity shown by the pattern of the registration of the respiratory movements. The increased respiration is probably related to a pre-anesthetic excitation phase. Although an effect on tidal volume was indicated, further pulmonary function tests would be necessary to draw any further conclusions. No clinical signs were reported in exposed rats.

Ten adult male Sprague-Dawley rats/group were exposed to 0 or 200 ppm PCE for 6 hours/day for 4 days (Savolainen et al., 1977). The vapor concentration was continuously monitored with infrared analysis. Two animals were killed 17 hours after the day 4 exposure, while additional groups of 2 were killed after an additional 2, 3, 4, or 6 hour exposure on the 5th day. Clinical observations found that animals had an increased ambulatory frequency 1 hour post exposure, but not 17 hours post exposure. The disposition of PCE measured in the various organs and tissues was perirenal fat>liver>cerebrum>cerebellum> lungs>blood, with concentrations increasing with exposure time on day 5. In exposed rats, brain RNA content was decreased, while the activity of a non-specific cholinesterase was increased, the degree of each again correlating with increases in exposure time.

A pilot study in which groups of 10 male Fischer 344 rats/group were exposed to 0 or 800 ppm PCE vapor for 6 hours/day for 4 days resulted in significant changes in flash and somatosensory evoked potentials and in an electroencephalogram in the 800 ppm rats as measured during exposure on the 4th day (Mattsson et al., 1998; Dow Chemical Company, 1991). Mattsson et al. (1998) then conducted a detailed evaluation of the potential neurotoxicity of PCE in groups of 14 Fischer 344 rats/sex/group following repeated exposures to 0, 50, 200, or 800 ppm PCE vapor for 6 hour/day, 5 days/week for 13 weeks. The only treatment-related effect was an increased amplitude of the flash evoked potential measured in the visual cortex in rats exposed to 800 ppm. However, no treatment-related differences were observed in body weight, clinical observations, rectal temperature, monthly enhanced clinical evaluations (based on the Functional Observation Battery by the U.S. EPA), neuropathological findings during a detailed neurotoxicity examination, grip performance, or changes in evoked potentials of other systems or peripheral nerves. Therefore, the authors concluded that there was no evidence of cumulative or progressive neurotoxicity under these study conditions.

Groups of six male Spartan-Sprague Dawley rats were exposed 4 or 7 hours/day for 8 days (4 days/week) to 1000 ppm PCE or 1,1,1,2-tetrachloroethane, while control rats were exposed for 7 hours to air (Piper and Sparschu, 1969). Rats exposed to PCE for 4 or 7 hours had statistically increased kidney weight (approximately +20% of controls) accompanied by minimal to moderate hyaline droplet formation in the convoluted tubules of the renal cortex. Minimal to moderate hepatic central fatty metamorphosis was also observed in rats exposed to PCE for 4 or 7 hours, respectively.

Rowe et al. (1952) repeatedly exposed 8 female albino rats to 1600 ppm PCE vapor for 7 hours/day, 5 days/week, for a total of 18 exposures in 25 days. During the first week of

exposure, the rats appeared drowsy or stuporous upon removal from the exposure chamber, but they quickly recovered. During the second week, clinical signs included "marked salivation, extreme 'restlessness' or 'nervousness' evidenced by continuous movement about the chamber and a 'biting reflex' on contact with one another, an apparent stuporous condition, a considerable disturbance of equilibrium and coordination, and a conspicuous 'scratch reflex'." To test the hypothesis that the response of the animals was due to a "cholinergic nervous tissue" response, 2 rats were i.p. injected with atropine sulfate prior to PCE exposure. The atropine sulfate prevented the appearance of the "excitable state" for approximately 4 hours. Necropsy of the exposed animals revealed decreased body weight, and enlargement of the liver and kidneys with no corresponding histopathological changes. Repeated exposure to 400 ppm PCE vapor for 7 hours/day, 5 days/week in fifteen male and fifteen female rats for a total of 130 exposures in 183 days, or in twenty-two female rats for 14 exposures in 18 days, did not result in any measurable adverse effects.

To assess the effect of chronic alcohol use on PCE-induced hepatotoxicity, groups of 20 male Wistar rats were assigned to one of four groups: a control group, a group administered 15% ethanol in the drinking water, a group exposed to air saturated with PCE for 10 minutes/day, and a group exposed to 15% ethanol in drinking water and air saturated with PCE for 10 minutes/day (Giovannini et al., 1992). An additional group of 5 rats was used as a starting control group. Five animals/group were sacrificed at the end of each treatment week: livers were weighed and fixed and blood was drawn and analyzed for triglycerides, cholesterol, erythrocytes, and hemoglobin. Hepatotoxicity was observed in all treatment groups, although the group treated with alcohol alone exhibited the most severe hepatotoxicity as indicated by increased triglyceride levels and histologic alterations. Co-exposure to PCE and alcohol did not result in increased hepatotoxicity, but rather reduced the hepatotoxic effects observed from alcohol treatment alone. Hepatotoxicity observed in animals exposed only to PCE included increased plasma triglyceride levels, necrotic foci, centrilobular steatosis, and lymphocytic infiltration in the portal space.

3.2.4. Mice

Groups of 10 male Swiss OF1 mice were exposed to air containing measured concentrations of 0, 596, 649, 684, or 820 ppm PCE for 4 hours, and were then placed into water to determine the period of immobility in the "behavioral despair" swimming test (De Ceaurriz et al., 1983). This test is based on the premise that "rodents which are forced to swim in a restricted space soon no longer attempt to escape and adopt a characteristic immobile posture which can be readily timed." It is suggested that solvent exposure causes a prolongation of the escape-directed activity, resulting in decreased immobility as measured during the first 3 minutes of the test. Mice exposed to PCE exhibited a dose-related decrease in the total duration of immobility of -24%, -31%, -52%, and -67%, respectively, compared with the controls. The calculated ID_{50}, or PCE concentration associated with a 50% decrease in the total duration of immobility, was 713 ppm.

Groups of 20 female albino mice were exposed for 4 hours to nominal concentrations of 0, 200, 400, 800, or 1600 ppm PCE vapors (Kylin et al., 1963). Half of the mice were killed 24 hours post exposure and the other half were killed 72 hours post exposure to assess liver damage as measured by fatty infiltration, cell necrosis, and serum ornithine carbamoyl transferase activity. No differences were noted in cell necrosis or serum ornithine carbamoyl transferase

activity in any of the exposed groups compared with the controls. Moderate hepatic fat infiltration was noted in most 200 ppm mice at 24 hours post exposure, but no increases were observed 3 days following exposure. Moderate to massive hepatic fat infiltration was observed in mice exposed to 400 ppm or greater; the increase in liver fat increased with exposure concentration. Kylin et al. (1965) also reported a subsequent study investigating the hepatotoxicity in groups of 20 female albino mice following exposure to 200 ppm PCE for 4 hours/day, 6 days/week, for 1, 2, 4, or 8 weeks. All animals survived to the scheduled kill date. Hepatic fatty degeneration in the liver was present histologically following only one week of exposure and showed a time-related increase in severity. The amount of fat extractable from the liver was also increased at one week, but did not increase with time. No kidney changes were evident.

Kjellstrand et al. (1985) measured motor activity in male NMRI mice during solvent exposure as a means to assess behavioral changes. Groups of 27 mice were exposed to 90, 320, 400, or 600 ppm PCE for 1 hour, and groups of 14 were exposed to 800, 1200, or 3600 ppm PCE for 1 hour (from 2300 to 2400 hours). Chamber concentrations were measured by a gas analyzer. The authors stated that the chambers generally reached 90% of the final concentration 25 minutes after the start of the exposures. Exposures were terminated by the ceasing of vapor generation. Activity of the mice was measured with a Doppler radar unit, which primarily recorded only large movement of the animals, i.e. walking or climbing the cage. Motor activity was rapidly increased in exposed mice at the onset of exposure, with small increases in activity measured even in mice exposed to the lowest concentration. There was no period of hypoactivity in the exposed mice. Although the smell of the vapor could be responsible for the increased activity, the study authors believe it was primarily due to a central nervous system effect because there was a rapid response to termination of the exposure and because mice exhibited a lack of response following exposure to strongly scented cologne.

Axelsson et al. (1953) investigated the potentiating effect of hypoxia on the anesthetic action of PCE at a nominal exposure concentration of 3600 ppm in groups of white mice. A mouse was placed in a 3 L glass bottle, and the bottle was rolled at a constant speed. The induction times were classified as the amount of time that elapsed from the beginning of rolling to the appearance of the following stages: the mouse slips for the first time; the mouse falls in a supine position; the mouse rolls 3 times without interruption; the mouse rolls altogether passively. The induction times were 1.09 minutes, 1.69 minutes, 3.02 minutes, and 7.08 minutes, respectively. Hypoxia, induced by pre-exposure for 1 hour to air containing 10% oxygen and 90% nitrogen, reduced the induction times.

The persistence of histopathological changes in the nasal mucosa were investigated in 20 male ddY mice exposed to a measured air concentration of 300 ppm PCE for 6 hours/day for 5 days compared with a control group of 10 mice (Suzaki et al., 1997). Groups of 4 experimental mice and 2 control mice were killed 2 or 3 weeks or 1, 2, or 3 months following the last exposure. No clinical signs were reported, and no animals died. Histopathological evaluation revealed more persistent damage in the olfactory mucosa compared with respiratory mucosa. Findings included ciliated epithelial cells and normal pseudostratified nonciliated columnar epithelium in an area previously covered by the olfactory epithelium, the presence of a basement membrane under the ciliated epithelium suggesting persistence of basal cells, and atrophy of olfactory nerves and Bowman's glands in the laminal propria of the olfactory mucosa.

Groups of 5 B6C3F$_1$ mice/sex were exposed for 6 hours/day to 200 ppm for 28 days or to 0 or 400 ppm for 14, 21, or 28 days, and were killed 18 hours after the last exposure (Odum et al., 1988). The vapor concentration in the exposure chamber was analyzed by gas chromatography. Exposed mice had statistically elevated hepatic levels of peroxisomal cyanide-insensitive palmitoyl coenzyme A activity, a marker for peroxisomal β-oxidation. When comparing the maximum response, males exhibited a 3.6-fold increase and females a 2.1-fold increase in this enzyme activity compared with controls. Light microscopic examination of the liver of exposed animals revealed centrilobular eosinophilia and centrilobular fatty vacuolation, and electron microscopic examination revealed proliferation of peroxisomes in the centrilobular region.

Aranyi et al. (1986) exposed groups of 140 female CD1 mice to 25 or 50 ppm PCE vapor for a single 3-hour exposure or to 25 ppm for five, 3-hour exposures. The treated and control mice were then challenged with an aerosol of *Streptococcus zooepidemicus* pneumonia five times to determine if exposure to PCE altered susceptibility to this infection, and the bactericidal activity of the lungs was assessed by measuring pulmonary bactericidal activity to *Klebsiella pneumoniae*. Exposure to 50 ppm PCE vapor resulted in statistically increased mortality following streptococcal aerosol challenge and decreased pulmonary bactericidal activity to inhaled *K. pneumonia*. Single or repeated exposures to 25 ppm, however, did not increase the mice's susceptibility to respiratory infection, nor reduce the pulmonary bactericidal activity.

In a repeated-exposure study by NTP (1986), five male and five female B6C3F$_1$ mice were exposed to target concentrations of 0, 100, 200, 425, 875, or 1750 ppm PCE vapor for 6 hours/day, 5 days/week for 2 weeks. All animals survived to the scheduled sacrifice. Effects noted in the 1750 ppm group included dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia, and final mean body weights that were 7% lower for males and 6% lower for females compared with the respective controls. Cytoplasmic vacuolation (fat) of the hepatocytes was observed in 4/5 males in the 875 ppm group, and in 5/5 males and 5/5 females in the 1750 ppm group.

3.2.5. Guinea pigs

Rowe et al. (1952) conducted several 7-hour repeated exposures to various concentrations of PCE in male and female guinea pigs for 7 hours/day, 5 days/week. Seven male and four female guinea pigs exposed 132 times to 100 ppm in 185 days exhibited minimal effects, including increased liver weight in females and the presence of a few, small fat vacuoles in some males and all females. Seven females exposed to 100 ppm 13 times in 17 days exhibited no adverse effects. A depression in growth, increased liver weight, slight to moderate central hepatic fatty degeneration, increased hepatic lipids, and esterified cholesterol were generally observed when groups of eight males and eight females were exposed to 200 ppm for 158 times in 220 days or to 400 ppm for 169 times in 236 days; at 400 ppm, animals also had slight cirrhosis. Depressed growth, increased liver and kidney weight, and slight to moderate hepatic fatty degeneration were observed in an additional fifteen males exposed to 400 ppm for 14 times in 18 days. Exposure of seven males to 1600 ppm for 8 exposures in 10 days resulted in decreased body weight, increased liver weight, moderate central hepatic fatty degeneration, and slight degenerative changes in the germinal epithelium of the testes. Groups of 4 male and 4 female guinea pigs exposed to 2500 ppm 18 times in 24 days exhibited a loss of equilibrium, coordination, strength, and body weight. Body weight rebounded during the 20 day observation

period. Examination of these and an additional 2 guinea pigs exposed 3 times and 3 guinea pigs exposed 18 times to 2500 ppm revealed increased liver weight, moderate to marked central hepatic fatty degeneration, and increased kidney weight with slight to moderate cloudy swelling of tubular epithelium.

3.2.6. Rabbits

No adverse effects were noted in groups of 2 male and 2 female albino rabbits exposed 179 times to 400 ppm PCE for 7 hours/day, 5 days/week (Rowe et al., 1952). When 2 males were exposed 28 times to 2500 ppm for 7 hours/day, 5 days/week, observations included marked central nervous system depression and slight central hepatic parenchymatous degeneration.

3.3. Developmental/Reproductive Effects

Schwetz et al. (1975) exposed groups of pregnant Swiss Webster mice or Sprague-Dawley rats to 0 or 300 ppm PCE vapor for 7 hours/day during gestation days (GD) 6-15. Animals were killed on GD 18 or 21, respectively, for maternal gross necropsy and fetal evaluation. Pregnant mice exposed to 300 ppm PCE had a statistically increased mean liver weight relative to body weight (+21%) compared with controls, and fetuses from the exposed mice had slight decreases in mean body weight (-8%; $p<0.05$). In rats, maternal body weight gain was slightly decreased in exposed dams (-4 to -5%; $p<0.05$) compared with controls, and a slight increase in the percentage of resorptions/implantation sites was also noted (9% vs. 4% of controls; $p<0.05$). No statistically significant increases in the litter incidences of developmental anomalies were observed in litters from the exposed groups of mice or rats. It should be noted that the number of litters from both exposed mice and rats were about half those of controls. No explanation for the reduced litter sizes was provided, but examination of the cesarean data did not reveal any significant differences that would impact litter size. It could be that fewer numbers of animals were assigned to the exposure groups. This difference in litter numbers, however, impacts the analysis of any potential treatment-related effects.

Groups of female Sprague-Dawley rats or New Zealand white rabbits were exposed to air containing 0 or 500 ppm PCE (91.43% pure) (Beliles et al., 1980). The rats and rabbits were divided into 6 treatment groups: PCE during GD 0-18 or 0-21, respectively; PCE for 3 weeks before mating through gestation day (GD) 18 or 21, respectively; PCE during GD 6-18 or 7-21, respectively; PCE for 3 weeks before mating and during (GD) 6-18 or 7-21, respectively; filtered air throughout pregnancy alone; filtered air 3 weeks before mating and throughout pregnancy. Exposures were for 7 hours/day, 5 days/week prior to mating, and 7 hours/day during gestation. Three rats from the same group died on the second day of pregestational exposure to 500 ppm, and other rats in that same group exhibited ataxia and loss of balance on the same day. However, these deaths cannot be ascribed with certainty to exposure to 500 ppm PCE. The study authors state that the chamber concentrations were 568 ppm at the time of measurement, 15 minutes before the end of exposure, but may not have reflected the maximum deviation from intended air concentrations. No other reports of ataxia and loss of balance occurred during the study, and no other rats died. It appears likely that exposure concentrations were much higher than the nominal on the pre-gestation exposure day 2 for the one exposure group. No definitive exposure-related maternal or developmental toxicity was observed in rats or rabbits exposed to 500 ppm PCE. Hardin et al. (1981) also reported that no maternal or developmental effects were noted in rats or New Zealand white rabbits exposed to 0 or 500 ppm PCE vapors for 6 to 7

hours/day during GD 1-19 or 1-24, respectively. Few of the experimental details were provided, and it was stated that some of the studies reported in Hardin et al. (1981) were contracted to other laboratories. It is likely that this study is the same as the Beliles et al. (1980) report.

Rats were exposed to air containing 1000 ±125 ppm PCE to determine the effects of exposure prior to mating and during pregnancy compared to exposure during pregnancy alone (Tepe et al., 1980). Female Long-Evans rats were divided into 4 treatment groups of 30 animals each: exposure to PCE for 2 weeks before mating through gestation day (GD) 20, PCE before mating alone, PCE during pregnancy alone, and filtered air before mating and throughout pregnancy. Exposures were for 6 hours/day, 5 days/week prior to mating, and 6 hours/day, 7 days/ week throughout gestation. Half of the dams were sacrificed on GD 21 for gross necropsy and fetal evaluation, the other half was permitted to litter. Maternal relative liver weights were increased and fetal body weights were decreased in the groups in which females were exposed to PCE prior to mating and throughout pregnancy and during pregnancy alone. Maternal body weights were not affected. An excess in the total number of fetal skeletal anomalies was observed in fetuses from dams exposed prior to mating and throughout pregnancy, while an increase in the fetal incidence of an enlarged renal medulla was observed in the group exposed during pregnancy alone. However, no increase in the litter incidences of these anomalies was observed.

Post-natal evaluation was conducted on the offspring of the dams allowed to litter in the above mentioned study (Tepe et al., 1980) to determine if the depression in body weight and excess fetal skeletal and soft tissue anomalies persisted (Manson et al., 1981). Additionally, the potential for gestational exposure to PCE to cause neoplastic lesions or neurobehavioral toxicity was evaluated. Prenatal exposure to PCE did not affect weight gain and survival of offspring up to 18 months of age, and did not affect the frequency of gross lesions determined at 6 and 18 month post-mortem examinations. In neurobehavioral testing, no measurable differences were observed in general activity in open field tests in prenatally exposed offspring 10 and 20 days old or in running in wheels in the prenatally exposed offspring 40 to 100 days old compared with control offspring. Negative results were obtained in the visual discrimination tests in prenatally exposed offspring 130-170 days old.

Nelson et al. (1980) investigated the potential neurotoxic effects on the offspring of dams exposed to PCE vapors during gestation. Presumed pregnant Sprague-Dawley rats were exposed to 0 or 900 ppm PCE for 7 hours/day on GD 7-13 or GD 14-20. In general, 4 male and 4 female pups were left with the mother after delivery. Dams exposed to 900 ppm on GD 7-13 had significantly reduced feed consumption, resulting in decreased body weight gain (not significant). No effects were noted in dams exposed during GD 14-20. Exposure to 900 ppm PCE did not result in any significant effects on numbers of offspring, proportion of offspring born alive, or in birth weights in either exposure group. Behavioral tests were conducted on offspring on various days (generally 3 separate days). For each test, one male and one female from each litter were selected, and the animals were generally sacrificed following each group of tests. Behavioral testing revealed a poorer performance in the ascent and rotorod tests (both assess neuromuscular coordination) in offspring from dams exposed during GD 7-13, but only on certain days of testing. Offspring from dams exposed during GD 14-20 had a poorer performance on the ascent test for one test day, but had a superior performance on rotorod testing and were more active in the open field exploratory testing. Neurochemical analysis of the whole brain (minus cerebellum) generally revealed decreased levels of dopamine and acetylcholine in

21-day-old offspring of exposed dams, but no changes were noted in newborns. No neuropathological lesions were detected in newborn or 21-day old offspring from exposed dams. An additional study in which presumed pregnant Sprague-Dawley rats were exposed to 0 or 100 ppm PCE for 7 hours/day during GD 14-20 did not reveal any significant differences in behavioral test outcomes of exposed animals compared with the controls.

Kyrklund and Haglid (1991; also in Kyrklund and Haglid, 1989 [Abstract]) investigated the gross lipid composition and fatty acid pattern of ethanolamine phosphoglyceride in the cerebral cortex of guinea pig pups from dams that were exposed to 160 ppm PCE vapor continuously during GD 33-65. The authors chose guinea pigs because their period of major brain growth occurs during intrauterine development in contrast to rats and mice. In addition, guinea pigs have a higher lipid concentration in the brain. Brains from pups of exposed dams had a slightly altered fatty acid pattern and a decrease in the stearic acid levels, consistent with previous studies. The authors concluded that intrauterine exposure to PCE during the rapid brain growth period did not alter pup brain lipids any more than that observed in adults.

No evidence for dominant lethality was observed when male rats were exposed to 100 or 500 ppm PCE for 5 days and then allowed to mate over a 7 week period with unexposed virgin females (Beliles et al., 1980).

In a two-generation reproduction study, groups of 24 male and 24 female Wistar rats were exposed to 0, 100, 300, or 1000 ppm PCE 6 hr/day, 5 d/week, for at least 11 weeks prior to mating (Tinston, 1995). One litter was produced in the first generation and two litters were produced in the second generation. Exposure for dams was discontinued from gestation day 20 through lactation day 6 or 7; dams and their litters were then exposed until lactation day 29. Clinical signs in the 1000-ppm F_0 and F_1 males and females included decreased activity and reduced response to sound during the first 2 weeks of exposure; thereafter, the animals developed tolerance to PCE and these clinical signs were not observed. Other signs observed in adults of both generations during exposure were salivation, breathing irregularities, piloerection, and tip-toe gait at 1000 ppm and piloerection and increased breathing rate at 300 ppm. Recovery from these effects was evident within 30 minutes after the end of exposure. In the 1000 ppm groups, body weight gains were reduced in the F_0 and F_1 males and females during premating, in the F_0 and F_1 females during lactation, and in the F_1 females during gestation. A similar but less marked effect on body weight was seen in both generations at 300 ppm. The only treatment-related lesion found at necropsy of the adults consisted of nuclear pleomorphism within proximal kidney tubules of F_0 males and females and F_1 males. Length of gestation and male and female fertility were not affected by PCE exposure in either generation. When exposure of the F_0 dams and their litters resumed on lactation day 6, sedation of the dams with consequent neglect of their litters was observed in the 1000 ppm group. For the 1000-ppm F_1 litters, pup survival was significantly reduced during lactation days 5-22 and body weights and weight gains were less than the controls. A similar but less marked effect on pup body weight occurred in the 300 ppm F_1 litters. Clinical signs in the 1000 ppm F_1 pups included sedation and hypothermia that persisted after exposure up to 2 hours on the first two days, 1.5 hours for the next 2 weeks, and 30-60 minutes up to lactation day 29. Due to the pronounced effects of 1000 ppm on the F_1 pups, exposure to this concentration was discontinued during lactation of the F_{2a} and F_{2b} pups. However for the F_2 litters, pup survival, body weights, and weight gains were reduced in the 1000 ppm group and pup body weights were reduced at 300 ppm during lactation days 1-5.

At the end of the study (Tinston, 1995), F_1 males were bred to untreated females to determine whether the effects on pup survival were male-mediated. No differences were observed for proportion of live born pups, pup survival, or pup growth between litters sired by treated and control males.

Carpenter (1937) reported that fertility was not negatively impacted when groups of 24 albino rats each (assumed to be mix of males and females) were exposed to 70, 230, or 470 ppm PCE vapor for 8 hours/day, 5 days/week for 7 months.

3.4. Genotoxicity

For a complete review of studies conducted to address the genotoxicity of PCE, the reader is referred to ATSDR, 1997; IARC, 1995; and Reichert, 1983. In general, PCE has tested negative with or without metabolic activation in *in vitro* bacterial tests including *Salmonella typhimerium* and *Escherichia coli*, and in yeast. Exceptions were seen when glutathione transferases were added to the incubation mixture. PCE did not cause an increase in the frequency of sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells, was not mutagenic in mouse lymphoma cells, and did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (NTP, 1986). Evidence of PCE binding to DNA is equivocal. It has been proposed that the epoxide of PCE is much less reactive than the epoxides of unsymmetrically substituted chlorinated ethylenes such as trichloroethylene and vinyl chloride (Costa and Ivanetich, 1980; Henschler, 1977).

3.5. Chronic Toxicity/Carcinogenicity

NTP (1986; also Mennear et al., 1986) exposed groups of fifty male and fifty female F344/N rats or groups of fifty male and fifty female $B6C3F_1$ mice to 0, 200, or 400 ppm PCE for 6 hours/day, 5 days/week, for 103 weeks. Clear evidence of carcinogenicity in male F344/N rats was reported based on increased incidences of mononuclear cell leukemia and uncommon renal tubular cell neoplasms, and some evidence of carcinogenicity was reported in female F344/N rats based on increased incidences of mononuclear cell leukemia (see Table 7). Nonneoplastic lesions in exposed rats included renal tubular cell karyomegaly in males and females, and renal cell hyperplasia and a dose-related increase in nasal cavity squamous metaplasia and/or thrombosis in males. In mice, clear evidence of carcinogenicity was reported based on increased incidences of both hepatocellular adenomas and carcinomas in males and of hepatocellular carcinomas in females. Nonneoplastic lesions in exposed male and female mice included renal tubular cell karyomegaly and increases in the incidence of hepatic degeneration, necrosis, and nuclear inclusion.

To assess the carcinogenicity of PCE, groups of 94 male and 94 female Sprague-Dawley rats were exposed to 300 or 600 ppm PCE vapor for 6 hours/day, 5 days/week for 52 weeks (Rampy et al., 1978). The controls consisted of a group of 189 rats of each sex that were held in the animal room used for the exposed rats when they were not in the exposure chambers. The 12 month exposure period was followed by an observation period extending through the rats lifetime (up to 31 months). No dose-related increase in tumor incidence was observed.

The National Cancer Institute (1977) found PCE to be a liver carcinogen in $B6C3F_1$ male and female mice following daily gavage of PCE in corn oil for 5 days/week for 78 weeks (males:

1072 or 536 mg/kg/day; females: 772 or 386 mg/kg/day). Treated animals had increased incidences of hepatocellular carcinomas, and additionally had treatment-related toxic nephropathy. Osborne-Mendel rats were similarly exposed, but an endemic of pneumonia precluded an evaluation of carcinogenesis following gavage with PCE. However, it was evident that mortality and toxic nephropathy in rats were dose-related.

IARC (1995) concluded that there is sufficient evidence in experimental animals for the carcinogenicity of PCE. In combination with the limited evidence for carcinogenicity in humans, IARC has classified PCE as a Group 2A carcinogen (probably carcinogenic to humans). The U.S. EPA (1997) does not have a published classification for the carcinogenicity of tetrachloroethylene.

TABLE 7. Inhalation Exposure to TCE: Summary of Carcinogenicity Studies

Animal Description			Exposure Protocol	Response		Reference
Species/ Strain	Sex	No./ Group		Tissue/Tumor Type	Incidence	
Mouse: $B6C3F_1$	M	50	0, 200, 400 ppm 6 h/d, 5 d/wk, 103 wk	Hepatocellular adenomas Hepatocellular carcinomas	1/49, 8/49, 18/50 7/49, 25/49, 26/50	NTP, 1986
	F	50	0, 200, 400 ppm 6 h/d, 5 d/wk, 103 wk	Hepatocellular carcinomas	1/48, 13/50, 36/50	
Rat: F344/N	M	50	0, 200, 400 ppm 6 h/d, 5 d/wk, 103 wk	Mononuclear cell leukemia Renal tubular cell Adenomas or Adenocarcinomas, combined	28/50, 37/50, 37/50 1/49, 3/49, 4/50	NTP, 1986
	F	50	0, 200, 400 ppm 6 h/d, 5 d/wk, 103 wk	Mononuclear cell leukemia	18/50, 30/50, 29/50	
Rat: Sprague-Dawley	M & F	94 (189 controls)	0, 300, 600 ppm 6 h/d, 5 d/wk, 52 wk	No neoplastic lesions observed	B	Rampy et al., 1978

3.6. Summary

A summary of lethal and nonlethal inhalation data in laboratory animals is presented in Tables 8 and 9, respectively. Mortality data in animals were limited: a 6-hour LC_{50} of 4100 ppm and 2978 ppm was reported for rats and mice, respectively, and a 4-hour LC_{50} of 5200 ppm was reported for mice. Clinical signs in rats and mice exposed to nonlethal concentrations included reversible central nervous system effects (hyperactivity, hypoactivity, drowsiness, ataxia, anesthesia), hepatotoxic effects (hepatic fat infiltration, hepatic congestion, increased liver weights; more effects seen in mice), and nephrotoxic effects (increased kidney weights, hyaline droplet formation; more pronounced in rats). The central nervous system effects were generally associated with acute exposure, while the liver and kidney effects were generally seen after repeated-exposures. As noted, the CNS effects were reversible, and animals appeared to develop a tolerance to the CNS effects with repeated exposures.

Studies investigating the potential of PCE to induce developmental toxicity have not reported any developmental anomalies associated with PCE exposure; however, decreases in fetal body weights were reported in mice and rats. Neurobehavioral testing of offspring from dams exposed during pregestation and/or during gestation have not revealed consistent decrements. Analysis of the brains from guinea pig pups exposed during gestation indicated that intrauterine exposure did not alter brain lipids any more than that observed in adults. A two-generation reproduction study did not reveal any effects of PCE exposure on fertility.

NTP has stated that there is clear evidence of carcinogenicity in male rats based on increased incidences of mononuclear cell leukemia and uncommon renal tubular cell neoplasms, and some evidence of carcinogenicity in female rats based on increased incidences of mononuclear cell leukemia. In mice, clear evidence of carcinogenicity was reported based on increased incidences of both hepatocellular adenomas and carcinomas in males and of hepatocellular carcinomas in females. IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of PCE.

TABLE 8. Summary of Lethal Inhalation Data in Laboratory Animals

Conc. (ppm)	Duration	Mortality and Other Effects	Reference
Rat			
4100	6 h	LC_{50}	Bonnet et al., 1980
3786	4 h	Lowest exposure concentration causing death (1/5 males; 4/5 females); no mortality at 2445 ppm	NTP, 1986
1750	6 h/d, 5d/wk for 2 wk	Killed 5/10; no mortality at 875 ppm or less	NTP, 1986
1600	6 h/d, 5d/wk for 13 wk	Killed 11/20; No mortality at 800 ppm or less	NTP, 1986
Mouse			
5200	4 h	LC_{50}	Friberg et al., 1953
2978	6 h	LC_{50}	Bonnet et al., 1980
3000	4 h	Lowest exposure concentration causing death (2/8) No mortalities at 2450 ppm	Friberg et al., 1953
2613	4 h	Lowest exposure concentration causing death in males; 2/5 females died at lowest dose of 2328 ppm	NTP, 1986
1600	6 h/d, 5d/wk for 13 wk	Killed 6/20; No mortality at 800 ppm or less	NTP, 1986
3700	Various time periods	Effective exposure duration for 50% of the animals was as follows: For the onset of anesthesia: 24.0 min; for hepatotoxicity: 470 min; for death: 730 min. Therefore, determined that CNS effects occur well before liver damage	Gehring, 1968

TABLE 9. Summary of Nonlethal Inhalation Data in Laboratory Animals			
Conc. (ppm)	**Duration**	**Effects**	**References**
Monkey			
400	7 h/d for 179 exp.	No effects	Rowe et al., 1952
Rat			
10,520-11,430	25 min	Increased respiratory rate	Janssen, 1990
2445	4 h	Highest concentration causing no mortality; Hypoactivity, ataxia, and anesthesia	NTP, 1986
2300	4 h	Overt ataxia during first exposure resulting in 80% loss of both avoidance and escape responses, disappeared during subsequent exposures; no effects at 1150 ppm	Goldberg et al., 1964
800	6 h/d for 4 d	Changes in flash and somatosensory evoked potential and in EEG	Mattsson et al., 1998
1600	7 h/d, 5 d/wk for 18 exp.	Animals appeared drowsy or stuporous upon removal from the chamber during the first week of exposure	Rowe et al., 1952
875	6 h/d, 5d/wk for 2 wk	Highest concentration causing no mortality; No clinical signs	NTP, 1986
800	6 h/d, 5d/wk for 13 wk	Highest concentration causing no mortality; No clinical sign; Dose-related hepatic congestion in 200, 400, or 800 ppm animals	NTP, 1986
1000	4 or 7 h/d, 4 d/wk for 2 wk	Increased kidney weights with minimal to moderate hyaline droplet formation in renal cortex; minimal to moderate hepatic central fatty metamorphosis	Piper and Sparschu, 1969
Mouse			
2445	4 h	Highest concentration causing no mortality in males (2/5 females died at 2328 ppm but none at 2445 ppm); Hypoactivity and anesthesia	NTP, 1986
200 400	4 h	Moderate hepatic fat infiltration 24 h post exp, but not 3 days post exp. Moderate to massive hepatic fat infiltration	Kylin et al., 1963
713	4 h	ID_{50}: 50% decrease in the total duration of immobility in behavioral despair swimming test	De Ceaurriz et al., 1983
875 1750	6 h/d, 5 d/wk for 2	Hepatic cytoplasmic vacuolation (fat) in males Dyspnea, hypoactivity, hyperactivity, anesthesia, ataxia, lower final body wts; hepatic cytoplasmic vacuolation (fat)	NTP, 1986
200 400 800	6 h/d, 5d/wk for 13 wk	No clinical signs or pathological lesions Hunched over posture and no movement on day 2; liver lesions Highest conc. with no mortality; panting, irritation on day 2; liver lesions	NTP, 1986

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

For more comprehensive reviews of the metabolism and disposition, the reader is referred to ATSDR (1997) and IARC (1995). Experimental evidence indicates that the predominant pathway for metabolism of PCE is mediated by the cytochrome P450 oxidative pathway, with major metabolites consisting of trichloroacetic acid (TCA), oxalic acid, and alkylated

macromolecules (Costa and Ivanetich, 1980; Dekant et al., 1987; Moslen et al., 1977). Mice are capable of metabolizing more PCE than are rats (Buben and O'Flaherty, 1985; Odum et al., 1988; Reitz et al., 1996; Schumann et al., 1980) or humans (Reitz et al., 1996). The metabolism of PCE has been determined to be saturable in humans (Ohtsuki et al., 1983) and in rats and mice (Buben and O'Flaherty, 1985; Pegg et al., 1979; Reitz et al., 1996; Schumann et al., 1980).

In addition to metabolism by cytochrome P450s, PCE can also be conjugated with glutathione to produce S-(1,2,2-trichlorovinyl)glutathione, which is further processed in the kidney by the enzymes responsible for mercapturic acid formation to produce S-(1,2,2-trichlorovinyl)-L-cysteine. This intermediate can be acylated to form mercapturic acid, or can be cleaved by renal β-lyases to a reactive metabolite capable of binding to macromolecules. PCE metabolites consistent with the aforementioned metabolic pathway have been identified in rats and mice (Dekant et al., 1986; 1987; Green et al., 1990), although rats, particularly males, have a relatively high rate of formation of the glutathione conjugate (Dekant et al., 1986; 1998; Green et al., 1990). However, these metabolites are not produced in appreciable amounts until the oxidative P450 pathway becomes saturated (Dekant et al., 1987). Evidence is equivocal for human formation of this PCE metabolite. Glutathione conjugation of PCE could not be detected *in vitro* in human liver (Dekant et al., 1998; Green et al., 1990), but N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine was detected in the urine of 4 workers occupationally exposed to 50 ppm PCE for 4 or 8 hours/day, 5 days/week (Birner et al., 1996).

Most of the information about PCE metabolism and elimination in humans has come from studies of controlled human exposures to PCE to develop biological standards for industrial work exposures. These experiments were designed to investigate the relationship between the magnitude of the exposures and the body burden of PCE as measured in expired breath, blood, and urine of the exposed test subjects. The PCE concentration in the expired (alveolar) air was proportional to the level of exposure and followed an exponential decay curve as determined by Fernandez et al. (1976: 23 males and 1 female exposed to 100 ppm for 1, 2, 4, or 8 hours; 150 ppm for 1, 4, 6, or 8 hours; 200 ppm for 2, 4, 8 hours), Jang et al. (1997: 6 male Caucasians and 6 male Orientals exposed to 50 ppm for 6 hours), Opdam and Smolders (1986: 3 male and 3 female volunteers exposed at rest to 0.5 to 9 ppm for 1 to 60 minutes), Stewart et al. (1961b: groups of six, healthy male workers ages 30-59 exposed to 194 ppm for 187 minutes, 194 ppm for 83 minutes, or 101 ppm for 183 minutes), Stewart et al. (1970: 12 male workers exposed once to 101 ppm for 7 hours or 5 male workers repeatedly exposed for 5 days), Stewart et al. (1981: 10 male workers and 11 females exposed for 1, 3, or 7.5 hours daily to 50 to 150 ppm for up to 4 weeks), and Monster et al. (1979: 6 healthy male workers ages 27-34 exposed for 4 hours to 72 ppm at rest, 144 ppm at rest, and 142 ppm at rest combined with work load). Clearance of PCE was slow, as PCE was measured in the breath for prolonged periods of time following the exposure (Fernandez et al, 1976; Monster et al., 1979; Stewart et al., 1961b; 1970). For example, Fernandez et al. (1976) reported that more than two weeks were required to eliminate PCE following an 8-hour exposure to 100 ppm.

In general, the decay curves were of similar slope and there were relatively small interindividual differences in measured PCE breath concentrations following exposures to the same PCE concentrations (Stewart et al., 1961b; 1970; Fernandez et al., 1976). A few exceptions were reported. Jang et al. (1997) noted no difference in the average concentration of PCE in expired air measured during exposure, but Caucasians had a slightly higher exhaled breath concentration of PCE post exposure compared with Orientals (9.5 ppm vs. 8.3 ppm,

respectively; $p<0.05$). Stewart et al. (1970) reported that chronically exposed individuals with a greater body mass had higher PCE breath concentrations noticeable at 100 hours post exposure, with the trend becoming more marked by 300 hours post exposure. The lower average PCE breath concentrations in females compared with males could not definitively be attributed to differences in sex, because males who exercised during the exposures were included in the averages; exercise appeared to increase the body burden and hence the expired PCE breath concentrations (Stewart et al., 1981). Monster et al. (1979) also reported that work load and lean body mass increased the uptake of PCE.

Autopsies conducted on victims of fatal PCE exposures provide information on the distribution of PCE at high exposure levels. Concentrations of PCE in the various tissues were reported as brain>blood>lung (Gaillard et al., 1995; Lukaszweski 1979), liver>blood>lung (Isenschmid et al., 1998; brain and kidney levels not determined), or liver>kidney≥brain>lung>blood (Levine et al., 1981). Levine et al. (1981) speculated that the higher levels of PCE observed in the liver compared to the other tissues could be the explained by the observation that the liver of the victim was extremely fatty, and PCE is expected to distribute according to the lipid content in the tissues.

Numerous animals studies have been conducted to investigate the metabolism and disposition of PCE. Yllner (1961) exposed 5 female mice for 2 hours to PCE vapor in doses of about 1.3 mg/kg body weight. Approximately 70% of the chemical was absorbed, with approximately 90% of the absorbed dose excreted by 4 days: 70% in air, 20% in urine, and less than 0.5% in feces. Analysis of the urine identified TCA as the main urinary metabolite (52%), followed by oxalic acid (11%) and trace amounts of dichloroacetic acid.

Groups of adult, male Sprague-Dawley rats were exposed for 6 hours to air containing 10 or 600 ppm [^{14}C]PCE (measured concentrations of 9 and 573 ppm) (Pegg et al., 1979). Within 72 hours of exposure to 10 ppm, 68% of the radiolabel was expired in the air unchanged, 4% expired as CO_2, 19% excreted in the urine, 5% recovered in the feces, and 4% remained in the carcass. Exposure to 600 ppm shifted the profile, with 88% being expired in the air unchanged, 1% expired as CO_2, 6% excreted in the urine, 3% recovered in the feces, and 2% remaining in the carcass. This shift reflects a saturation of the metabolic capacity of the animal. Pulmonary excretion and the decline of PCE in the blood followed apparent first-order kinetics, with an approximate half-life of 7 hours for both. Oxalic acid was identified as the major urinary metabolite. The distribution of the radiolabel 72 hours after exposure to 10 or 600 ppm PCE was kidney>liver>fat>lung>heart. No radiolabel was detected in the brain. The amount of whole liver radioactivity and nonextractable radioactivity in the liver (representing the fraction bound to macromolecules) was determined 0, 6, 24, and 72 hours after exposure. Approximately 85 to 90% of the radioactivity in the liver was cleared by 72 hours, while the nonextractable radioactivity was cleared at a slower rate.

Schumann et al. (1980) investigated the differences in pharmacokinetics and molecular interactions of (^{14}C)PCE in male Sprague-Dawley rats and B6C3F$_1$ mice. The metabolism studies were designed to be compared with Pegg et al. (1979). Seventy-two hours after mice were exposed to 10 ppm PCE for 6 hours, 12% of PCE was expired in air unchanged, 8% expired as CO_2, 63% was excreted in urine, 9% recovered in feces, and 3% remained in the carcass. From these data, mice metabolized 8.5 times more PCE than did rats. Evaluation of hepatic macromolecular binding, assessed by the amount of nonextractable radiolabel in liver

following exposure to 10 or 600 ppm, indicated that mice had 4.7- and 5.8-fold higher levels of peak binding compared with rats, respectively. None of the radioactivity was associated with DNA. Repeated oral administration of PCE for 11 days resulted in hepatic changes in mice at doses as low as 100 mg/kg/day, while only mild hepatic effects were noted in rats dosed with 1000 mg/kg/day. Dosing with 500 and 1000 mg/kg/day resulted in a 2-fold increase in hepatic DNA synthesis in mice, but not rats.

Following exposure to 400 ppm PCE vapor for up to 6 hours, male and female $B6C3F_1$ mice had much higher peak blood levels of TCA (130 μg/mL) than male and female Fischer 344 rats (7 μg/mL) (Odum et al., 1988). Male and female mice also had statistically elevated levels of peroxisomal cyanide-insensitive palmitoyl coenzyme A activity, a marker for peroxisomal β-oxidation, following exposure for 6 hours/day to 200 ppm for 14 days or to 400 ppm for 14, 21, or 28 days. When comparing the maximum response, males exhibited a 3.6-fold increase and females a 2.1-fold increase in this enzyme activity compared with controls. Rats exposed under identical conditions exhibited only a small increase in the enzyme activity, with the greatest response occurring in male rats (1.3-fold increase).

In addition to the measurements made from controlled exposure experiments and assessments following occupational exposures of humans, many studies in which physiologically-based pharmacokinetic (PBPK) models for PCE have been developed and validated predict and/or compare the distribution and metabolism of PCE in humans, rats, mice, and even dogs (Bois et al., 1996; Dallas et al., 1994; Hattis et al., 1990; 1993; Jang and Droz; 1997; Reitz et al., 1996; Ward et al., 1988; for a review see ATSDR, 1997). Byczkowski and Fisher (1994; 1995) and Schreiber (1993) have also developed and validated a PBPK model for the lactational transfer of PCE in humans and rats.

4.2. Mechanism of Toxicity

Mice are more susceptible to the hepatotoxic and hepatocarcinogenic effects of PCE than rats. Investigations of the reason for this difference in susceptibility have found that hepatotoxicity in mice is directly related to the metabolism of PCE to TCA and ~~other~~ reactive metabolites, and mice produce much more TCA than do rats (Buben and O'Flaherty, 1985; Schumann et al., 1980; Odum et al., 1988). TCA production not only results in cytotoxicity, but has also been demonstrated in mice to induce peroxisomal proliferation, another potential epigenetic mechanism for liver cancer (Odum et al., 1988; Schumann et al., 1980). Because human studies to date have found only limited amounts of TCA excreted in urine following exposure to PCE, it is likely that humans are not as sensitive as mice to the hepatic effects of PCE. Another paper suggests that PCE can directly affect the liver, however. Kukongviriyapan et al. (1990) have reported that PCE interferes with energy-dependent hepatic transport functions in rat hepatocytes, and suggests that a mechanism of inhibition of cell membrane ATPases and/or a decrease in ATP levels may be responsible for cellular dysfunction.

While mice are most susceptible to the hepatotoxic effects of PCE, male and female rats are more susceptible to PCE-induced nephrotoxicity and male rats to PCE-induced nephrocarcinogenicity. With regard to the increased incidence of kidney tumors in male rats, several mechanisms for PCE-induced rat kidney tumors have been proposed, including: chronic cytotoxicity (Green et al., 1990), hyaline droplet nephropathy (Bergamaschi et al., 1992; Green et al., 1990), and generation of a reactive intermediate via the glutathione/β-lyase pathway

(Dekant et al., 1986; 1987; 1998; Green et al., 1990). Hyaline droplet nephropathy, in which proteins accumulate in renal proximal tubular cells (tubular segment S2), is a condition selectively found in male rats. As discussed above, metabolism of PCE by the glutathione/β-lyase pathway does not occur in appreciable amounts until the P450 oxidative pathway becomes saturated (Dekant et al., 1987).

The mechanism by which PCE causes CNS depression is not yet known. In general, organic solvents are known to accumulate in the CNS, and can become incorporated into brain membranes. Many studies found that repeated exposure to PCE resulted in measurable changes in the fatty acid pattern of phospholipids (primarily ethanolamine phospholipid) and amino acids in brains of rats (Honma et al., 1980; Kyrklund et al., 1988; 1990) and gerbils (Briving et al., 1986; Kyrklund et al., 1984). Rosengren et al. (1985) found that chronic exposure to PCE resulted in atrophy of the front cerebral cortex of the gerbil brain, while astroglial hypertrophy and/or proliferation were indicated in other areas of the brain. Wang et al. (1993) also reported that PCE exposure in rats resulted in a reduced number of brain cells (glial cells), and interfered with the metabolism of cytoskeletal elements in glial and neuronal cells in the brain.

4.3. Structure-Activity Relationships

The use of structure-activity relationships was not necessary for derivation of inhalation exposure guidelines for tetrachloroethylene.

4.4. Other Relevant Information

4.4.1. Interspecies Differences

For differences in species, the reader is referred to Sections 4.1 and 4.2.

4.4.2. Intraspecies Differences

The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature, where the concentrations of various anesthetic gases in the lung which produce "anesthesia" (i.e., lack of movement) have been measured (Gregory et al., 1969; Katoh and Ikeda et al., 1992; Lerman et al., 1983; Matthew et al., 1996; Stevens et al., 1975; LeDez and Lerman, 1987). Values are usually reported as the Minimum Alveolar Concentration (MAC) which produces lack of movement in 50% of persons exposed to that concentration. MAC's for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest MAC) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitive (highest MAC values) are in older infants, toddlers, and children compared to normal adults. The total range of sensitivity is 2-3 fold. Many organic vapors, particularly those which are strongly lipophilic, produce an anesthetic effect in exposed humans. On the basis of this knowledge, it is reasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for PCE.

4.4.3. Concentration-Exposure Duration Relationship

To scale exposure values to AEGL time frames, the equation $C^n \times t = k$ is used, where C = concentration, t = time, k is a constant, and *n* generally ranges from 1 to 3.5 (ten Berge et al.,

1986). The value of *n* used for PCE was the calculated and published value of *n* = 2 (ten Berge et al., 1986) based upon the Rowe et al. (1952) rat mortality data for PCE.

4.4.4. Concurrent Exposures

Studies in humans and animals addressing concurrent exposures to PCE and alcohol or diazepam have not reported any additive or interactive effects (Stewart et al., 1977; 1981; Giovannini et al. 1992)

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Controlled human exposures to PCE have demonstrated CNS effects and irritation. Subjects exposed to 101 ppm for 7 hours reported a number of subjective symptoms including headache, mild eye, nose, or throat irritation, and difficulty speaking, and had an abnormal Romberg test (subject balancing on one foot with his eyes closed and with both arms at his side) the first 3 hours of exposure but a normal Romberg test by the end of the exposure (Stewart et al., 1970). Exposure to 75-80 ppm for 1-4 minutes caused slight eye irritation, and exposure to 194 ppm for 187 minutes resulted in slight lightheadedness and an increased effort to maintain a Romberg test (Stewart et al., 1961b). Rowe et al. (1952) reported that exposure to 106 ppm for 1 hour resulted in very slight eye irritation, and one of six subjects experienced a slight fullness in the head. Unfortunately, no control exposures were included in these studies.

5.2. Animal Data Relevant to AEGL-1

No animal data consistent with the effects defined for an AEGL-1 were available.

5.3. Derivation of AEGL-1

The AEGL-1 derivation is based on the exposure of 6 volunteers to 106 ppm for 1 hour (Rowe et al., 1952). At this level, an apparent non-objectionable odor and eye irritation were noted, and one subject experienced a slight fullness in the head An interspecies uncertainty factor was not applicable. An intraspecies uncertainty factor of 3 was applied because mucous membrane irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect which should not vary over time, the AEGL-1 value was not scaled across time, but rather the same value was applied to all times. AEGL-1 values are presented in Table 10.

TABLE 10. AEGL-1 Values for PCE

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human data consistent with AEGL-2 endpoints were limited. Studies in which effects consistent with an AEGL-2 endpoint were reported did not provide control exposures. Volunteers exposed to 475 ppm for 2 hours, 10 minutes reported salivation, slight eye irritation, tightness in the frontal sinuses, increased hand perspiration, and increased nasal irritation (Carpenter, 1937). One volunteer also felt nauseous, while another felt elated. Following a meal, volunteers were again exposed to 934 ppm for 1 hour, 35 minutes, and reported tightness of the frontal sinuses, increased hand perspiration, nostril irritation, congestion of eustachian tubes, lassitude, slight mental fogginess, stinging eyes, and exhilaration; the tip of the nose and lips were anesthetized in one subject (Carpenter, 1937). Exposure of other subjects to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort (Rowe et al., 1952). Rowe et al. (1952) also reported that exposure to 280 ppm for up to 2 hours resulted in eye irritation, lightheadedness, and impaired motor coordination, but recovery generally occurred within 1 hour. The exact time period of exposure is unknown, because subjects did not necessarily stay in the room for the full 2 hours.

Other CNS data reported effects that were below the definition of an AEGL-2 endpoint. EEG changes consistent with cortical depression were noted in 3/4 male volunteers and 4/5 female volunteers exposed to 100 ppm for 7.5 hours (Stewart et al., 1981). No other changes, such as subjective symptoms or neurological test measurements, were noted at this concentration in male or female volunteers. Exposure to 150 ppm for 7.5 hours resulted only in a reduced score on the Flanagan coordination test (test requires the subject to rapidly follow a spiral pathway with a pencil). Another study by Stewart et al. (1977) also reported a reduced score on the Flanagan coordination test in subjects exposed to 100 ppm for 5.5 hours, but no EEG changes were recorded.

6.2. Animal Data Relevant to AEGL-2

Rats exposed to 2300 ppm for 4 hours/day, 5 days/week for 2 weeks exhibited reversible ataxia, while rats exposed to 1150 ppm for the same period of time did not develop ataxia (Goldberg et al., 1964). Significant changes in flash and somatosensory evoked potentials and in an EEG were observed in rats on the 4th day of exposure to 800 ppm for 6 hours/day, for 4 days (Mattsson et al., 1998). However, these effects were not observed when rats were exposed to up to 800 ppm PCE for 6 hours/day, 5 days/week, for 13 weeks. Rats and mice exposed to 800 ppm for 6 hours/day, 5 days/week for 13 weeks had liver congestion or lesions, respectively (NTP, 1986). Panting and irritation were noted in mice during the 2nd day of exposure.

6.3. Derivation of AEGL-2

The AEGL-2 values are based upon the no-effect level for ataxia in rats following exposure to 1150 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (the time period of 4 hours was used for the derivation) (Goldberg et al., 1964). Exposure to the next higher concentration of 2300 ppm resulted in reversible ataxia. The endpoint of 1150 ppm is supported by the Rowe et al. (1952) study in which rats inhaling 1600 ppm for 7 hours daily over 25 days appeared drowsy or stuporous. A total uncertainty factor of 3 is applied to the no-effect level for ataxia of

1150 ppm. An intraspecies uncertainty factor of 3 is applied based on the previously described argument that the MAC for volatile anesthetics should not vary by more than a factor of 2-3-fold (see section 4.4.2). An interspecies uncertainty factor of 1 would normally be applied based on the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants, giving a total uncertainty factor of 3. However, a total uncertainty factor of 3 would result in AEGL-2 values of 1100, 1100, 770, 380, and 270 ppm for the 10- and 30-minute and 1-, 4-, and 8-hour exposure durations, respectively. These concentrations seem too high when placed in the context of available human data reported by Rowe et al. (1952): exposure of subjects to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort), and exposure to 280 ppm for up to 2 hours resulted in eye irritation, lightheadedness, and impaired motor coordination, with recovery generally occurring within 1 hour. Therefore, the interspecies uncertainty was assigned a factor of 3, resulting in a total uncertainty factor of 10.

The experimentally derived exposure values were then scaled to AEGL time frames using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and *n* is the calculated and published value of *n* = 2 for PCE (ten Berge et al., 1986) based upon the Rowe et al. (1952) rat mortality data. The 10- and 30-minute AEGL-2 values were set equal to the 1-hour value of 230 ppm because a human study demonstrated exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort; Rowe et al., 1952). After applying an uncertainty factor of 3 (for intraspecies variation), the AEGL values based upon this Rowe et al. study are consistent with the 1-hour AEGL-2 value of 230 ppm. AEGL-2 values are presented in Table 11.

TABLE 11. AEGL-2 Values for PCE

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	230 ppm (1600 mg/m^3)	230 ppm (1600 mg/m^3)	230 ppm (1600 mg/m^3)	120 ppm (810 mg/m^3)	81 ppm (550 mg/m^3)

These values are supported by the Carpenter (1937) inhalation study in which volunteers exposed to 475 ppm for 2 hours and 10 minutes reported salivation, slight eye irritation, tightness in the frontal sinuses, increased hand perspiration, and increased nasal irritation. These effects are milder than those defined by AEGL-2. An AEGL derivation based on exposure parameters, a total uncertainty factor of 3 (3 to account for intraspecies variability; an interspecies uncertainty factor not needed because the derivation is based on human data), and an *n* of 2 result in identical AEGL-2 values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Carpenter (1937) reported that exposures to 2000 or 5000 ppm for only a few minutes were intolerable to test subjects. Symptoms reported included faintness, tinnitus, vertigo, eye irritation, nasal congestion, salivation, nausea, retarded mental activity, and dyspnea following exertion. Rowe et al. (1952) reported that exposure to 1060 ppm for 1-2 minutes was intolerable, with volunteers experiencing marked eye and upper respiratory tract irritation and dizziness.

7.2. Animal Data Relevant to AEGL-3

No mortalities were reported in mice exposed to 2450 ppm for 4 hours (Friberg et al., 1953). Rats exposed to 2300 ppm for 4 hours/day, 5 days/week for 2 weeks exhibited overt ataxia following the first 4 hour exposure, but the ataxia disappeared after subsequent exposures (Goldberg et al., 1964). No mortalities were observed in male or female rats exposed to 2445 ppm for 4 hours, but signs of hypoactivity, ataxia, and anesthesia were noted (NTP, 1986). No mortalities occurred in male or female mice exposed to 2445 ppm, but signs of hypoactivity and anesthesia were again noted (NTP, 1986). Two female mice died at the lower concentration of 2328 ppm, but the NTP study did not specifically ascribe the deaths to treatment as it did the mortalities at the higher concentrations. No mortalities were reported in rats repeatedly exposed to 1600 ppm for 7 hours/day, 5 days/week for 18 exposures (Rowe et al., 1952). The rats appeared stuporous or drowsy upon removal from the chamber during the first week of exposure.

7.3. Derivation of AEGL-3

The AEGL-3 derivation is based on one-third of the 4-hour mouse LC_{50} value of 5200 ppm, resulting in a point of departure of 1733 ppm (Friberg et al., 1953). An interspecies uncertainty factor of 1 was applied based on similar exposure effects in humans compared with animals, and pharmacokinetic data indicating an interspecies uncertainty factor for toxicokinetic differences of less than 1 when using rat data to derive exposure values for humans. An intraspecies uncertainty factor of 3 is applied based on the previously described argument that the MAC for volatile anesthetics should not vary by more than a factor of 2-3-fold (see section 4.4.2). The experimentally derived exposure values were scaled to AEGL time frames using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and *n* is the calculated and published value of $n = 2$ for PCE (ten Berge et al., 1986) based upon the Rowe et al. (1952) rat mortality data. The 10-minute value was set equal to the 30-minute value because of the uncertainty in extrapolating from the exposure duration of 4 hours to 10 minutes. AEGL-3 values are presented in Table 12.

TABLE 12. AEGL-3 Values for PCE

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	1600 ppm (11,000 mg/m^3)	1600 ppm (11,000 mg/m^3)	1200 ppm (8100 mg/m^3)	580 ppm 3900 mg/m3	410 ppm 2800 mg/m^3

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values for tetrachloroethylene are summarized in Table 13 AEGL-1 values are based upon mild eye irritation in human volunteers, AEGL-2 values are based upon a no-effect level for ataxia in rats, and the AEGL-3 values are based upon one-third of a mouse 4-hour LC_{50} value.

TABLE 13. Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1 (Nondisabling)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (240 mg/m^3)
AEGL-2 (Disabling)	230 ppm (1600 mg/m^3)	230 ppm (1600 mg/m^3)	230 ppm (1600 mg/m^3)	120 ppm (810 mg/m^3)	81 ppm (550 mg/m^3)
AEGL-3 (Lethal)	1600 ppm (11,000 mg/m^3)	1600 ppm (11,000 mg/m^3)	1200 ppm (8100 mg/m^3)	580 ppm 3900 mg/m3	410 ppm 2800 mg/m^3

A useful way to evaluate the AEGL values in context of existing empirical data is presented in Figure 1. For this plot, the toxic response was placed into severity categories. The severity categories fit into definitions of the AEGL health effects: 0 = no effects; 1 = discomfort; 2 = disabling; 3 = lethal; and PL = partially lethal (an experimental concentration at which some of the animals died and some did not). The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The concentrations often span a number of orders of magnitude, especially when human data exist. Therefore, the concentration is placed on a log scale. The graph in Figure 1 plots the PCE AEGL values along with the existing acute human and animal toxicity data for PCE in terms of the categories assigned to them.

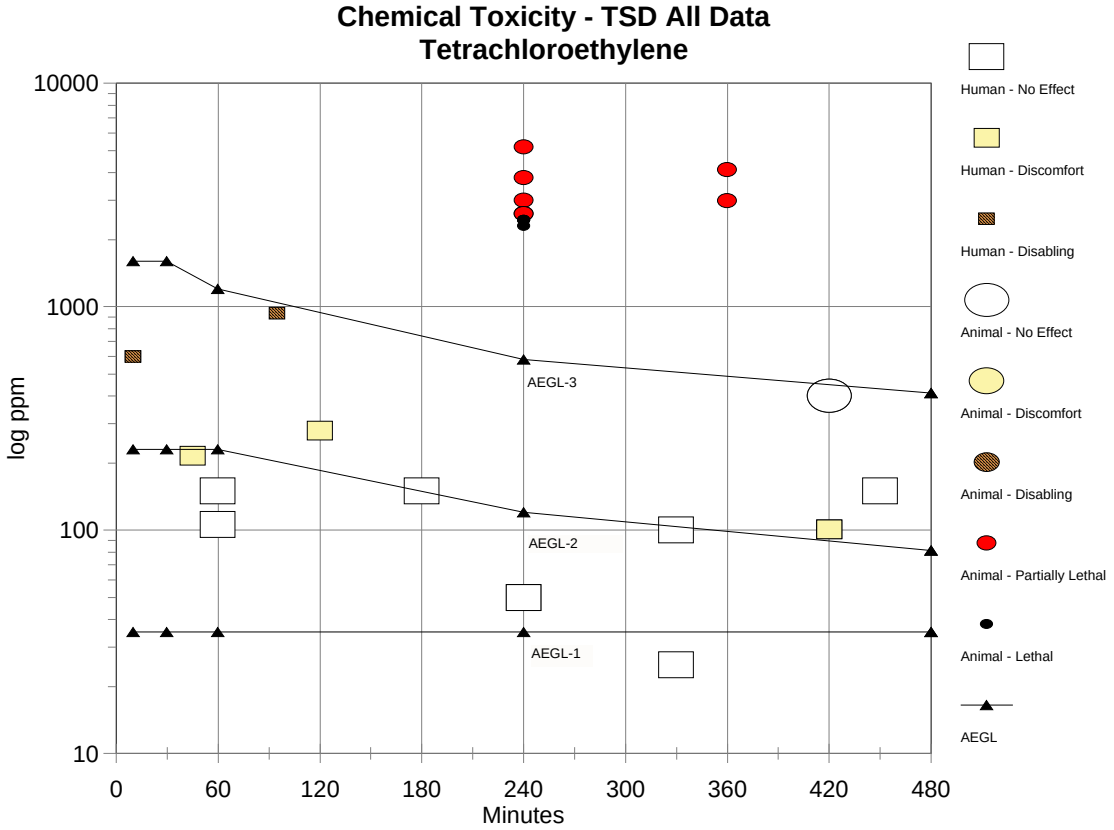

Figure 1. Category Plot of Toxicity Data Compared to AEGL Values.

8.2. Comparisons with Other Standards

Standards and guidance levels for workplace and community exposures are listed in Table 14. No MAK has been established for tetrachloroethylene because it is considered a carcinogen (German Research Association, 2000).

TABLE 14. Extant Standards and Guidelines for PCE (ppm unless otherwise indicated)

Guideline	Exposure Duration					
	5-min	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1		35	35	35	35	35
AEGL-2		230	230	230	120	81
AEGL-3		1600	1600	1200	580	410
ERPG-1 (AIHA)[a]				100		
ERPG-2 (AIHA)				200		
ERPG-3 (AIHA)				1000		
PEL-TWA (OSHA)[b]						100 ppm
Acceptable Ceiling Concentration (OSHA)	200 ppm					
Acceptable Maximum Peak: 5 minutes in any 3 hours (OSHA)	300 ppm					
IDLH (NIOSH)[c]	150					
REL-TWA (NIOSH)[d]						Ca; minimize workplace exposure
TLV-TWA (ACGIH)[e]						25 ppm
STEL-C (ACGIH)[f]		100 ppm				
MAK (Germany)[g]						Cancer
MAC (The Netherlands)[h]						240 mg/m^3 35 ppm

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2008)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1996) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1994; 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1994, 2005)
is defined analogous to the ACGIH-TLV-TWA.

[e]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 1996, 2008)
is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 1996, 2000)
is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[g]**MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [DFG; German Research Association] 2000)
is defined analogous to the ACGIH-TLV-TWA.

[h]**MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000)
is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

The AEGL-1, -2, and -3 levels should be protective of human health. For each of these levels, the values derived from the key studies are supported by another study which results in similar, if not identical, AEGL values. Additionally, the AEGL levels are based on conservative endpoints: the AEGL-1 levels are based on mild irritant effects, the AEGL-2 is based upon a no-effect level for ataxia, and the AEGL-3 is based on one-third of a 4-hour LC_{50} in mice.

9. REFERENCES

Abedin, Z., Cook, R.C., Jr., and Milberg, R.M. 1980. Cardiac toxicity of perchloroethylene (a dry cleaning agent). South. Med. J. 73: 1081-1083.

ACGIH (American Conference of Governmental Industrial Hygienists). 1996. Documentation of the Threshold Limit Values and Biological Exposure Indices: (Tetrachloroethylene). Supplements to the Sixth Ed., ACGIH, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2008. Threshold Limit Values and Biological Exposure Indices: Tetrachloroethylene.

Ahlborg, G. 1990. Pregnancy outcome among women working in laundries and dry-cleaning shops using tetrachloroethylene. Am. J. Ind. Med. 17: 567-575.

AIHA (American Industrial Hygiene Association). 2008. The AIHA 2008 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guidelines Handbook. AIHA, Fairfax VA.

Altmann, L., Böttger, A., and Wiegand, H. 1990. Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans. Int. Arch. Occup. Environ. Health 62: 493-499.

Altmann, L., Neuhann, H.-Florian, Krämer, U., Witten, J., and Jermann, E. 1995. Neurobehavioral and neurophysiological outcome of chronic low-level tetrachloroethene exposure measured in neighborhoods of dry cleaning shops. Environ. Res. 69: 83-89.

Altmann, L., Wiegand, H., Böttger, A., Elstermeier, F., and Winneke, G. 1992. Neurobehavioral and neurophysiological outcomes of acute repeated perchloroethylene exposure. Applied Psychology: an International Review. 41: 269-279

Andrýs, C., Hanovcová, I., Chýlková, V., Tejral, J., Eminger, S., and Procházková, J. 1997. Immunological monitoring of dry-cleaning shop workers-exposure to tetrachloroethylene. Centr. Eur. J. Publ. Health 5: 136-142.

Anttila, A., Pukkala, E., Sallmén, M., Hernberg, S., and Hemminki, K. 1995. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J. Occup. Environ. Med. 37: 797-806.

Aranyi, C., O'Shea, W.J., Graham, J.A., and Miller, F.J. 1986. The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fund. Appl. Toxicol. 6: 713-720.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Tetrachloroethylene (Update). Atlanta, GA: U.S. Department of Health and Human Services, U.S. Public Health Service.

Axelsson, B., Forssman, S., Goldberg, L., and Skog, E. 1953. Potentiating effect of hypoxia on the anesthetic action of organic volatile anesthetics. Arch. Int. Pharmacodyn. Ther. 95: 333-350.

Beliles, R.P., Brusick, D.J., and Mecler, F.J. 1980. Teratogenic-mutagenic risk of workplace contaminants: trichloroethylene, perchloroethylene, and carbon disulfide. Conducted by Litton Biogenetics, Inc., 5516 Nicholson Ln., Kensington, MD 20795. Submitted by Shell Oil Company on April 24, 1992, EPA/OTS; Doc. # 88-920001972.

Bergamaschi, E., Mutti, A., Bocchi, M.C., Alinovi, R., Olivetti, G., Ghiggeri, G.M., and Franchini, I. 1992. Rat model of perchloroethylene-induced renal dysfunctions. Environ. Res. 59: 427-439.

Birner, G., Rutkowska, A., and Dekant, W. 1996. N-acetyl-S-(1,1,2-trichlorocinyl)-L-cysteine and 2,2,2-trichloroethanol: two novel metabolites of tetrachloroethene in humans after occupational exposure. Drug Metab. Disp. 24: 41-48.

Blair, A., Stewart, P.A., Tolbert, P.E., Grauman, D., Moran, F.X., Vaught, J., and Rayner, J. 1990. Cancer and other causes of death among a cohort of dry cleaners. Br. J. Ind. Med. 47: 162-168.

Bois, F.Y., Gelman, A., Jiang, J., Maszle, D.R., Zeise, L., and Alexeef, G. 1996. Population toxicokinetics of tetrachloroethylene. Arch. Toxicol. 70: 347-355.

Bonnet, P., Francin, J.M., Gradiski, D., Raoult, G., and Zissu, D. 1980. Détermination de la concentration léthale$_{50}$ des principaux hydrocarbures aliphatiques chlorés chez le rat. Arch. Mal. Prof., 41: 317-321.

Bosco, M.G., Figá-Talamanca, I., and Salerno, S. 1987. Health and reproductive status of female workers in dry cleaning shops. Int. Arch. Occup. Environ. Health 59: 295-301.

Briving, C., Jacobson, I., Hamberger, A., Kjellstrand, P., Haglid, K.G., and Rosengren, L.E. 1986. Chronic effects of perchloroethylene and trichloroethylene on the gerbil brain amino acids and glutathione. NeuroToxicology 7: 101-108.

Brodkin, C.A., Daniell, W., Checkoway, H., Echeverria, D., Johnson, J., Wang, K., Sohaey, R., Green, D., Redlich, C., Gretch, D., and Rosenstock, L. 1995. Hepatic ultrasonic changes in workers exposed to perchloroethylene. Occup. Environ. Med. 52: 679-685.

Buben, J.A., and O'Flaherty, E.J. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. Toxicol. App. Pharmacol. 78: 105-122.

Budavari, S. M.J. O'Neil, A. Smith, P.E. Heckelman and J.F. Kinneary (Eds.). 1996. The Merck Index, 12th ed. Merck & Co., Inc., Rahway, NJ.

Byczkowski, J.Z. and Fisher, J.W. 1994. Lactational transfer of tetrachloroethylene in rats. Risk Analysis 14: 339-349.

Byczkowski, J.Z. and Fisher, J.W. 1995. A computer program linking a physiologically based pharmacokinetic model with cancer risk assessment for breast-fed infants. Comp. Meth. and Prog. Biomed. 46: 155-163.

Cai, S.-X., Huang, M.-Y., Chen, Z., Liu, Y.-T., Jin, C., Watanabe, T., Nakatsuka, H., Seiji, K., Inoue, O., and Ikeda, M. 1991. Subjective symptoms increase among dry-cleaning workers exposed to tetrachloroethylene vapor. Ind. Health 29: 111-121.

Cavalleri, A., Gobba, F., Palrinieri, M., Fantuzzi, G., Righi, E., and Aggazzitti, G. 1994. Perchloroethylene exposure can induce colour vision loss. Neuroscience Let. 179: 162-166.

Carpenter, C.P. 1937. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol. 19: 323-336.

Costa, A.K., and Ivanetich, K.M. 1980. Tetrachloroethylene metabolism by the hepatic microsomal cytochrome P-450 system. Biochem. Pharmacol. 29: 2863-2869.

Crump, K.S., and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk. Anal. 4:163-176.

Dallas, C.E., Chen, X.M., Muralidhara, S., Varkonyi, P., Tackett, R.L., and Bruckner, J.V. 1994. Use of tissue disposition data from rats and dogs to determine differences in input parameters for a physiological model for perchloroethylene. Environ. Research 67: 54-67.

De Ceaurriz, J., Desiles, J.P., Bonnet, P., Marignac, B., Muller, J., and Guenier, J.P. 1983. Concentration-dependent behavioral changes in mice following short-term exposure to various industrial solvents. Toxicol. Appl. Pharmacol. 67: 383-389.

Dekant, W., Martens, G., Vamvaka, S., Metzler, M., and Henschler, D. 1987. Bioactivation of tetrachlorotheylene. Role of glutathione S-transferase-catalyzed conjugation versus cytochrome P-450 dependent phospholipid alkylation. Drug Metab. Dispos. 15: 702-709.

Dekant, W., Metzler, M., and Henschler, D. 1986. Identification of S-1,1,2-trichlorovivnly-N-acetylcysteine as a urinary metabolite of tetrachloroethylene: bioactivation through glutathione conjugation as a possible explanation of its nephrotoxicity. J. Biochem. Toxicol. 1: 57-72.

Dekant, W., Mirner, G., Werner, M., and Parker, J. 1998. Glutathione conjugation of perchloroethene in subcellular fractions from rodent and human liver and kidney. Chemico-Biolog. Interactions 116: 31-43.

DFG (Deutsche Forschungsgemeinschaft; German Research Association). 2000. List of MAK and BAT Values, 2000. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Federal Republic of Germany: Wiley-VCH.

Doyle, P., Roman, E., Beral, V., and Brookes, M. 1997. Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. Occup. Environ. Med. 54: 848-853.

Dow Chemical Company. 1991. Initial submission: study of acute neurophysiologic effects of 1,1,2,2-tetrachloroethylene in rats (final report) with cover letter dated 060492. Submitted by Dow Chemical Company, EPA/OTS; Doc # 88-920003407.

Echeverria, D., White, R.F., and Sampaio, C. 1995. A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects. J. Occup. Environ. Med. 37: 667-680.

Eskenazi, B., Fenster, L., Hudes, M., Wyrobek, A.J., Katz, D.F., Gerson, J., Rempel, D.M. 1991a. A study of the effect of perchloroethylene exposure on the reproductive outcomes of wives of dry-cleaning workers. Am. J. Ind. Med. 20: 593-600.

Eskenazi, B., Wyrobek, A.J., Fenster, L., Katz, D.F., Sadler, M., Lee, J., Hudes, M., Rempel, D.M. 1991b. A study of the effect of perchloroethylene exposure on semen quality in dry cleaning workers. Am. J. Ind. Med. 20: 575-591.

Fernandez, J., Guberan, E., and Caperos, J. 1976. Experimental human exposures to tetrachloroethylene vapor and elimination in breath after inhalation. Amer. Ind. Hyg. Assoc. J. 37: 143-150.

Ferroni, C., Selis, A., Mutti, A., Folli, D., Bergamaschi, E., and Franchini, I. 1992. Neurobehavioral and neuroendocrine effects of occupational exposure to perchloroethylene. NeuroToxicology. 13: 243-248.

Franchini, I., Cavatorta, A., Falzoi, M., Lucertini, S., and Mutti, A. 1983. Early indicators of renal damage in workers exposed to organic solvents. Int. Arch. Environ. Health. 52: 1-9.

Friberg, L., Kylin, B., and Nyström, Å. 1953. Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyrindine-alkali reaction. Acta Pharmacol. et Toxicol. 9: 303-312.

Gaillard, Y., Billault, F., and Pépin, G. 1995. Tetrachloroethylene fatality: case report and simple gas chromatographic determination in blood and tissues. Forensic Sci. Int. 76: 161-168.

Gehring, P.J. 1968. Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice. Toxicol. Appl. Pharmacol. 13: 287-298.

Gennari, P., Naldi, M., Motta, R., Nucci, M.C., Giacomini, C., Violante, F.S., Raffi, G.B. 1992. Gamma-glutamyltransferase isoenzyme pattern in workers exposed to tetrachloroethylene. Am. J. Ind. Med. 21: 661-671.

Giovannini, L., Guglielmi, G., Casini, T., Bertelli, A., Galmozzi, E., and Bertelli, A.A.E. 1992. Effect of ethanol chronic use on hepatotoxicity in rats exposed to tetrachloroethylene. Int. J. Tiss. Reac. 14: 281-285.

Goldberg, M.E., Johnson, H.E., Pozzani, U.C., and Smyth, H.F. 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvent vapors on pole-climb performance in rats. Am. J. Ind. Hyg. 25: 369-375.

Green, T., Odum, J., Nash, J.A., Foster, J.R. 1990. Perchloroethylene-induced rat kidney tumors: an investigation of the mechanisms involved and their relevance to humans. Toxicol. Appl. Pharmacol. 103: 77-89.

Gregory, G.A., Eger, E.I., and Munson, E.S. 1969. The relationship between age and halomethane requirements in man. Anesthesiology. 30: 488-491.

Hardin, B.D., Bond, G.P., Sikov, M.R., Andrew, F.D., Beliles, R.P., and Niemeier, R.W. 1981. Testing of selected workplace chemicals for teratogenic potential. Scan. J. Work Environ. Health (suppl.)4:66-75.

Hattis, D., White, P., and Koch, P. 1993. Uncertainties in pharmacokinetic modeling for perchloroethylene: II. Comparison of model predictions with data for a variety of different parameters. Risk Analysis 13: 599-610.

Hattis, D., White, P., Marmorstein, L., and Koch, P. 1990. Uncertainties in pharmacokinetic modeling for perchloroethylene. I. Comparison of model structure, parameters, and predictions for low-dose metabolism rates for models derived by different authors. Risk Analysis 10: 449-458.

Hemminki, K., Franssila, E., Vainio, H., et al. 1980a. Spontaneous abortion among female chemical workers in Finland. Int. Arch. Occup. Environ. Health 45: 123-126.

Hemminki, K., Saloniemi, I., Luoma, K., et al. 1980b. Transplacental carcinogens and mutagens: Childhood cancer, malformation and abortions as risk indicators. J. Toxicol. Environ. Health 6: 1115-1126.

Henschler, D. 1977. Metabolism and mutagenicity of halogenated olefins: a comparison of structure and activity. Environ. Health Perspect. 21: 61-64.

Honma, T., Hasegawa, H., Sato, M., and Sudo, A. 1980. Changes in free amino acid content in rat brain after exposure to trichloroethylene and tetrachloroethylene. Ind. Health 18: 1-7.

Honma, T., Sudo, A., Miyagawa, M., Sato, M., and Hasegawa, H. 1990. Effects of exposure to trichloroetheylene and tetrachloroethylene on the contents of acetylcholine, dopamine, norepinephrine, and serotonin in rat brain. Ind. Health 18: 171-178.

IARC (International Agency for Research on Cancer). 1995. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 63. Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. Lyon, France: International Agency for Research on Cancer, pp. 159-221.

Ikeda, M., Koizumi, A., Watanabe, T., Endo, A., and Sato, K. 1980. Cytogenic and cytokinetic investigations on lymphocytes from workers occupationally exposed to tetrachloroethylene. Toxicol. Let. 5: 251-256.

Ikeda, M., Ohtsuji, H., Imamura, T., and Komoike, Y. 1972. Urinary excretion of total trichloro-compounds, trichloroethanol, and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. Brit. J. Ind. Med. 29: 328-333.

Isenschmid, D.S., Cassin, B.J., Hepler, B.R., and Kanluen, S. 1998. Tetrachloroethylene intoxication in an autoerotic fatality. J. Forensic Sci. 43: 231-234.

Jang, J-Y. and Droz, P.O. 1997. Ethnic differences in biological monitoring of several organic solvents. II. A simulation study with a physiologically based pharmacokinetic model. Int. Arch. Occup. Environ. Health 70: 41-50.

Jang, J-Y., Droz, P.O., and Berode, M. 1997. Ethnic differences in biological monitoring of several organic solvents. I. Human exposure experiment. Int. Arch. Occup. Environ. Health 69: 343-349.

Janssen, P.J.M. 1990. Acute inhalation study to investigate the respiratory irritating properties of tetrachloroethylene in male rats. Duphar, B.V., Department of Toxicology, Weesp, The Netherlands, Report No. S.8923. Sponsored and conducted by Solvay Corp.

Katoh, T., and Ikeda, K. 1992. Minimum alveolar concentration of seroflurane in children. Brit. J. Anaesth. 68: 139-141.

Kjellstrand, P., Holmquist, B., Jonsson, I., Romare, S., and Månsson, L. 1985. Effects of organic solvents on motor activity in mice. Toxicology 35: 35-46.

Kukongviriyapan, V., Kukongviriyapan, U., and Stacey, N.H. 1990. Interference with hepatocellular substrate uptake by 1,1,1-trichloroethane and tetrachloroethylene. Toxicol. Appl. Pharmacol. 102: 80-90.

Kulig, B.M., Lammers, J.H.C.M., and Jaspers, R.M.A. 1992. Acute and persistent neurotoxic effects of perchloroethylene in the rat [Abstract]. Toxicologist 12: 276.

Kylin, B., Reichard, H., Sümegi, I., and Yllner, S. 1963. Hepatotoxicity of inhaled trichloroethylene, tetrachloroethylene and chloroform. Single exposure. Acta Pharmacol. et Toxicol. 20: 16-26.

Kylin, B., Sümegi, I., and Yllner, S. 1965. Hepatotoxicity of inhaled trichloroethylene and tetrachloroethylene. Long-term exposure. Acta Pharmacol. et Toxicol. 22: 379-385.

Kyrklund, T., Alling, C., Kjellstrand, P., and Haglig, K.G. 1984. Chronic effects of perchloroethylene on the composition of lipid and acyl groups in cerebral cortex and hippocampus of the gerbil. Toxicol. Let. 22: 343-349.

Kyrklund, T., and Haglid, K.G. 1989. Brain lipid and fatty acid composition of the cerebral cortex of guinea pig pups after intrauterine exposure to perchloroethylene [Abstract]. J. Neurochem. 52: S115.

Kyrklund, T., and Haglid, K.G. 1991. Brain lipid composition in guinea pig pups after intrauterine exposure to perchloroethylene. Pharmacol. Toxicol. 68: 146-148.

Kyrklund, T., Kjellstrand, P., and Haglid, K.G. 1988. Effects of exposure to Freon 11, 1,1,1-trichloroethylene or perchloroethylene on the lipid and fatty-acid composition of rat cerebral cortex. Scan. J. Work Environ. Health 14: 91-94.

Kyrklund, T., Kjellstrand, P., and Haglid, K.G. 1990. Long-term exposure of rats to perchloroethylene, with and without a post-exposure solvent-free recovery period: effects on brain lipids. Toxicol. Let. 52: 279-285.

Kyyrönen, P., Taskinen, H., Lindbohm, M.-J., Hemminki, K., and Heinonen, O.P. 1989. Spontaneous abortions and congenital malformations among women exposed to tetrachloroethylene in dry cleaning. J. Epi. Community Health 43: 346-351.

Lauwerys, R., Herbrand, J., Buchet, J.P., Bernard, A., and Gaussin, J. 1983. Health surveillance of workers exposed to tetrachloroethylene in dry-cleaning shops. Int. Arch. Environ. Health 52: 69-77.

LeDez, K.M., and Lerman, J. 1987. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology. 67: 301-307.

Lerman, J., Robinson, S., Willis, M.M., and Gregory, G.A. 1983. Anesthetic requirements for halothane in young children 0-1 months and 1-6 months of age. Anesthesiology. 59: 421-424.

Levine, B., Fierro, M.F., Goza, S.W., and Valentour, J.C. 1981. A tetrachloroethylene fatality. J. Forensic Sci. 26: 206-209.

Lide, D.R. and Frederikse, H.P.R. (editors). 1993. CRC Handbook of Chemistry and Physics, 74th Edition, pp. 16-24.

Ling, S., and Lindsay, W.A. 1971. Perchloroethylene burns. Br. Med. J. 3:115.

Lukaszewski, T. 1979. Acute tetrachloroethylene fatality. Clin. Toxicol. 15: 411-415.

Manson, J.M., Tepe, S.J., Sowry, B., and Hastings, L. 1981. Postnatal evaluation of offspring exposed prenatally to perchloroethylene. Department of Environmental Health, University of Cincinnati, Cincinnati, OH, 45267. Submitted by Dow Chemical Company September 4, 1987, EPA/OTS; Doc. # 86-870002174.

Matthew, M.T.V., Mainland, P., and Gin, T. 1996. Minimum alveolar concentration of halothane and enflurane are decreased in early pregnancy. 85: 782-786.

Mattsson, J.L., Albee, R.R., Yano, B.L., Bradley, G.J., and Spencer, P.J. 1998. Neurotoxicologic examination of rats exposed to 1, 1, 2, 2-tetrachloroethylene (perchloroethylene) vapor for 13 weeks. Neurotoxicol. Teratol. 20: 83-98.

McDonald, A.D., Armstrong, B., Cherry, N.M., Delorme, C., Diodati-Nolim, A., McDonald, J.C., and Robert, D. 1986. Spontaneous abortion and occupation. J. Occup. Med. 28: 1232-1238.

McLaughlin, J.K., and Blot, W.J. 1997. A critical review of epidemiology studies of trichloroethylene and perchloroethylene and risk of renal-cell cancer. Int. Arch. Occup. Environ. Health 70: 222-231.

Meckler, L.C., and Phelps, D.K. 1966. Liver disease secondary to tetrachloroethylene exposure. J. Am. Med. Assoc. 197: 144-145.

Mennear, J., Maronpot, R., Boorman, G., Eustis, S., Huff, J., Haseman, J., McConnell, E., Ragan, H., and Miller, R. 1986. Toxicologic and carcinogenic effects of inhaled tetrachloroethylene in rats and mice. Dev. Toxicol. Environ. Science 12: 201-210.

Monster, A.C., Boersma, G., and Steenwegl;, H. 1979. Kinetics of tetrachloroethylene in volunteers; influence of exposure concentration and work load. Int. Arch. Occup. Environ. Health 42: 303-309.

Moslen, M.T., Reynolds, E.S., and Szabo, S. 1977. Enhancement of the metabolism and hepatotoxicity of trichloroethylene and perchloroethylene. Biochem. Pharmacol. 26: 369-375.

Mutti, A., Alinovi, R., Bergamaschi, E., Biagini, C., Cavazzini, S., Franchini I., Lauwerys, R.R., Bernard, A.M., Roels, H., Gelpi, E., Rosello, J., Ramis, I., Price, R.G., Taylor, S.A., DeBroe, M., Nuyts, G.D., Stolte, H., Fels, L.M., and Herbort, C. 1992. Nephropathies and exposure to perchloroethylene in dry-cleaners. Lancet 340: 189-193.

Nakatsuka, H., Watanabe, T., Takeuchi, Y., Hisanaga, N., Shibata, E., Suzuki, H., Huang, M.-Y, Chen, Z., Qu, Q.-S., and Ikeda, M. 1992. Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below occupational exposure limits. Int. Arch. Occup. Environ. Health 64: 113-117.

National Cancer Institute. 1977. Bioassay of tetrachloroethylene for possible carcinogenicity. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publ. (NIH) 77-183.

Nelson, B.K., Taylor, B.J., Setzer, J.V., and Hornung, R.W. 1980. Behavioral teratology of perchloroethylene in rats. J. Environ. Pathol. Toxicol. 3: 233-250.

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. NIOSH Publication 94-116, U.S. Department of Health and Human Services; U.S. Government Printing Office, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHS). National Institute for Occupational Safety and Health, Cincinnati, OH; PB94195047, National Technical Information Service, Springfield, VA.

NRC (National Research Council). 1986. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-term Public Emergency Guidance Level (SPEGL), and

Continuous Exposure Guidance Level (CEGL) Documents. Committee on Toxicology, National Academy Press, Washington, D.C., pp. 25-27.

NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in F344/N Rats and B6C3F_1 Mice (Inhalation Studies). NTP TR 311, NIH Publ. No. 86-2567, U.S. Department of Health and Human Services, Research Triangle Park, NC.

Odum, J., Green, T., Foster, J.R., and Hext, P.M. 1988. The role of trichloroacetic acid and peroxisome proliferation in the differences in carcinogenicity of perchloroethylene in the mouse and rat. Toxicol. Appl. Pharmacol. 92: 103-112.

Ogata, M., Takasuka, Y., and Tomokuni, K. 1971. Excretion of organic chlorine compounds in the urine of persons exposed to vapors of trichloroethylene and tetrachloroethylene. Brit. J. Ind. Med. 28: 386-391.

Ohtsuki, T., Sato, K., Koizumi, A., Kumai, M., and Ikeda, M. 1983. Limited capacity of humans to metabolize tetrachloroethylene. Int. Arch. Occup. Environ. Health 51: 381-390.

Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyrönen, P., Taskinen, H., Lindbohm, M.-J., Heinonen, O.P., Brandt, L., Kolstad, H., Halvorsen, B.A., and Egenæs, J. 1990. Low birth weight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia. Scan. J. Work Environ. Health 16: 163-168.

Onofrj, M., Thomas, A., Paci, C., D'Andreamatteo, G., Toma, L., and Rotilio, D. 1999. Optic neuritis with residual tunnel vision in perchloroethylene toxicity. Eur. Neur. 41: 51-53.

Opdam, J.J.G., and Smolders, J.F.J. 1986. Alveolar sampling and fast kinetics of tetrachloroethylene in man. I. Alveolar sampling. 43: 814-824.

OSHA. 1996. Limits for Air Contaminants. CFR, Title 29, Part 1910.1000, Table Z-1, p. 19.

Patel, R., Janakiraman, N., Johnson, R., and Elman, J. 1973. Pulmonary edema and coma from perchloroethylene. J. Amer. Med. Assoc. 223: 1510.

Pegg, D.G., Zempel, J.A., Braun, W.H., and Watanabe, P.G. 1979. Disposition of tetrachloro(^{14}C)ethylene following oral and inhalation exposure in rats. Toxicol. Appl. Pharmacol. 51: 465-474.

Piper, W.N. and Sparschu, G.L. 1969. A comparison of the inhalation toxicity of 1,1,1,2-tetrachloroethylene and perchloroethylene in the rat. Biochemical Research Laboratory. Submitted by Dow Chemical Company September 4, 1987, EPA/OTS; Doc. # 86-870002181.

Rampy, L.W., Quast, J.F., Balmer, M.F., Leong, B.K.J., and Gehring, P.J. 1978. Results of a long-term inhalation toxicity study on rats of a perchloroethylene (tetrachloroethylene) formulation. Dow Chemical Company. Submitted by Dow Chemical September 4, 1987, EPA/OTS; Doc. # 86-870002178.

Reichert, D. 1983. Biological actions and interactions of tetrachloroethylene. Mut. Res. 123: 411-429.

Reinhardt, C.F., Mullin, L.S., Maxfield, M.E. 1973. Epinephrine-induced cardiac arrhythmia potential of some common industrial solvents. J. Occ. Med. 15: 953-955.

Reitz, R.H., Gargas, M.L., Mendrala, A.L., and Schumann, A.M. 1996. *In vivo* and *in vitro* studies of perchloroethylene metabolism for physiologically based pharmacokinetic modeling in rats, mice, and humans. Toxicol. Appl. Pharmacol. 136: 289-306.

Rosengren, L.E., Kjullstrand, P., and Hadlid, K.G. 1985. Tetrachloroethylene: levels of DNA and S-100 in the Gerbil CNS after chronic exposure. Neurobehav. Toxicol. Teratol. 8: 201-206.

Rowe, V.K., McCollister, D.D., Spencer, H.C., Adams, E.M., and Irish, D.D. 1952. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. AMA Arch. Ind. Hyg. Occup. Med. 5: 566-579.

Ruder, A.M., Ward, E.M., and Brown, D.P. 1994. Cancer mortality in female and male dry-cleaning workers. J. Occup. Med. 36: 867-874.

Saland, G. 1967. Accidental exposure to perchloroethylene. N.Y. State J. Med. 67: 2359-2361.

Savolainen, H., Pfäffli, P., Tengén, M., and Vainio, H. 1977. Biochemical and behavioral effects of inhalation exposure to tetrachloroethylene and dichloromethane. J. Neuorpathol. Exp. Neurol. 36: 941-949.

Sax, N. I. and R. J. S. Lewis, Eds. 1989. Dangerous Properties of Industrial Materials, 7th ed. Van Nostrand Reinhold Co., Inc., 3, New York..

Schreiber, J.S. 1993. Predicted infant exposure to tetrachloroethylene in human breastmilk. Risk Analysis 13: 515-524.

Schumann, A.M., Quast, J.F., and Watanabe, P.G. 1980. The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. Toxicol. Appl. Pharmacol. 55: 207-219.

Schwetz, B.A., Leong, B.K.J., and Gehring, P.J. 1975. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal developmental in mice and rats. Toxicol. Appl. Pharmacol. 32: 84-96.

SDU Uitgevers (Ministry of Social Affairs and Employment). 2000. Nationale MAC (Maximum Allowable Concentration) List, 2000. The Hague, The Netherlands.

Seeber, A. 1989. Neurobehavioral toxicity of long-term exposure to tetrachloroethylene. Neurotoxicol. Teratol. 2: 579-583.

Seiji, K., Jin, C., Watanabe, T., Nakatsuka, H., and Ikeda, M. 1990. Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene, or tetrachloroethylene, with reference to smoking habits. Int. Arch. Occup. Environ. Health 62: 171-176.

Solet, D., and Robins, T.G. 1991. Renal function in dry cleaning workers exposed to perchloroethylene. Am. J. Ind. Med. 20: 601-614.

Spirtas, R., Stewart, P.A., Lee, J.S., Marano, D.E., Forbes, C.D., Grauman, D.J., Pettigrew, H.M., Blair, A., Hoover, R.N., and Cohen, J.L. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br. J. Ind. Med. 48: 515-530.

Stevens, W.C., Dolan, W.M., Gibbons, R.T., White, A., Eger, E.I., Miller, R., deJong, R.H., and Elashoff, R.M. 1975. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology. 42: 196-200.

Stewart, R.D. 1969. Acute tetrachloroethylene intoxication. J. Amer. Med. Assoc. 208: 1490-1492.

Stewart, R.D., Baretta. E.D., and Dodd, H.C. 1970. Experimental human exposure to tetrachloroethylene. Arch. Environ. Health 20: 224-229.

Stewart, R.D., Erley, D.S., Sachaffer, A.W., and Gay, H.H. 1961a. Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene . Ind. Med. Surg. 30: 327-330.

Stewart, R.D., Gay, H.H., Erley, D.S., Hake, C.L., and Schaffer, A.W. 1961b. Human exposure to tetrachloroethylene vapor. Arch. Environ. Health 2: 40-46.

Stewart, R.D., Hake, C.L., Forster, H.V., Lebrun, A.J., Peterson, J.E,, and Wu, A. 1981. Tetrachloroethylene: development of a biologic standard for the industrial worker by breath analysis. Cincinnati, OH: National Institute for Occupational Safety and Health. Contract no. HSM 99-72-84. NIOSH-MCOW-ENVM-PCE-74-6. NTIS No. PB82-152166.

Stewart, R.D., Hake, C.L., Wu, A, Kalbfleisch, J., N ewton, P.E., Marlow, S.K., and Vucicevic-Salama, M. 1977. Effects of perchloroethylene/drug interaction on behavior and neurological function. Final Report. Cincinnati, OH: National Institute for Occupational Safety and Health. Contract no. CDC 201-75-0059. NTIS No. PB83-174607.

Suzaki, H., Aoki, A., and Nomura, Y. 1997. Regeneration of olfactory mucosa in mice after inhalation exposure to perchloroethylene. ORL 59: 91-96.

ten Berge, W.F., Zwart, A., and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mat. 13: 301-309.

Tepe, S.J., Dorfmueller, M.A., York, R.G., and Manson, J.M. 1980. Teratogenic evaluation of perchloroethylene in rats. Department of Environmental Health, University of Cincinnati, Cincinnati, OH, 45267. Submitted by Dow Chemical Company September 4, 1987, EPA/OTS; Doc. # 86-870002175.

Tinston, D.J. 1995. Perchloroethylene: multigenerational inhalation study in the rat. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No.: CTL/P/4097. Submitted by Halogenated Solvents Industry Alliance, Inc. on July 6, 1995, EPA/OTS; Doc. # 88-950000190.

U.S. EPA (U.S. Environmental Protection Agency). 1985. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Prepared by the Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/005F. Available from: National Technical Information Service, Springfield, VA; PB-85-249704/AS.

U.S. EPA (U.S. Environmental Protection Agency). 1986. Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Prepared by the Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/005FA. Available from: National Technical Information Service, Springfield, VA; PB-86-174489/AS.

U.S. EPA (Environmental Protection Agency). 1992. Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990. Office of Research and Development, Washington, D.C.

U.S. EPA (U.S. Environmental Protection Agency). 1997. IRIS. Tetrachloroethylene.

van der Gulden, J.W.J. and Zielhuis, G.A. 1989. Reproductive hazards related to perchloroethylene. Int. Arch. Occup. Environ. Med. 61: 235-242.

Vaughan, T.L., Stewart, P.A., Davis, S., and Thomas, D.B. 1997. Work in dry cleaning and the incidence of cancer of the oral cavity, larynx, and oesophagus. Occup. Environ. Med. 54: 692-695.

Vyskoćil, A., Emminger, S., Tejral, J., Fiala, Z., Ettlerova, E., and Cermanovà, A. 1990. Study on kidney function in female workers exposed to perchloroethylene. Hum. Exp. Toxicol. 9: 377-380.

Wang, S., Karlsson, J.-E., Kyrklund, T., and Haglid, K. 1993. Perchloroethylene-induced reduction in glial and neuronal cell marker proteins in rat brain. Pharmacol. Toxicol. 72: 273-278.

Ward, R.C., Travis, C.C., Hetrick, D.M., Andersen, M.E., and Gargas, M.L. 1988. Pharmacokinetics of tetrachloroethylene. Toxicol. Appl. Pharmacol. 93: 108-117.

Windham, G.C., Shusterman, D., Swan, S.H., Fenster, L., and Eskenazi, B. 1991. Exposure to organic solvents and adverse pregnancy outcome. Am. J. Ind. Med. 20: 241-259.

Yllner, S. 1961. Urinary metabolites of ^{14}C-tetrachloroethylene in mice. Nature 191: 820.

APPENDIX A: DERIVATION OF AEGL VALUES

AEGL-1

Key study:	Rowe et al., 1952
Toxicity endpoint:	106 ppm for 1 hour resulted in eye irritation in the 6 exposed volunteers, and a slight fullness in the head noted by one subject.
Scaling:	The derived value was set equal for all AEGL time-points because the endpoint is irritation, which is not expected to vary over time.
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability
Modifying factor:	None applied
Calculations:	C/Uncertainty factor = 106 ppm/3 = 35 ppm

10-minute, 30-minute, 1-hour, 4-hour, 8-hour AEGL-1: 35 ppm across all time points because the endpoint is irritation.

AEGL-2

Key study:	Goldberg et al., 1964
Toxicity endpoint:	No-effect level for ataxia in rats exposed to 1150 ppm for 4 hours/day, 5 days/week for 2 weeks (4 hour duration used in derivation)
Scaling:	$C^n \times t = k$ where n = 2.0; calculated and published value based upon rat mortality data (ten Berge et al., 1986)
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	None applied
Calculations:	$(C/\text{Uncertainty Factors})^2 \times t = k$ $[(1150 \text{ ppm})/10]^2 \times 4 \text{ hr} = 52900 \text{ ppm hr}$
10-and 30-min AEGL-2	The 10-and 30-minute value was set equal to the 1-hour value of 230 ppm because a human study demonstrated an exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort; Rowe et al., 1952)
1-hr AEGL-2	$C^2 \times 1 \text{ hr} = 52900 \text{ ppm hr}$ $C^2 = 52900 \text{ ppm}$ $C = 230 \text{ ppm}$
4-hr AEGL-2	$C^2 \times 4 \text{ hr} = 52900 \text{ ppm hr}$ $C^2 = 13225 \text{ ppm}$ $C = 115 \text{ ppm} = 120 \text{ ppm}$
8-hr AEGL-2	$C^2 \times 8 \text{ hr} = 52900 \text{ ppm}$ $C^2 = 6612.5 \text{ ppm}$ $C = 81.3 \text{ ppm} = 81 \text{ ppm}$

AEGL-3

Key study:	Friberg et al., 1953
Toxicity endpoint:	One-third of the 4-hour mouse LC_{50} of 5200 ppm = 1733 ppm
Scaling:	$C^n \times t = k$ where n = 2.0; calculated and published value based upon rat mortality data (ten Berge et al., 1986)
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 3
Modifying factor:	None applied
Calculations:	$(C/\text{Uncertainty Factors})^2 \times t = k$ $[(1733 \text{ ppm})/3]^2 \times 4 \text{ hr} = 1{,}334{,}795 \text{ ppm hr}$
10-min AEGL-3	The 10-minute value was set equal to 30-minute value of 1600 ppm because of the uncertainty in extrapolating from 4 hours to 10 minutes.
30-min AEGL-3	$C^2 \times 0.5 \text{ hr} = 1{,}334{,}795 \text{ ppm·hr}$ $C^2 = 2669590 \text{ ppm}$ $C = 1637 \text{ ppm} = 1600 \text{ ppm}$
1-hr AEGL-3	$C^2 \times 1 \text{ hr} = 1{,}334{,}795 \text{ ppm·hr}$ $C^2 = 1{,}334{,}795 \text{ ppm}$ $C = 1155 \text{ ppm} = 1200 \text{ ppm}$
4-hr AEGL-3	$C^2 \times 4 \text{ hr} = 1{,}334{,}795 \text{ ppm·hr}$ $C^2 = 333{,}699 \text{ ppm}$ $C = 578 \text{ ppm} = 580 \text{ ppm}$
8-hr AEGL-3	$C^2 \times 8 \text{ hr} = 1{,}334{,}795 \text{ ppm·hr}$ $C^2 = 166{,}849 \text{ ppm}$ $C = 408 \text{ ppm} = 410 \text{ ppm}$

APPENDIX B: CARCINOGENICITY ASSESSMENT

PRELIMINARY CANCER ASSESSMENT OF TETRACHLOROETHYLENE

No inhalation slope factor is available for tetrachloroethylene in the U.S. EPA Integrated Risk Information System (IRIS). An inhalation risk estimate was proposed in a 1985 Health Assessment Document for Tetrachloroethylene (U.S. EPA, 1985) and was revised in 1986 (U.S. EPA, 1986). The proposed inhalation risk estimate has not yet been verified by the IRIS CRAVE Workgroup, and is currently for internal use at the U.S. EPA. The proposed inhalation slope factor is 2.0×10^{-3} per mg/kg/day, which, based upon a human inhalation rate of 20 m^3/d and a body weight of 70 kg, is equivalent to 5.7×10^{-4} $(mg/m^3)^{-1}$.

The calculations for AEGL values following the method presented by NRC (1986) are presented below:

To calculate a "virtually safe dose" (VSD of d) at a cancer risk of 10^{-4}:

dose = risk/slope
$d = (1 \times 10^{-4})/(5.7 \times 10^{-4}\ (mg/m^3)^{-1}) = 0.175\ mg/m^3$

To convert a 70-y exposure to a 24-h exposure, the virtually safe dose is multiplied by the number of days in 70 yr:

$total\ d = d \times 25{,}600 = 0.175\ mg/m^3 \times 25{,}600 = 4480\ mg/m^3$

To adjust for uncertainties in assessing potential cancer risks for short-term exposures under the multistage model, the 24-h exposure is divided by an adjustment factor of 6 (Crump and Howe, 1984).

$(4480\ mg/m^3)/6 = 747\ mg/m^3$ (112 ppm)

Therefore, a single exposure to tetrachloroethylene at 747 mg/m^3 (112 ppm) for 24 hours would present a cancer risk of 10^{-4}.

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f x 24 h (NRC, 1986).

24 hours	=	747 mg/m^3 (112 ppm)
8 hours	=	2241 mg/m^3 (336 ppm)
4 hours	=	4482 mg/m^3 (672 ppm)
1 hour	=	17,928 mg/m^3 (2689 ppm)
0.5 hour	=	35,856 mg/m^3 (5378 ppm)
0.167 hour	=	107,353 mg/m^3 (16,103 ppm)

These values based on carcinogenicity exceed the values based on acute toxicity and are therefore not proposed for AEGL-3. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

REFERENCES

Crump, K.S., and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk. Anal. 4:163-176.

NRC (National Research Council). 1986. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents. Committee on Toxicology, National Academy Press, Washington, D.C., pp. 25-27.

U.S. EPA (U.S. Environmental Protection Agency). 1985. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Prepared by the Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/005F. Available from: National Technical Information Service, Springfield, VA; PB-85-249704/AS.

U.S. EPA (U.S. Environmental Protection Agency). 1986. Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Prepared by the Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/005FA. Available from: National Technical Information Service, Springfield, VA; PB-86-174489/AS.

APPENDIX C: DERIVATION SUMMARY FOR TETRACHLOROETHYLENE AEGLS

ACUTE EXPOSURE GUIDELINE LEVELS FOR TETRACHLOROETHYLENE (CAS Reg. No. 127-18-4) DERIVATION SUMMARY

AEGL-1 VALUES				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
35 ppm	**35 ppm**	**35 ppm**	**35 ppm**	**35 ppm**

Key Reference:
Rowe, V.K., McCollister, D.D., Spencer, H.C., Adams, E.M., and Irish, D.D. 1952. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. AMA Arch. Ind. Hyg. Occup. Med. 5: 566-579.

Test Species/Strain/Number: 6 Hman volunteers

Exposure Route/Concentrations/Durations: Inhalation: 106 ppm for 1 hour

Effects: Mild eye irritation

Endpoint/Concentration/Rationale: 106 ppm for 1 hour resulted only in mild eye irritation

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable
Intraspecies: 3 - applied because mucous membrane irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals.

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: value set equal across time because endpoint is irritancy and the response is not expected to vary greatly with time

Data Adequacy: The AEGL-1 level is based upon a conservative endpoint: eye irritation. The values are consistent with values that would be obtained based on a study addressing minor central nervous effects.

1

AEGL-2 VALUES				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
230 ppm	**230 ppm**	**230 ppm**	**120 ppm**	**81 ppm**

Key Reference:
Goldberg, M.E., Johnson, H.E., Pozzani, U.C., and Smyth, H.F. 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvent vapors on pole-climb performance in rats. Am. J. Ind. Hyg. 25: 369-375.

Test Species/Strain/Sex/Number: Groups of 8-10 female rats (Carworth Farms Elias)

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to 0, 1150, or 2300 ppm for 4 hours/day 5 days/week for 2 weeks.

Effects: No effects were observed at 0 or 1150 ppm. Rats exposed to 2300 ppm displayed overt ataxia during the first 4-hour exposure, resulting in an 80% loss of both avoidance and escape responses. This effect was not observed during subsequent exposures.

Endpoint/Concentration/Rationale: Exposure to 1150 ppm for 4 hours was a no-effect level for overt ataxia

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 - An interspecies uncertainty factor of 1 would normally be applied based on the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants, giving a total uncertainty factor of 3. However, a total uncertainty factor of 3 would result in AEGL-2 values of 1100, 1100, 770, 380, and 270 ppm for the 10- and 30-minute and 1-, 4-, and 8-hour exposure durations, respectively. These concentrations seem too high when placed in the context of available human data reported by Rowe et al. (1952): exposure of subjects to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination requiring great effort), and exposure to 280 ppm for up to 2 hours resulted in eye irritation, lightheadedness, and impaired motor coordination, with recovery generally occurring within 1 hour. Therefore, the interspecies uncertainty was assigned a factor of 3, resulting in a total uncertainty factor of 10.

Intraspecies: 3 - An intraspecies uncertainty factor of 3 is applied because the Minimum Alveolar Concentration (MAC; the concentration that produces lack of movement in 50% of persons exposed) for volatile anesthetics does not vary by more than a factor of 2-3-fold.

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$ where $n = 2.0$; derived by ten Berge et al. (1986) from rat mortality data presented in Rowe et al. (1952). The 10-and 30-minute value was set equal to the 1-hour value because a human study demonstrated an exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort)

Data Adequacy: The AEGL-2 level is based upon a conservative endpoint: a no-effect level for reversible ataxia in rats. The values are supported by human data in which the effects noted were milder than those defined by the AEGL-2 definition.

1

AEGL-3 VALUES				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
1600 ppm	**1600 ppm**	**1200 ppm**	**580 ppm**	**410 ppm**

Key Reference:
Friberg, L., Kylin, B., and Nyström, Å. 1953. Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyrindine-alkali reaction. Acta Pharmacol. et Toxicol. 9: 303-312.

Test Species/Strain/Sex/Number:
Groups of 8 female white mice (Friberg et al., 1953)

Exposure Route/Concentrations/Durations: Inhalation for 4 hours to:
2450, 3000, 3950, 5200, 5900, 6750, 7250, or 8900 ppm PCE (Friberg et al., 1953)

Effects: Mortality occurred in all groups exposed to 3000 ppm or higher (Friberg et al., 1953)

Endpoint/Concentration/Rationale:
4-hour LC_{50} of 5200 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - An UF of 1 was applied based on similar exposure effects in humans compared with animals, and pharmacokinetic data indicating an interspecies uncertainty factor for toxicokinetic differences of less than 1 when using rat data to derive exposure values for humans.
Intraspecies: 3 - An intraspecies uncertainty factor of 3 is applied because the Minimum Alveolar Concentration (MAC; the concentration that produces lack of movement in 50% of persons exposed) for volatile anesthetics does not vary by more than a factor of 2-3-fold.

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$ where $n = 2.0$; derived by ten Berge et al. (1986) from rat mortality data presented in Rowe et al. (1952). Because of the uncertainty in extrapolating from 4 hours to 10 minutes, the 10-minute value was set equal to the 30-minute value of 1600 ppm.

Dat**a Adequacy:** The AEGL-3 level is based on one-third of an LC_{50} in mice mice. The values are supported by a human study in which the effects noted were milder than those defined by the AEGL-3 definition and another animal study with the endpoint of reversible ataxia.

2