1,1,1-TRICHLOROETHANE
CAS REG. NO. 71-55-06

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For
NAS/COT Subcommittee for AEGLs

June 2000

INTERIM 1: 6/2000

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

1,1,1-TRICHLOROETHANE
CAS REG. NO. 71-55-06

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. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 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 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 odor, taste, and sensory irritation, or certain non-symptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

TABLE OF CONTENTS

TABLE OF CONTINUED

LIST OF TABLES

FIGURE

EXECUTIVE SUMMARY

1,1,1-Trichloroethane is a colorless, nonflammable liquid used primarily as an industrial metal degreasing agent. It is also used as a solvent for adhesives, inks, and coatings and as an aerosol propellant (Kirk-Othmer, 1991; WHO, 1992). Solvent vapor is readily absorbed from the respiratory tract and distributed throughout the body, accumulating in tissues with high lipid content. In both humans and animals, the primary response to acute inhalation exposures involves effects on the central nervous system (CNS). This chemical is arrhythmogenic and there is some evidence that it produces transient hepatotoxicity (McLeod et al., 1987; Stahl et al., 1969; Hodgson et al., 1989). It has little effect on other organs and is not a reproductive/ developmental toxicant at concentrations that are not maternally toxic, although reliable epidemiological data for humans are unavailable. 1,1,1-Trichloroethane did not demonstrate carcinogenic activity based on the available animal studies. A considerable amount of human and animal data are available for derivation of AEGLs. Rat ataxia and lethality data were used for the regression analyses of the concentration-exposure durations. The relationship between time and concentration was $C^n \times t = k$, where n = 3.3 based on ataxia in rats and 3 based on lethality in the rat.

The AEGL-1 was based on consistent complaints of eye irritation and slight dizziness experienced by humans in an atmosphere controlled setting with exposures of 450 ppm for two 4-hour sessions separated by a 1.5 hour interval (Salvini et al., 1971). The 4-hour exposure duration was chosen as the relevant time period for these effects. An intraspecies uncertainty factor of 2 was applied based on the observation that the severity of the eye irritation did not increase with time and the threshold for mild CNS effects does not vary by more than 2-3 fold among individuals. The resulting value of 230 ppm was used for all AEGL-1 time points based on the information reported by Salvini et al. (1971) indicating that this exposure represented a threshold for these effects and the severity did not increase with duration of exposure. This value is supported by several additional studies with human subjects. Torkelson et al. (1958) reported a NOAEL for the Romberg test in humans after exposure to a TWA of 506 ppm for 7.5 hours. Exposure of healthy human subjects to 500 ppm for 78 or 186 minutes resulted in only mild eye irritation (Stewart et al., 1961). Repeated exposures to 500 ppm for 7 hours for 5 days resulted in a consistent complaint of mild sleepiness, and two of the subjects that initially had trouble performing the Romberg test, were unable to do so during the exposure; all other neurological tests were performed normally by these two subjects (Stewart et al., 1969).

The AEGL-2 was based on more serious CNS effects which might impede escape. Mullin and Krivanek (1982) calculated EC_{50} values for ataxia in rats at 30 minutes and 1-, 2-, and 4-hour exposures to be 6740, 6000, 4240, and 3780 ppm, respectively. These individual values were used as the basis for the respective AEGL-2 values using an uncertainty factor of 10. Extrapolations were made to the 10-minute and 8 hour time points using the equation $C^n \times t = k$, where n = 3.3 based on the data presented by Mullin and Krivanek (1982). The uncertainty factor of 10 includes a factor of 3 to account for sensitive individuals and a factor of 3 for interspecies extrapolation. These uncertainty factors were based on the 2-3 fold variation of Minimum Alveolar Concentration (MAC) values among humans and the similarities in toxicity, metabolism, and excretion of 1,1,1-trichloroethane in rats compared to humans. The resulting concentrations are similar to the concentrations and exposure durations in experimental human studies that resulted in effects that could impede escape, i.e., CNS intoxication.

The AEGL-3 values were derived from a lethality concentration-effect curve in the rat for a 6-hour exposure-duration (Bonnet et al., 1980). The concentration causing no deaths was conservatively estimated from this curve as a concentration of 7000 ppm for a 6-hour exposure duration. An extrapolation was made to the 30 minute and 1-, 4-, and 8-hour time points using the equation $C^n \times t = k$, where n = 3 based on the rat lethality data. A total uncertainty factor of 3 was applied. An intraspecies factor of 3 was used to account for sensitive individuals based on the 2-3 fold variation of MAC values observed among humans and an interspecies factor of 1 was used because of the similarities in toxicity, metabolism, and excretion of 1,1,1-trichloroethane in the rat compared with humans. The interspecies uncertainty factor of 1 is justified by the existence of a higher blood:air partition coefficient for rodents compared to humans. This principle determines the relative blood concentration for a vapor and because it is higher in rats than humans by a two-fold factor at the same exposure concentration, a higher blood concentration is achieved in rats.

The calculated values are listed in the table below.

Summary of Interim Values for 1,1,1-Trichloroethane [ppm (mg/m^3)]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	230 (1255)	230 (1255)	230 (1255)	230 (1255)	230 (1255)	Eye irritation and slight dizziness in humans (Salvini et al., 1971)
AEGL-2 (Disabling)	930 (5074)	670 (3656)	600 (3274)	380 (2073)	310 (1691)	EC_{50} for ataxia in rats (Mullin and Krivanek, 1982)
AEGL-3[a] (Lethal)	4200 (22,915)	4200 (22,915)	4200 (22,915)	2700 (14,731)	2100 (11,458)	Estimated concentration causing no deaths in rats (Bonnet et al., 1980)

[a] The 1-hour value was used as the 10-minute and 30-minute values so as not to exceed the threshold for cardiac sensitization of 5000 ppm observed in dogs (Reinhardt et al., 1973).

References

Bonnet, P., J.M. Francin, D. Gradiski, G. Raoult, and D. Zissu. 1980. Determination of the median lethal concentration of principle chlorinated aliphatic hydrocarbons in the rat. Arch. Mal. Prof. 41:317-321.

Mullin, L.S., and N.D. Krivanek. 1982. Comparison of unconditioned avoidance tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, and toluene or ethanol. Neurotoxicol. 3:126-137.

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

Salvini, M., S. Binaschi, M. Riva. 1971. Evaluation of the psychophysiological functions in humans exposed to the threshold limit value of 1,1,1-trichloroethane. Brit. J. Ind. Med. 28:286-292.

1. INTRODUCTION

1,1,1-Trichloroethane is a colorless liquid with a sweet pungent odor detectable at about 100 ppm. It is manufactured from vinyl chloride or vinylidene chloride by chlorination. It was first prepared in 1840 by Regnault. World production was reported at 680,000 tons in 1988. The primary use of this solvent is metal degreasing and cleaning of various electrical equipment, electronic components, and instruments, missile hardware, paint masks, photographic film, printed circuit boards, and various metal and certain plastics components during manufacture (Kirk-Othmer, 1991). Other uses include pesticides, textile processing, cutting fluids, aerosols, lubricants, cutting oil formulations, drain cleaners, shoe polishes, spot cleaners, printing inks, correction fluids, and stain repellents (WHO, 1992).

Inhalation is the primary route of exposure for both occupationally exposed individuals and the general population. Workers have been chronically exposed to concentrations up to 249 ppm with no untoward effects (Kramer, 1978). Concentrations of up to 65 ppb have been determined in air sampled near industrial sites (ATSDR, 1995).

1,1,1-Trichloroethane is rapidly absorbed into the respiratory tract after inhalation exposures to the vapor; it is then widely distributed in the body tissues and readily crosses the blood-brain and placental barriers. After cessation of exposure, clearance of the chemical from the blood is rapid; 60-80% is eliminated within 2 hours, and greater than 95% is eliminated within 50 hours (Astrand et al., 1973; Monster et al., 1979; Nolan et al., 1984). The biological half-life as measured by its presence in human urine is 8.7 ± 1.8 hours (NIOSH, 1979). 1,1,1-Trichloroethane is largely excreted unchanged in exhaled air regardless of the route of exposure. Less than 10% is metabolized to trichloroethanol and its glucuronide conjugate, trichloroacetic acid, and carbon dioxide (ATSDR, 1995; Nolan et al., 1984). The trichloroethanol and trichloroacetic acid metabolites have much longer half-lives than 1,1,1-trichloroethane itself (27 and 76 hours, respectively) and may accumulate with repeated exposures (Nolan et al., 1984).

The primary mechanism of toxicity in humans and in animals is manifested as CNS effects. Observable effects range from slight behavioral changes (accompanied by eye irritation in humans) at 500 ppm to unconsciousness and respiratory arrest at higher concentrations (10,000-30,000 ppm). There is some limited evidence that exposure to 1,1,1-trichloroethane may be associated with transient hepatotoxic effects. No adequate epidemiological data on the carcinogenic potential of this compound in humans exists. However, a chronic inhalation study conducted by Quast et al. (1988) in rats and mice exposed to 1500 ppm revealed no evidence of any carcinogenic effect. Developmental toxicity, but not teratogenicity, in the form of developmental delays has been identified in rats and rabbits at concentrations that produced maternal toxicity. No developmental effects have been identified in humans. Limited epidemiological evidence on possible reproductive effects is inconclusive.

The chemical and physical properties of 1,1,1-trichloroethane are given in Table 1.

TABLE 1. Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Methyl chloroform, chlorotene, methyltrichloromethane, trichloroethane, α-trichloroethane, trichloromethylmethane	ATSDR, 1995
CAS registry no.	71-55-6	www.chemfinder.com, 1999
Chemical formula	CCl_3CH_3	www.chemfinder.com, 1999
Molecular weight	133.4	www.chemfinder.com, 1999
Physical state	clear liquid	www.chemfinder.com, 1999
Vapor pressure	103 mm at 20°C	Weast, 1986
Vapor density (air = 1)	4.6	HSDB, 1999
Specific gravity	1.3249 (26/4°C)	Torkelson, 1994
Boiling/flash point	74.1°C	Torkelson, 1994
Melting point	-30.4°C	HSDB, 1999
log Kow	2.49	HSDB, 1999
Solubility in water	0.480 g/L at 20 °C	Pearson, 1982
Conversion factors in air	1 ppm in air = 5.456 mg/m^3	ACGIH, 1999
Odor threshold	390 ppm detection, 710 ppm recognition (range 16-714 ppm)	AIHA, 1999

2. HUMAN TOXICITY DATA

The acute toxicity of inhaled 1,1,1-trichloroethane in mammalian species is low. The primary response to high concentrations is depression of the central nervous system. There is little capacity to produce organ injury from either single or repeated exposures, possibly as a result of the minimal metabolism of the compound. High concentrations, particularly in confined spaces can sensitize the heart to epinephrine, possibly leading in some cases to death (Torkelson, 1994).

2.1. Acute Lethality

2.1.1. Case Reports

Droz et al. (1982) reported on two cases of sudden cardiac death after intentional inhalation of 1,1,1-trichloroethane. In one case, a 17-yr-old male filled a 6 L can with 2 L of 1,1,1-trichloroethane, and began inhaling. He was found by his foreman in a semi-conscious state with his shoulders shaking from spasms. Another person arrived and found no pulse or respiration, resuscitative efforts were undertaken, and spontaneous cardiac activity was achieved. Upon arrival at the hospital, cerebral death was diagnosed. Another young male (20-yr-old) intentionally inhaled 1,1,1-trichloroethane from a soaked rag. He vomited and collapsed about five minutes later, extensive resuscitative efforts failed. The authors devised an elaborate scheme to recreate the abuse situations in order to approximate the levels of 1,1,1-trichloroethane to which

these victims were exposed. They determined that in the first case, the boy exposed himself to between 6000 and 14,000 ppm, and in the second case, the young man exposed himself to concentrations between 10,000 and 20,000 ppm. Other situations of intentional intoxications which resulted in fatalities have been reported by Gowitt and Hanzlick (1992) and Hall and Hine (1966). These cases included young to middle age men who were abusing 1,1,1-trichloroethane recreationally.

Two case reports of fatal exposures to 1,1,1-trichloroethane were reported by Jones and Winter (1983). In both cases, the deaths were the result of occupational exposures in which the solvent was being used as a degreasing agent. In the first case, a 20-yr-old male was using 1,1,1-trichloroethane from an open bowl in an enclosed area, he was found dead 2 hours after having been seen alive by a coworker. The blood concentration of the solvent was 42.0 mg/L and the brain concentration was 1230.0 mg/kg. Death resulted from suppression of the respiratory center secondary to severe central nervous system depression. In the second case, a 17-yr-old male cleaning car upholstery with 1,1,1-trichloroethane was found unconscious with his head on the floor and was transferred to a hospital by ambulance but was dead on arrival. Post-mortem examination revealed a blood solvent concentration of 18 mg/L; the brain and liver contained 80 mg/kg. The cause of death was designated as solvent intoxication with aspiration of vomitus. A simulation exercise revealed that the victim could have been inhaling 36-440 ppm in an upright position, however concentrations of solvent on the floor, where he was found could have been as high as 6410 ppm.

Six cases of fatal exposure to 1,1,1-trichloroethane were analyzed by Stahl et al. (1969) from the forensic pathology records of the Armed Forces Institute of Pathology. In each case, young men aged 17-24 yr were cleaning or stripping paint with 1,1,1-trichloroethane in enclosed spaces and were found dead by their coworkers. The post-mortem autopsies of the deceased revealed congested lungs, liver, spleen, kidneys, and brain as well as edematous lungs and evidence of a prolonged period of cyanosis. Blood concentrations of 1,1,1-trichloroethane in these cases ranged between 1.5-120.0 mg/L (275 - 22,000 ppm). Other occupational exposures resulting in fatalities under similar circumstances were described by NIOSH (1986), Silverstein (1983), and Bonventre et al. (1977).

Two accidental deaths resulting from the use of 1,1,1-trichloroethane in home repair projects were reported by Bonventre et al. (1977) and Caplan et al. (1976). In both cases the decedents were working in confined spaces using large amounts of solvent. The autopsy findings were similar to those described above. One case involved a middle-aged house-wife and the other involved a thirteen-year-old boy.

In a paper by Bass (1970), several reports of what the author characterizes as “sudden sniffing death syndrome” (SSD) are described. The eyewitness accounts of the events prior to death in these case reports were similar and included 1) inhalation of volatile hydrocarbons from a bag, 2) panic, 3) physical exertion (usually running about 200 yds), and 4) sudden collapse and death. This sequalae is characterized by the author as being the result of severe cardiac arrhythmia associated with fulminant pulmonary edema, the excitement of a light plane anesthesia, hyperadrenergic crisis, or some combination of these and maybe unknown factors. The author suggests a mechanism of action involving sensitization of the myocardium by volatile

hydrocarbons and subsequent physical exertion coalescing to produce sudden and severe arrhythmia.

2.1.2. Epidemiologic Studies

The results of an epidemiologic survey conducted by Bass (1970) revealed that abuse of 1,1,1-trichloroethane was associated with 29 deaths in the United States between 1964-1969.

Anderson et al. (1982) determined that between 1971-1981 there were 140 deaths in the United Kingdom due to volatile solvent abuse; the rate of occurrence was about 30 deaths per year. The median ages of the deceased ranged from 11 to 63, the median age was 16.8 years. In 79% of these cases, the victims were under age 20 and the male:female ratio was 3:1. Twenty of these deaths were associated with abuse of products containing 1,1,1-trichloroethane as the primary solvent.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Ingber (1991) reported a rare case of severe acute hand eczema in a metal factory worker. The patient had been using 1,1,1-trichloroethane to clean metal plates. Patch testing with 1,1,1-trichloroethane in olive oil gave positive results at 1, 0.1, and 0.01 % dilutions. Five control subjects were also tested and no positive responses were obtained even at the highest concentration.

Hodgson et al. (1989) reported on four cases of fatty liver disease that were associated with exposure to 1,1,1-trichloroethane. The patients in these four cases had heavy occupational exposure to 1,1,1-trichloroethane for periods of 1 - 19 years that consisted of working near heated and cold 1,1,1-trichloroethane tanks, and cleaning various machine parts. Other risk factors for liver disease could not be identified among these workers with the exception of obesity in two of the cases. The authors state that 1,1,1-trichloroethane could be a potential hepatotoxin in humans after substantial chronic exposure. Some discussion on the lack of an association between 1,1,1-trichloroethane exposure and hepatoxicity as well as the exact circumstances of exposure and recovery (transient vs. chronic and/or preexisting disease) was published in the form of letters to the editor concerning these case reports by Guzelian (1991) and a reply to these questions by Hodgson and Van Thiel (1991). However, another case of transient liver damage combined with renal damage, associated with 1,1,1-trichloroethane intoxication was reported by Halevy et al. (1980). The medical history for this patient revealed an episode of hepatitis that could have contributed to his vulnerability in this case. This patient made a full recovery.

Two case reports presented by McLeod et al. (1987) indicate that 1,1,1-trichloroethane produces chronic cardiac toxicity after chronic inhalation exposures to the solvent. In the first case, a 14-year-old boy had been abusing 1,1,1-trichloroethane and was administered halothane for anesthesia during a routine tonsillectomy. During the procedure he developed multiple ventricular extra systoles, but was successfully treated with drugs and his condition improved. After the operation, he continued to experience arrhythmias and a pacemaker was inserted. Six months later, he was asymptomatic. In the second case, a 54 year old man had been heavily exposed to 1,1,1-trichloroethane occupationally and developed atrial fibrillation and congestive

heart failure. After his condition stabilized, he did not return to work. He was given general halothane anesthesia a few years later for inguinal hernia repair and again developed symptoms of congestive heart failure.

A case of sensory peripheral neuropathy associated with 1,1,1-trichloroethane exposure was presented by House et al. (1994). In this case, a woman who had daily occupational exposure to 1,1,1-trichloroethane developed peripheral sensory neuropathy. Her symptoms consisted of perioral tingling and a burning sensation on her tongue as well as discomfort in her hands and feet including cramping which made it difficult to stand or walk. These symptoms were accompanied by reduced amplitudes of sural sensory responses. Her condition improved rapidly after discontinuing the exposure.

Two similar cases of peripheral sensory neuropathy were described by Liss (1988). In these cases, two women were exposed to 1,1,1-trichloroethane occupationally for several hours a day while they were cleaning motors for appliances. The first patient presented with numbness in all limbs. The second patient presented with numbness in the hands and cheeks. Nerve-conduction studies revealed prolongation of the median distal sensory latency and ulnar motor distal sensory latencies.

The incidence of industrial solvent intoxication involving 1,1,1-trichloroethane in Great Britain from 1961-80 was described by McCarthy and Jones (1983). Fifty-two intoxications were reported, and 2 deaths resulted from these exposures. Most of these cases involved use of 1,1,1-trichloroethane in the cold portable form.

2.2.2. Occupational Exposures

Kramer et al. (1978) conducted an epidemiologic study of 151 matched pairs of employees in two adjacent textile plants owned by Burlington Industries, NC. In the study plant, 1,1,1-trichloroethane was used as a cleaning solvent, but was not used in the control plant. The study population was exposed to the solvent for 6 years or less at varying concentrations. Each job classification was assigned to one of 5 concentration categories based on the current sampling data and knowledge of various job descriptions, these assignments were based on the TWA level of exposure. There were 11 employees exposed to <15 ppm, 5 were exposed to 15-49 ppm, 19 were exposed to 50-99 ppm, 48 were exposed to 100-149 ppm, and 68 were exposed to 150-249 ppm. No recognizable clinical pattern nor any evidence of adverse effects from exposure to the solvent were identified based on ECG monitoring, hepatic function as measured by enzyme levels, or renal function as measured by monitoring of blood urea nitrogen. Also, no CNS effects were reported for even the highest exposure group. Therefore, ~250 ppm is recognized as a NOAEL for chronic occupational exposure to 1,1,1-trichloroethane.

Maroni et al. (1977) examined the neurophysiological and behavioral effects of 1,1,1-trichloroethane among female workers who were exposed to concentrations of solvent ranging from 110 - 990 ppm. Only one person was exposed to concentrations as high as 990 ppm; all of the other subjects were exposed to concentrations $\geq$350 ppm. An unexposed group of female workers served as the control group. No significant differences were observed between the exposed and unexposed females with respect to clinical features, maximal motor conduction

velocity, conduction velocity of slow fibers, and psychometric data. The exposed workers had a slightly (not statistically significant) higher incidence of headache and anxiety.

2.2.3. Experimental Studies

The CNS effects produced in humans under experimental conditions are summarized in Table 2. Several of these tests measure very subtle effects on the CNS and do not necessarily indicate cognitive or equilibrium impairment. The modified Romberg test for example is a measure of equilibrium with the eyes closed while balancing on one foot and does not necessarily indicate loss of equilibrium when the eyes are open. In these studies impairment of the Romberg test indicates a very subtle effect on the CNS.

The effect of inhalation exposure to 200 or 400 ppm 1,1,1-trichloroethane for 4 hours on visual evoked potentials (VEP) among nine healthy human males (aged 20-25) was evaluated by Seppalainen et al. (1983). The VEP represents a response to a visual stimulus which is characterized as the summed neuronal electrical activity produced as a result of the stimulus. Changes in amplitude, timing, and shape of the waveforms can be measured to determine the effect of CNS depressants and stimulants. The 400 ppm concentration produced significant changes in the pattern-VEP, namely the latency of the start of the cortical response was decreased. The significance of this effect is obscured because a concentration-effect relationship was not established and a CNS depressant or anesthetic is expected to produce an increase in latency and a decrease in amplitude.

Savolainen et al. (1982) examined the effects of a 4-hour inhalation exposure to 200 and 400 ppm (TWA) on the psychophysiological function of nine healthy males. The battery of behavioral test included a questionnaire to determine the perceived effects, tests for body sway and nystagmus, reaction time, and flicker fusion. These tests were performed before the exposures began, twice during the exposure, and once after the exposure. None of the parameters were adversely effected as a result of these exposures.

In a similar study, Laine et al. (1996) examined the effects of an inhalation exposure to 200 ppm on the VEP, electroencephalograms (EEG), and body sway of nine healthy males, ages 21-24 years. The initial exposure lasted 3 hours and was followed by a 40-minute break. The subjects returned to the chambers for an additional 40 minutes. Each subject exercised with a bicycle ergometer for 10 minutes at the beginning of each session. The following day the subjects were exposed to morning and afternoon sessions starting with an initial concentration of 135 ppm and followed by a transient peak concentrations of 400 ppm. The transient peak was generated over a 20-minute period at the beginning of each session. EEG reading from a control session showed that exercise induced an increase in the dominant alpha frequency and, after an initial drop, an increase in the alpha percentage with a concomitant decrease in theta whereas delta and beta bands remained unaffected. Exposure to 1,1,1-trichloroethane did not affect the alpha, theta, or delta activities but induced changes in beta during the morning recordings at the peak exposure. The body sway tended to decrease slightly during the fluctuating exposure and the later peaks in VEPs showed slight prolongations. The authors concluded that there were no deleterious effects of exposure.

Mackay et al. (1987) exposed twelve healthy male volunteers to measured concentrations of 0, 175, or 350 ppm for 3.5 hours with peppermint oil used to mask the odor of the solvent. Neurobehavioral testing was performed immediately before the experiment and at four separate time periods during each of the exposures, 20, 60, 120, and 180 minutes after entry. No subjective symptoms were reported by the participants and the measure of mood as determined by a self-reported stress and arousal test revealed no significant effects. This finding indicates that in humans this solvent may produce subtle effects on the CNS without a subjective sense of untoward effects. The authors reported changes in performance on the neurobehavioral tests which occurred early on in the exposure period. The results of this experiment are difficult to interpret because the data are not reported with respect to concentration-effect changes and statistical significance compared to the control. Simple reaction time was the most sensitive test as shown by an increase with respect to concentration and duration. A complicated cognitive task, the Stroop test, showed improvement in performance with increasing concentration and duration of exposure.

Stewart et al. (1961) conducted several experiments using healthy human male subjects, ages 30 to 60 years. Controlled exposures to measured concentrations of 1,1,1-trichloroethane were carried out in a chamber. Six subjects were exposed to 500 ppm for 78 minutes with only mild eye irritation reported by 3/6 volunteers. After this exposure, blood concentrations of all six subjects ranged from 1.5 to 6.0 ppm (0.01 - 0.03 mg/L) within 30, 60, and 75 minutes after the exposure. In the next experiment, 6 male volunteers were exposed to 500 ppm for 186 minutes with no untoward effects reported. When three subjects were exposed to 955 ppm for 73 minutes, greater mental effort was required to perform the Romberg test (a test of postural stability with the eyes closed) and 1/3 subjects still had a positive Romberg test 15 minutes after the exposure had ended. Two subjects were exposed to 910 ppm for 35 minutes, one person reported a feeling of lightheadedness, and greater mental effort was required to perform the Romberg test. After three subjects were exposed to 900 ppm for 20 minutes, one subject had a positive Romberg test, and again greater mental effort was required in order to perform this test after the exposure. In the last experiment, 7 subjects were exposed to a constantly increasing atmospheric concentration of 1,1,1-trichloroethane ranging from 0 to 2650 ppm over a 15-minute period. At concentrations ranging from 0 - 1000 ppm subjects stated that they were aware of a sweet odor, from 1000 - 1100 ppm, 6 of 7 subjects reported mild eye irritation, 1900 - 2000 ppm produced mild throat irritation in 6 of 7 subjects, at 2600 ppm one subject stated that he felt very lightheaded, and at 2650 ppm 2 subjects were unable to stand, 3 subjects felt very lightheaded, and 6 subjects demonstrated a normal Romberg test. Subjects exposed at the highest concentration complained of feelings of malaise that lasted approximately three hours after the experiment.

TABLE 2. Effects of Exposure to 1,1,1-Trichloroethane in Humans

Concentration (ppm)	Duration	Effect	Reference
200	3 hours	no effects on visual evoked potential, body sway, EEG	Laine et al., 1996
250	0.5 hours	NOAEL for reaction time and perceptual speed	Gamberale and Hultengren, 1973

TABLE 2. Effects of Exposure to 1,1,1-Trichloroethane in Humans

Concentration (ppm)	Duration	Effect	Reference
350	0.5 hours	subtle but statistically significant changes in perceptual speed	Gamberale and Hultengren, 1973
400 TWA	4 hours	NOAEL for body sway, reaction time and critical flicker fusion	Savolainen et al., 1982
400	4 hours	⇓ latency of cortical response for Visually Evoked Potentials	Seppalainen et al., 1983
450	0.5 hours	subtle but statistically significant changes in perceptual speed, reaction time, manual dexterity	Gamberale and Hultengren, 1973
450 TWA	4 hours, 2 sessions, 1.5 hour interval	eye irritation, slight dizziness and mental fatigue (symptoms did not increase in severity during the second session)	Salvini et al., 1971
500 (440-561)	6.5 - 7 hours, 5/days	mild sleepiness, abnormal Romberg test	Stewart et al., 1969
546 (450-710)	1.5 hours	subjective NOAEL normal Romberg test	Torkelson et al., 1958
506 (415-590)	7.5 hours	odor detection that dissipated, NOAEL for Romberg test	Torkelson et al., 1958
500	1.3 hours 3.1 hours	eye irritation in 3 of 6 subjects no effects reported	Stewart et al. 1961
900	20 minutes	lightheadedness, positive Romberg test in 1 of 2 subjects	Stewart et al., 1961
910	35 minutes	lightheadedness in 1 of 2 subjects, Romberg test difficult	Stewart et al., 1961
955	1.2 hours	positive Romberg test in 1 of 3 subjects	Stewart et al., 1961
1900 (1740-2180) 920 (900-1000)	5 minutes 1.3 hours	equilibrium disturbance strong odor, loss of equilibrium; lightheadedness in 3 of 4 subjects	Torkelson et al., 1958
10,000 - 26,000	2 minutes	induction of light plane anesthesia	Dornette and Jones, 1960
6000 - 22,500 (with nitrous oxide)	–	maintenance of light anesthesia during surgical procedures	Dornette and Jones, 1960

TWA = time-weighed average.

In a study conducted by Torkelson et al. (1958), no adverse effects were experienced when four human volunteers were exposed to measured concentrations of 1,1,1-trichloroethane ranging between 450 - 710 ppm for 90 minutes, 415 - 590 ppm for 450 minutes, or 890 - 1190 ppm for 30 minutes. Subjects did report noticing a definite odor at these concentrations. When subjects were exposed to concentrations ranging between 900 - 1000 ppm for 70 minutes, 2/4 reported a strong odor, 1/4 reported eye irritation, 3/4 reported feelings of light - headedness, and Flannigan tests given during the exposure as well as the Romberg test administered after the exposure revealed slight loss of equilibrium among these individuals. Subjects who were exposed to concentrations ranging between 1740 - 2180 ppm for 5 minutes experienced a noticeable odor as well as obvious disturbances of equilibrium.

Subjective and objective psychophysiological functions were evaluated after 30 minute exposures to increasing measured concentrations of 1,1,1-trichloroethane (Gamberale and Hultengren, 1973). Twelve healthy male subjects were repeatedly tested during exposure to 250, 350, 450, and 550 ppm with a five minute break between increasing concentrations. The subjects were asked to breathe normally via mouth through a tube with very low resistance during the exposures. One test for perceptual speed was significantly impaired at 350 ppm. Subject reaction time, perceptual speed, and manual dexterity were significantly impaired after exposure to concentrations of 450 ppm and higher. The odor of 1,1,1-trichloroethane was masked with menthol crystals (an agent which possesses pharmacological activity) and the results of the subjective questionnaire indicated that the subjects were unable to distinguish between control and experimental conditions. This experiment again demonstrates that subtle effects on the CNS can be produced by solvent exposure without a subjective sense of untoward effects. The experimental methods employed in this study limit its usefulness for derivation of AEGL values because the subjects were breathing the solvent vapor through the mouth only, menthol crystals were used to mask the odor of the solvent, and the subjects were exposed to successively increasing concentrations of the solvent without enough time for any appreciable clearance. The solvent could not have been cleared from the blood to any extent between exposures (5 minutes). This means the blood concentrations were increasing during the 2 hour exposure and were not reflective of actual solvent concentrations administered during each 0.5 hour exposure period.

Stewart et al. (1969) conducted a similar study with eleven healthy subjects (ages 31 to 62 years) exposed to measured concentrations ranging between 440 - 561 ppm for 6.5 to 7 hours during eight different sessions. Five subjects participated on five consecutive days in order to simulate a work week. Seventy-five percent of these subjects described the odor as moderately strong shortly after the initiation of the experiment, 25% were unable to detect the odor after 2 hours, and 50% were unable to detect the odor after 6 hours. The only consistent subjective complaint for each of the five consecutive exposures was mild sleepiness; other subjective symptoms of exposure like mild eye irritation and mild headache were reported sporadically. The only objective untoward effect was an abnormal modified Romberg test in two of the subjects during the exposures; within ten minutes following cessation of exposure, both subjects were able to perform this test normally. These two subjects had trouble with the Romberg test during the preexposure trial.

Six healthy male students were exposed to average vapor concentrations of 450 ppm (TWA range 400-500 ppm) for two periods of 4 hours separated by a 1.5-hour interval. The subjects

participated in a battery of psychophysiological tests before the exposures and at the end of the day after both exposures. This exposure did not produce disturbances in motor function, coordination, equilibrium, or behavior patterns. Some complaints of eye irritation were made and perception tests revealed an association between exposure to 1,1,1-trichloroethane and mental fatigue at the end of the 8 hour day (Salvini et al. 1971). The complaints of eye irritation were accompanied by complaints of slight dizziness during the peak exposure periods during the first 4 hour session. These complaints did not increase in severity or frequency during the second exposure period.

Dornette and Jones (1960) reported 50 cases of experimental anesthetic administrations of 1,1,1-trichloroethane. The subjects consisted of 44 females and 6 males with ages ranging from 0 to70 years and were candidates for elective operations. These patients also received a mixture of nitrous oxide-oxygen in a 4:1 ratio as a supplemental anesthetic agent. The concentrations required for induction of light plane anesthesia were 10,000-26,000 ppm and maintenance of light anesthesia during the surgical procedures required 6000-22,500 ppm. At these levels, the odor was relatively non-irritating. Normal respiratory activity was neither stimulated nor depressed by the administration. There were no cardiac effects that could be attributed to 1,1,1-trichloroethane as all instances of rhythm changes were associated with respiratory obstruction and were resolved when normal ventilation was restored. Recovery from anesthesia and regaining of reflexes was rapid, usually occurring within 3-5 minutes after discontinuation of the anesthetic. One patient who was undergoing a serious surgical procedure suffered cardiac arrest and died two weeks later. It could not be ascertained whether of not 1,1,1-trichloroethane contributed to the death.

2.3. Developmental/Reproductive Toxicity

No information was found regarding the developmental or reproductive toxicity of 1,1,1-trichloroethane in humans. Several epidemiological studies have implicated occupational exposure during pregnancy to organic solvents with increased incidences of spontaneous abortions (Wrensch et al., 1990; Lindbohm et al., 1990; Windham et al., 1991). However, no clear association with 1,1,1-trichloroethane exposure has been determined.

2.4. Genotoxicity

No information was found regarding the genotoxicity of 1,1,1-trichloroethane in humans.

2.5. Carcinogenicity

No information was found regarding the carcinogenicity of 1,1,1-trichloroethane in humans.

2.6. Summary

Human deaths have been reported following exposure to high concentrations of 1,1,1-trichloroethane in occupational as well as abuse situations. These deaths typically result from respiratory failure following CNS depression or cardiac arrhythmias following sensitization of the heart to epinephrine. Human response to 1,1,1-trichloroethane is typically characterized by eye irritation and subtle CNS effects which become measurable at levels above 450 ppm at exposure durations of about 4 hours. Observable effects range from slight behavioral changes (accompanied by eye irritation in humans) at 500 ppm to unconsciousness and respiratory arrest at higher concentrations (10,000-30,000 ppm). Based on the available data, a NOAEL for the threshold of subtle CNS effects is 350 ppm for durations up to 8 hours, the established ACGIH TLV. Concentrations above 900 ppm for periods of 70-75 minutes appear to be the threshold for loss of equilibrium concomitant with feelings of light-headedness and eye irritation (Torkelson et al., 1958). Disturbances in equilibrium occurred at 1740 ppm after 5 minutes of exposure, and at levels above 2650 ppm, a definite loss of equilibrium is evident after only a few minutes exposure Torkelson et al. (1958). Hepatotoxicity has been implied as a possible untoward effect associated with chronic 1,1,1-trichloroethane exposure, however, adequate data on this effect does not exist. Epidemiological data concerning the potential for this compound to produce developmental or teratogenic toxicity in humans is unavailable. No studies have been located on the carcinogenic potential of this compound in humans. Overall, 1,1,1-trichloroethane is considered to be one of the safest chlorinated hydrocarbon solvents in use today (WHO 1992).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

LC_{50} data for rats and mice are summarized in Table 3.

3.1.1. Rats

Clark and Tinston (1982) determined a 15-minute LC_{50} in the rat by exposing six Alderly Park rats/sex to concentrations of 1,1,1-trichloroethane so as to produce a concentration-effect curve representing 0-100% effect. The 15-minute LC_{50} was determined to be 38,000 ppm. Death was characterized by slight ataxia, loss of righting reflex, prostration, shallow respiration, and respiratory depression.

Adams et al. (1950) reported measured inhalation LC_{50} values of 18,000 ppm and 14,250 ppm for 3 and 7 hour exposures, respectively in five Wistar rats/sex/group. At 5000 ppm a narcotic effect was noticed within 1 hour and was characterized by hypoactivity and increased ease of handling. After exposure to 10,000 ppm, decreased activity was noticeable initially, followed by ataxia and prostration; after 3 hours, loss of color in the feet and ears, coldness, and irregular respiration were accompanied by anesthesia or death. Recovery from nonlethal exposures was complete within 24 hours. At 15,000 and 18,000 ppm effects were the same but with a more rapid onset.

A measured inhalation LC_{50} value for a six hour exposure in 12 male Sprague-Dawley rats/group was reported by Bonnet et al. (1980) as 10,305 ppm (C.L., 9947-10,671). Intoxication

was characterized by hypoactivity followed by unconsciousness and then death. No histopathological abnormalities of the liver, lungs, or kidneys were reported.

In an acute inhalation study, five Fischer 344 rats/sex/group were exposed for four hours to measured concentrations of 15,523, 18,425, or 21,063 ppm. All rats exposed to 21,063 ppm died during exposure as well as 3 females that were exposed to 18,425 ppm. Clinical signs observed at every exposure concentration included lethargy and unresponsiveness; body weights were slightly depressed among surviving rats the first week after exposure. Rats surviving until the end of a 2-week observation period had no gross exposure-related abnormalities. An LC_{50} of between 18,425 and 21,033 ppm was reported for males, and 18,000 ppm was reported for female rats (Calhoun et al., 1988). Similar results were obtained in a 4-hour acute inhalation exposure conducted by Siegel et al. (1971). In this experiment, an LC_{50} of 18,400 ppm was obtained using Sprague-Dawley rats.

In another acute inhalation toxicity study conducted at Hazelton Laboratories (1989) five Sprague-Dawley rats/sex/group were exposed to measured concentrations between 12,564 and 16,017 ppm for four hours. In this study, LC_{50} values were calculated to be 13,268 ppm, 13,426, and 13,338 for males, females, and combined, respectively. Clinical signs included observations of neuromuscular dysfunction, increased secretory responses, as well as general “poor condition”. An increased incidence of rough/pitted/granular spleens was observed in rats sacrificed at 14 days postexposure.

3.1.2. Mice

Moser and Balster (1985) calculated LC_{50} values for CD-1 male albino mice at 10, 30, and 60 minutes exposure durations, two groups of six were exposed at each concentration. Mice were exposed to at least three concentrations of solvent for each time point such that a concentration-effect curve was produced representing 0 - 100% mortality. The LC_{50} values obtained were 29,492, 20,616, and 18,358 for the 10, 30, and 60 minute time points, respectively. The concentration-lethality curves were steep, as evidenced by the finding that 68% of all deaths in the study occurred within only a 3-9% change in concentration in either direction from the LC_{50} values. Lower concentrations of solvent produced ataxia and as the concentration was increased, behavior progressed from hyperactivity to lethargy, then to anesthesia followed by death.

Woolverton and Balster (1981) conducted a similar experiment with groups of six CD-1 male albino mice in which a 30 minute LC_{50} of 22,241 ppm was calculated. Clinical signs observed during the exposure were ataxia followed by anesthesia and death at higher concentrations. The authors attributed the deaths to acute respiratory depression.

TABLE 3. Summary of Animal LC_{50} Toxicity Data With 1,1,1-Trichloroethane

Species	Duration	Concentration	Reference
mouse	10 minutes	29,492	Moser and Balster, 1985
rat	15 minutes	38,000	Clark and Tinston, 1982
mouse	30 minutes	20,616	Moser and Balster, 1985
mouse	30 minutes	22,241	Woolverton and Balster, 1981
mouse	60 minutes	18,358	Moser and Balster, 1985
rat	3 hours	18,000	Adams et al., 1950
rat	4 hours	18,000	Calhoun et al., 1988
rat	4 hours	18,400	Siegel et al., 1971
rat	6 hours	10,305	Bonnet et al., 1980
mouse	6 hours	13,414	Gradiski et al., 1978
rat	7 hours	14,250	Adams et al., 1950

3.2. Nonlethal Toxicity

The primary nonlethal effect of exposure to 1,1,1-trichloroethane is on the CNS, resulting in neurobehavioral changes. Results of neurobehavioral studies with several species of animals are summarized in Table 4 and discussed below.

3.2.1. Nonhuman Primates

Belej et al. (1974) exposed Rhesus monkeys (*Macaca mulatta*) to 25,000 - 50,000 ppm 1,1,1-trichloroethane while under sodium penobarbital anesthesia and continuously recorded the lead II electrocardiograph, the aortic blood pressure, and the myocardial contraction. 1,1,1-Trichloroethane produced cardiac arrhythmia and myocardial depression as well as tachycardia. Aortic blood pressure, left atrial pressure, and pulmonary arterial pressure were increased at these concentrations.

In a series of acute inhalation experiments, four young male baboons (*Papio anubis*) were exposed to measured concentrations of 700, 1400, 1800, and 2100 ppm for 4 hours in an atmosphere controlled chamber (Geller et al., 1982). Behavioral tasks were carried out during the third and fourth hour of the exposures. Although accuracy of responses was not significantly affected by 1,1,1-trichloroethane exposure, the baboons attempted 29% and 33% fewer trials under the influence of 1800 and 2100 ppm, respectively. A concentration-related trend was evident even at the lower doses where significance was not obtained. The mean response time was significantly increased during the 2100 ppm exposure and a concentration-effect relationship was evident beginning with the 1400 ppm exposure.

Adams et al. (1950) made observations on a monkey exposed to 5000 ppm for 7 hours. The animal displayed ataxia after about 1 hour, and after about 5 hours, coarse trembling of the hands

and forearms was observed. Once the animal was removed from the chamber, recovery was complete within a few minutes and he began eating at once.

Three squirrel monkeys were exposed to 12,060 mg/m^3 (~2200 ppm) of 1,1,1-trichloroethane for 8 hours/day, 5 days/week, for 30 exposures (Prendergast et al., (1967). Atmospheres were generated from a liquid reservoir with a high-pressure air stream and monitored continuously by infrared analysis. No animals died and no toxic signs were observed, although there was a slight body weight loss of 3% over the exposure period. Histopathologic examination of the heart, lung, liver, spleen, and kidney did not reveal any abnormalities attributable to the exposure, although there were nonspecific inflammatory changes in the lungs. Similar results were obtained following continuous 90-day exposures to 2059 or 754 mg/m^3 (~380 or 140 ppm) although there was a 3% weight gain at the lower exposure concentration.

3.2.2. Dogs

Five mature cross-bred dogs were acutely exposed to measured concentrations of 200, 500, 700, 1000, 1500, or 2000 ppm 1,1,1-trichloroethane for 1 hour in order to study the effect on hematological parameters (Hobara et al., 1984). An additional group of five dogs was exposed to a concentration of 700 ppm for four hours. A transient decrease in leukocytes was observed after 1 hour at 700 ppm where a decrease of 60-70% was evident 30 minutes after exposure compared to controls; the dogs showed recovery within one hour. During the four hour exposure, the same results were observed with recovery occurring during the exposure. No changes were observed in erythrocyte counts, hematocrit values, or thrombocyte counts.

The potential for 1,1,1-trichloroethane-induced cardiac sensitivity to epinephrine in healthy male beagle dogs was investigated by Reinhardt et al. (1973). Dogs were exposed to measured concentrations of 2500, 5000, or 10,000 ppm for ten minutes via a one-way face mask then were given two pharmacologic doses of epinephrine (8 µg/kg) in the cephalic vein with a ten minute interval between each dose. Standard electrocardiograph tracings were made during each experiment. 1,1,1-trichloroethane was a sensitizer after exposures of 5000 ppm or higher in that arrhythmias were produced in response to the subsequent epinephrine injections and were not observed among control animals. Beagle dogs with experimentally induced myocardial infarctions were sensitized to epinephrine at the same concentration (5000 ppm) as healthy dogs (Trochimowicz et al., 1976).

Herd et al. (1974) found that 1,1,1-trichloroethane produces a biphasic decrease in the arterial pressure of anesthetized mongrel dogs. Peripheral vasodilation was responsible for the initial decrease, the second phase was associated with depression of myocardial function. The concentration of solvent administered to these animals was not measured.

Two beagle dogs were exposed to 12,060 mg/m^3 (~2200 ppm) of 1,1,1-trichloroethane for 8 hours/day, 5 days/week, for 30 exposures (Prendergast et al., (1967). Atmospheres were generated from a liquid reservoir with a high-pressure air stream and monitored continuously by infrared analysis. No animals died and no toxic signs were observed, although there was a slight body weight loss of ~2% over the exposure period. Histopathologic examination of the heart, lung, liver, spleen, and kidney did not reveal any abnormalities attributable to the exposure.

Similar results were obtained following continuous 90-day exposures to 2059 or 754 mg/m^3 (~380 or 140 ppm) although there were weight gains at these exposure concentrations.

3.2.3. Rats

A study conducted by Landry et al. (1988) failed to produce mortalities or any signs of toxicity aside from a light anesthetic effect among rats exposed to concentrations of up to 6427 ppm for four hours.

The 10-minute EC_{50} for CNS effects in rats (ataxia and loss of righting reflex) was determined by Clark and Tinston (1982). Six Alderly Park rats/sex were exposed to a range of 1,1,1-trichloroethane concentrations in order to produce a concentration-effect curve representing 0-100% effect. Hypoactivity was followed by ataxia and then loss of righting reflex. A 10-minute EC_{50} was determined to be 5000 ppm .

The effect of 1,1,1-trichloroethane inhalation exposure on schedule-controlled operant behavior of rats was assessed by Warren et al., (1998). Rats trained to press a lever for evaporated milk on a variable interval schedule were exposed to vapor concentrations ranging from 500-5000 ppm for 100 minutes. At the 1000 ppm concentration, response rates were increased. At 2000, 3500, and 5000 ppm, there was a concentration-dependent decrease in response rates.

Mullin and Krivanek (1982) exposed six male Charles River-CD rats/group for up to 4 hours to nominal concentrations of 1,1,1-trichloroethane of 0, 1500, 3000, 6000, or 12,000 ppm. The animals were tested for behavioral changes at 0.5, 1, 2, and 4 hours during exposure and 18 hours after exposure. The EC_{50} values for loss of righting reflex and ataxia are presented in Table 3. Rats began to fail the unconditioned reflex tests after 2 hours at 3000 ppm, while conditioned avoidance responses became impaired at 6000 ppm.

Fifteen Long-Evans rats were exposed to 12,060 mg/m^3 (~2200 ppm) of 1,1,1-trichloroethane for 8 hours/day, 5 days/week, for 30 exposures (Prendergast et al., (1967). Atmospheres were generated from a liquid reservoir with a high-pressure air stream and monitored continuously by infrared analysis. No animals died and no toxic signs were observed and there was a weight gain of 32% over the exposure period. Histopathologic examination of the heart, lung, liver, spleen, and kidney did not reveal any abnormalities attributable to the exposure. Similar results were obtained following continuous 90-day exposures to 2059 or 754 mg/m^3 (~380 or 140 ppm). At the lower exposure concentration, 2 rats died, one on day 27 and one on day 77.

3.2.4. Mice

Several experiments have focused on the effects of 1,1,1-trichloroethane on behavior in mice. Typically, solvent exposures produce an initial increase in activity/response followed by a decrease in activity characterized by an anesthetic-like effect, hypoactivity, and finally, loss of consciousness.

TABLE 4. Summary of Animal Neurobehavioral Data with 1,1,1-Trichloroethane

Species	Duration	Concentration (ppm)	Effect	Reference
Baboon	4 hours	1800, 2100	no effect on correct responses in behavioral tasks, but 29 and 33% fewer trials, respectively	Geller et al., 1982
Rat	10 minutes	5000	EC_{50} for loss of righting reflex	Clark and Tinston, 1982
Rat	1.6 hours	2000, 3500, and 5000	concentration-related decrease in responding in a schedule-controlled situation	Warren et al., 1998
Rat	2 hours	3000	EC_{50} failure of unconditioned responses	Mullin and Krivanek, 1982
Rat	0.5, 1, 2, 4 hours	8480	EC_{50} loss of righting reflex	Mullin and Krivanek, 1982
Rat	0.5 hours 1 hour 2 hours 4 hours	6740 6000 4240 3780	EC_{50} Ataxia	Mullin and Krivanek, 1982
Rat	4 hours	6427	light anesthetic effect	Landry et al., 1988
Mouse	1 hour	890 1300 2000	no effect on activity slight decrease in activity increase in activity	Kjellstrand et al., 1985
Mouse	30 minutes	500-12,500	significant increase in locomotor activity at 1250 or 2500 ppm (2 experiments), returning to baseline or below at 10,000 ppm	Bowen and Balster, 1996
Mouse	20 minutes	8000 8,000-10,000 >10,000	disruption of the righting reflex increased activity hypoactivity	Bowen et al., 1996
Mouse	40, 60, and 180 minutes	5000	sustained increased level of activity at all exposure durations	Kjellstrand et al., 1990
Mouse	10 minutes 30 minutes 60 minutes	7807 5216 5674	EC_{50} failure on inverted screen test	Moser and Balster, 1985

In the previously described studies (Section 3.1.2) by Woolverton and Balster (1981) and Moser and Balster (1985) groups of six CD-1 albino mice were exposed to concentrations of 1,1,1-trichloroethane to produce deficits (0-100% effect) on the inverted screen test. No exact concentration range was reported. The concentration required to produce a deficit among 50% of mice (EC_{50}) was calculated for 10, 30, and 60 minutes exposure periods by Moser and Balster (1985). These concentrations were 7807, 5216, and 5674 ppm for the 10, 30, and 60 minute time points, respectively. Woolverton and Balster (1981) determined the EC_{50} for a 30 minute exposure to be 5173 ppm. Half the animals recovered within five minutes of the exposure and all recovered within 60 minutes even at the highest concentration tested (7000 ppm).

Kjellstrand et al. (1985) examined the effect of 1 hour exposures to measured concentrations of 890, 1300, or 2000 ppm on motor activity of five male NMRI mice/group. At 890 ppm, no effects were observed, 1300 ppm produced a slight decrease in activity, and 2000 ppm produced an increase in activity. In another experiment by Kjellstrand et al. (1990), groups of 10 male NMRI mice were constantly exposed to 5000 ppm for periods of 40, 60, and 180 minutes. These exposures produced an increase in motor activity with no measurable decrease over time, indicating that 1,1,1-trichloroethane does not produce tolerance at this concentration.

The effect of 1,1,1-trichloroethane on locomotor activity was evaluated by Bowen and Balster (1996). Ten male CFW Charles River mice were exposed to measured concentrations of 500, 1250, 2500, 5000, 7500, or 10,000 ppm for 30 minutes under static or dynamic conditions (flow rates of 10 L/min). Under static conditions there was an additional exposure to 12,500 ppm. Under both exposure conditions there was a biphasic response to 1,1,1-trichloroethane exposure. Under static conditions activity increased from the 500 ppm concentration up to a peak at 5000 ppm, then decreased with higher concentrations, reaching baseline at 12,500 ppm. Under dynamic conditions, the greatest increase in activity occurred at 1250 ppm and gradually decreased with increasing exposures up to 10,000 ppm.

Following a 20-minute inhalation exposure to nominal concentrations of 1,1,1-trichloroethane at 0, 4000, 8000, 10,000, 13,300, or 18,000 ppm, Bowen et al. (1996) assessed neuromuscular function in male CFW albino mice by administering a Functional Observational Battery (FOB) which was composed of 21 qualitative and quantitative measures of behavior. A profile of depressant effects was observed which included changes in posture, decreased arousal, disturbances in gait, decreased forelimb grip strength, increased landing foot splay, and impaired psychomotor coordination. This profile of effects was similar to that produced by ether and ethanol. Lower concentrations (8000 - 10,000) ppm, produced excitement, while higher concentrations produced hypoactivity and an anesthetic effect. Concentrations of $\geq$8000 ppm significantly disrupted the righting reflex. The authors concluded that the FOB can be used to compare and contrast profiles of depressant and excitatory effects of inhalants.

Aviado and Belej (1974) established 1,1,1-trichloroethane as a propellant that produces cardiac arrhythmia in Swiss mice. Mice were anesthetized with sodium pentobarbital and exposed to solvent vapor at a concentration of 400,000 ppm for 6 minutes. This exposure produced 2nd degree block during all exposures and there was no difference in the arrhythmia when epinephrine (6 µg/kg) was introduced intravenously.

3.2.5. Rabbits

Taylor et al. (1976) exposed anesthetized male New Zealand rabbits to 50,000 ppm (nominal concentration) 1,1,1-trichloroethane for 1.5 minutes and measured the degree of cardiac depression in this model. A significant decline in peak left ventricular dP/dt, cardiac output, stroke volume, left ventricular stroke volume, and mean arterial pressure were observed. Heart rate, left ventricular end-diastolic pressure, and central venous pressure remained unaffected.

Carlson (1981) found that rabbits exposed to 5600 ppm 1,1,1-trichloroethane did not respond with arrhythmias spontaneously, but infusion of pharmacologic doses of epinephrine (3 µg/kg) induced premature ventricular contractions. These premature contractions occurred within

7.5 minutes of commencement of exposure, but were abolished with discontinuation of 1,1,1-trichloroethane exposure.

Three New Zealand rabbits were exposed to 12,060 mg/m^3 (~2200 ppm) of 1,1,1-trichloroethane for 8 hours/day, 5 days/week, for 30 exposures (Prendergast et al., (1967). Atmospheres were generated from a liquid reservoir with a high-pressure air stream and monitored continuously by infrared analysis. No animals died and no toxic signs were observed, although animals did not gain weight during the exposure. Histopathologic examination of the heart, lung, liver, spleen, and kidney did not reveal any abnormalities attributable to the exposure. Similar results were obtained following continuous 90-day exposures to 2059 or 754 mg/m^3 (~380 or 140 ppm) although there were positive weight gains during these exposures (but less than in the control group). Nonspecific inflammatory changes were present in the lungs of animals in the 2059 mg/m^3 exposure group. One rabbit died on day 38 at the lower exposure concentration.

3.2.6. Guinea pigs

In a subacute inhalation study conducted by IHFA (1965), 15 albino female guinea pigs were exposed to 1000 ppm 1,1,1-trichloroethane for 7 hours/day, 5 days/week for 4 weeks. No fatalities were attributable to administration of the solvent. The only signs of toxicity observed were decreases in body weight gain, relative liver weight, and absolute kidney weight among exposed animals compared to controls. However, animals seemed to recover body weight gains rapidly upon cessation of the exposures and were comparable to controls after a 2-week observation period.

Fifteen Hartley guinea pigs were exposed to 12,060 mg/m^3 (~2200 ppm) of 1,1,1-trichloroethane for 8 hours/day, 5 days/week, for 30 exposures (Prendergast et al., (1967). Atmospheres were generated from a liquid reservoir with a high-pressure air stream and monitored continuously by infrared analysis. No animals died and no toxic signs were observed. There was a positive weight gain over the exposure period. Histopathologic examination of the heart, lung, liver, spleen, and kidney did not reveal any abnormalities attributable to the exposure. Similar results were obtained in the same study following continuous 90-day exposures to 2059 or 754 mg/m^3 (~380 or 140 ppm).

3.3. Developmental/Reproductive Toxicity

Four groups of 40 female Long-Evans rats were exposed by inhalation to 2100 ± 200 ppm for 6 hours/day, 5 days/week, according to the following experimental paradigm: 1) exposed to solvent before and during pregnancy, 2) exposed only before mating, 3) exposed only during pregnancy, 4) received filtered air before and during pregnancy. Half of each group were sacrificed at term and the other half delivered and were subjected to behavioral evaluation and examination for gross lesions. When dams were exposed during pregnancy alone a decrease in fetal body weight was observed. When exposures were conducted before mating and during pregnancy, significant variations in fetal morphology indicative of developmental delay were observed. The authors concluded that there were no persistent detrimental effects with exposures at this concentration as none of the neurobehavioral parameters revealed abnormalities, and the developmental delays were reversible (York et al., 1982).

In a developmental toxicity study of inhaled 1,1,1-trichloroethane, groups of 30 pregnant Sprague-Dawley rats were exposed to mean analytical concentrations of 0, 1017, 3122, or 5906 ppm for 6 hours/day during gestational days 6-15. Significant decreases in body weight or body weight gain among dams were observed at different times in the 3000 and 6000 ppm groups. Significant decreases in food (3000 and 6000 ppm groups) and water (6000 ppm group) consumption were also observed among dams. Clinical signs of toxicity including hypoactivity and perioral wetness were limited to dams in the 6000 ppm group. Mean fetal body weight per litter among females in the 6000 ppm group was significantly reduced and two skeletal variants were evident at 6000 ppm that indicated fetotoxicity. The authors determined the maternal NOAEL to be >1000 ppm and the fetal NOAEL was established as 3000 ppm. No embryo-toxicity or teratogenicity was observed at any exposure concentration (BRRC 1987a).

Schwetz et al. (1975) exposed 13 pregnant Swiss-Webster mice and 23 pregnant Sprague-Dawley rats to 1,1,1-trichloroethane vapor at a concentration of 875 ± 27 ppm for 7 hours daily during gestation days 6-15. Exposures at this concentration had no effect on implantation, litter size, incidence of fetal resorptions, fetal sex ratios, fetal body measurements, incidence of fetal anomalies, skeletal anomalies, or incidence of microscopic abnormalities.

Pregnant New Zealand white rabbits were exposed by inhalation to 1,1,1-trichloroethane vapor for 6 hours/day on gestational days 6-18. The mean analytical concentrations were 0, 1017, 3122, or 5906 ppm. Maternal toxicity characterized as significant weight gain reduction and an apparent decrease in gestational weight gain was observed at the 3122 and 5906 ppm exposures. The only significant variation among pups was an increased incidence of the bilateral thirteenth rib at 6000 ppm. The NOAEL for maternal toxicity was 1000 ppm and the NOAEL for fetal toxicity was 3000 ppm (BRRC, 1987b).

Groups of timed-pregnant female CD-1 mice were exposed to either 2000 ppm for 17 hours daily during gestation days 12-17 (10 mice) or to 8000 ppm for 60 minutes, 3 times/day, during gestation days 12-17 (20 mice) (Jones et al., 1996). Similar groups of mice were untreated or sham treated. Although there were no differences on pregnancy outcome, pups exposed prenat-ally to 1,1,1-trichloroethane-treated gained less weight, exhibited delays in developmental landmarks and acquisition of the righting reflex, had poorer performance on tests of motor coordination and exhibited delays in negative geotaxis relative to sham or untreated pups.

In a follow-up to the above study, nine pregnant Sprague-Dawley rats were exposed to 1,1,1-trichloroethane a concentration of 7000 ppm for 1 hour, three times daily, on gestation days 13-19 (Coleman et al., 1999). There was a 1-hour recovery period between each exposure. Control groups consisted of sham air exposed females (n = 10) and untreated females (n = 19). Atmos-pheres were continuously monitored by an infrared spectrophotometer. Offspring of the treated and sham-air control group were fostered to untreated dams. 1,1,1-Trichloroethane-treated dams exhibited neurotoxic effects immediately after each exposure. These signs consisted of saliva-tion, lacrimation, and gait abnormalities. Total weight gain and food and water consumption did not differ among the groups, but there was a significant effect on maternal weight gain during gestation days 13-19. Treated dams delivered a smaller number of litters and there were fewer live pups per litter. Although there were no significant delays in the physical development of pups treated prenatally, this exposure regime caused significant fetotoxicity involving delays in pup weight gain, lower brain weights, reduced locomotor activity and ability to perform in the

negative geotaxis, forelimb grip strength, inverted screen, and vertical screen tests. The authors reported that in a range-finding study, preliminary to the present study, concentrations of 7500 and 8000 ppm usually caused total resorption of litters in rats.

3.4. Genotoxicity

In vivo assays to determine the genotoxic potential in various mouse systems have provided mostly negative results. The micronucleus test in mouse erythrocytes (Tsuchimoto and Matter 1981) and mouse bone marrow (Gocke et al., 1981; Katz et al., 1981; Mackay 1990; and Salamone et al., 1981) have provided negative results. An assay for DNA unwinding was found to be negative by Taningher et al. (1991) in mouse liver. A weakly positive result was obtained for DNA adducts in mouse liver by Turina et al. (1986).

3.5. Carcinogenicity

Quast et al. (1988) conducted a chronic inhalation study in Fischer 344 rats and $B6C3F_1$ mice; 80/sex/group were exposed to vapor concentrations of 0, 150, 500, or1500 ppm 1,1,1-trichloroethane 6 hours/day, 5 days/week, for 2 years. A significant decrease in body weight among female rats in the 1500 ppm exposure group was observed. In the livers of male and female rats exposed to 1500 ppm, an accentuation of the normal hepatic lobular pattern was observed at the 6, 12, and 18 month sacrifices. These changes were not discernible at the final 24 month sacrifice. In mice, there were no detectable exposure-related effects. The authors concluded that exposure to 1,1,1-trichloroethane for 2 years did not result in oncogenic effects in rats or mice. These results are consistent with oral gavage studies conducted by NTP (1992) in rats and mice.

3.6. Summary

A summary of the LC_{50} data and the neurobehavioral data available in rats and mice is presented in Tables 3 and 4, respectively. Data on lethality were available for the rat and the mouse. Although these species exhibit similar sensitivity to the toxic effects of 1,1,1-trichloroethane, the rat may be slightly more sensitive as evidenced by a lower LC_{50} value at the 6-hour exposure duration (rat, 10,305 ppm; mouse, 13,414 ppm [Bonnet et al., 1980; Gradiski et al., 1978]). The primary toxic effect with high acute exposures to 1,1,1-trichloroethane is the same as in humans, CNS depression. Also similar to humans is the cause of death which is usually described as severe CNS depression resulting in respiratory failure and/or cardiac arrest. Upon cessation of exposure to this compound, surviving animals recover rapidly and completely with no lingering untoward effects. Acute exposures to 1,1,1-trichloroethane have been associated with changes in the ultrastructure of the liver; however, these changes occur at concentrations that approach lethality in most cases. Developmental toxicity has been observed at concentrations that produce maternal toxicity as well. These effects occur in the form of reversible developmental (behavioral) delays in rats and mice. Most genotoxicity tests yield negative results and chronic inhalation studies in rats and mice indicate no carcinogenic potential of this compound in these species.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Exposure to 1,1,1-trichloroethane vapor results in rapid and efficient absorption by the lungs of humans and animals. As exposure duration increases, absorption decreases because steady-state levels are approached in the blood and well perfused tissues. While several studies have shown that steady-state levels are approached within a few hours of continuous exposure, (Astrand et al., 1973; Monster et al. 1979; Nolan et al. 1984), it was predicted by Nolan et al. (1984) using a physiologically-based pharmacokinetic model that 12 consecutive, continuous days of exposures to 350 ppm would be required in order to reach 95% of steady-state because elimination exceeds intake. Metabolism occurs at a very slow rate which contributes to the slow acquisition of steady-state levels. 1,1,1-Trichloroethane is largely excreted unchanged in exhaled air regardless of the route of exposure.

Once absorbed, 1,1,1-trichloroethane is widely distributed throughout the body to tissues and organs with preferential distribution to fatty tissues. It readily crosses the blood-brain barrier (Stahl et al., 1969) and crosses the placenta to the developing fetus in mice as reported by Danielson et al. (1986). The blood:air partition coefficients reported by Reitz et al. (1988) for humans, rats, and mice were 2.53, 5.76, and 10.8, respectively. Therefore, small rodents will experience greater systemic uptake than humans, with mice receiving the highest dose. Accordingly, healthy humans would experience greater systemic uptake compared to those with pulmonary diseases due to impaired alveolar/blood transfer of the solvent. The predominant pathway of elimination in humans and animals (rats, mice, guinea pigs, and dogs) is exhalation of the unchanged compound. Upon cessation of the exposure, the compound is rapidly cleared from the body as evidenced by the rapid recovery rates observed after anesthetic concentrations were discontinued in humans and in rodents.

1,1,1-Trichloroethane is metabolized oxidatively, at very low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed function oxidase system (Monster et al., 1979; Reitz et al. 1988; Nolan et al. 1984). Both metabolites are excreted in the urine. Only small fractions of 1,1,1-trichloroethane doses are metabolized, the same toxicokinetic profile is evident in humans, rats, and mice. After cessation of exposure, clearance of the chemical from the blood is rapid; 60-80% is eliminated within 2 hours, and greater than 95% is eliminated within 50 hours (Astrand et al., 1973; Monster et al., 1979; Nolan et al., 1984). Less than 10% is metabolized to trichloroethanol and its glucuronide conjugate, trichloroacetic acid, and carbon dioxide (ATSDR, 1995; Nolan et al., 1984). The trichloroethanol and trichloroacetic acid metabolites have much longer half-lives than 1,1,1-trichloroethane (27 and 76 hours, respectively) and may accumulate with repeated exposures (Nolan et al., 1984).

4.2. Mechanism of Toxicity

The primary toxic effects of 1,1,1-trichloroethane in humans are 1) eye irritation 2) CNS effects with diminished neurological responses (anesthetic effect at higher doses), 3) peripheral nervous system effects, and 4) cardiac effects ancillary to anesthetic hypotension which precipitates arrhythmia and can result in sudden cardiac death. Transient hepatotoxicity has been associated with 1,1,1-trichloroethane exposure, however, the animal and human data are inconsistent with respect to acute exposures.

Respiratory arrest as a result of CNS depression is the primary mechanism of concern with respect to acute potentially lethal exposures among humans. This can occur as a result of sudden apnea of central origin, either in the induction phase or late in anesthesia when humans are exposed to high concentrations of 1,1,1-trichloroethane. Cardiac failure secondary to respiratory failure or as a result of myocardial depression and ventricular fibrillation has also been proposed as a mechanism of death in acute solvent exposures (Hall and Hine, 1966).

The mechanism by which 1,1,1-trichloroethane produces cardiac effects has been extensively studied in dogs. Aoki et al. (1997) reported that inhalation exposure to 1,1,1-trichloroethane results in a direct effect on the cardiovascular system characterized by a decrease in peripheral vascular resistance and a disturbance of pulmonary blood flow accompanied by subsequent pressure overloading in the right ventricle. If these effects become severe enough, sudden cardiac death may result. This cascade of events could be precipitated by hypoxic vasoconstriction or pulmonary interstitial damage; the latter is supported by autopsy findings among 1,1,1-trichloroethane produced human fatalities.

The mechanism by which anesthetics depress the CNS and the site of action remain controversial. Depression of synaptic transmission is thought to be involved as a result of interaction or the presence of these lipid soluble compounds in the neural membranes. One theory is that these volatile compounds interact with hydrophobic portions of cell proteins thereby altering membrane-bound enzyme activity, receptor-site specificity, as well as receptor or channel function. It is known that volatile anesthetics potentiate the actions of GABA (gamma-aminobutyric acid), this is accomplished by an increase in the affinity of the $GABA_A$ receptor. Anesthetic agents increase the GABA-induced chloride current by over 50% (Franks and Lieb, 1994).

General nonspecific CNS depressants (including anesthetic gases and vapors) share the ability to depress excitable tissue at all levels of the CNS, leading to a decrease in the amount of transmitter released by the nerve impulse, as well as to general depression of postsynaptic responsiveness and ion movement. At subanesthetic concentrations, these agents (e.g. ethanol) can exert relatively specific effects on certain groups of neurons, which may account for differences in their behavioral effects, especially the propensity to produce dependence. This mechanism may also be relevant to the variability of actions exerted by 1,1,1-trichloroethane at lower concentrations and at concentrations that may produce euphoria (Koob and Bloom, 1988).

A minor metabolite of 1,1,1-trichloroethane, trichloroethanol, produces anesthetic effects by interacting with hydrophobic portions of cell proteins thereby altering ligand-gated channels of cell membranes (Peoples and Weight, 1994). Specifically this action may be related to potentiation of GABA-mediated responses as described by the in vitro observations of Peoples and Weight (1994). Trichloroethanol has also been shown to inhibit ion currents activated by excitatory amino acids (Peoples et al., 1990). This is similar to the mechanism of action by which trichloroethylene exerts its anesthetic effects, via its primary metabolite, trichloroethanol (Savolainen, 1977). This metabolite is unlikely to be substantially involved in the manifestation of CNS effects observed with 1,1,1-trichloroethane inhalation because this solvent is not appreciably metabolized to trichloroethanol (< 10%). Since very brief exposures can result in CNS disturbances (Torkelson et al. 1958), a minor metabolite probably would not be involved in this manifestation to any large extent.

4.3. Structure-Activity Relationships

The 1,1,2-isomer of trichloroethane, known as vinyl trichloride has much greater toxic potential with respect to lethality, hepatic, and renal toxicity. Paa et al. (1958) rated 1,1,1-trichloroethane at 1 for lethality, and 1,1,2-trichloroethane was rated at 71. The 1,1,2-isomer is metabolized and excreted much differently compared to the 1,1,1-isomer. 1,1,1-Trichloroethane is largely excreted unchanged in expired air after inhalation exposures. 1,1,2-Trichloroethane is metabolized by mice and has several urinary metabolites; these differences are accepted as the primary reason for the disparity in toxicity among these two isomers. In situations where an inhalation exposure might consist of a mixture of both isomers, the guidelines for 1,1,2-isomer should be consulted. This situation would be very rare since the two isomers are manufactured separately and the use of vinyl trichloride is restricted.

4.4. Other Relevant Information

4.4.1. Species Variability

Comparison of LC_{50} values for the rat and mouse shows a slight difference in sensitivity between these species. The 6-hour LC_{50} in rats was calculated by Bonnet et al. (1980) as 10,305 ppm and the LC_{50} in mice for the same time point was calculated by Gradiski et al. (1978) to be 13,414 ppm. The sequence of death in both species was similar with observations of CNS depression characterized by ataxia, hypoactivity, prostration, shallow respiration, and unconsciousness followed by death. Deaths are usually attributed to either respiratory or cardiac failure. CNS depression including ataxia and narcosis has also been observed in several accidental and intentional human exposures. Most human deaths associated with 1,1,1-trichloroethane inhalation exposure have also been attributed to either respiratory or cardiac failure. Little variability is observed among species for less serious CNS effects as evidenced by comparison of the 1-hour mouse EC_{50} for failure of the inverted screen test which is approximately 6000 ppm; this is the same concentration calculated by Mullin and Krivanek (1982) for the 1-hour EC_{50} for ataxia in rats.

4.4.2. Susceptible Subpopulations

Studies indicate that children, and particularly infants are more resistant than adults to the effects of various volatile anesthetics (Gregory et. al., 1969; Katoh and Ikeda, et. al., 1992; Lerman et. al., 1983; Chan et al., 1996; Stevens et al., 1975; and LeDez and Lerman, 1987). 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. 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 values) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitive (highest MAC values) occur in older infants, toddlers and children as 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. CNS effects of these agents are thought to be additive if mixtures are involved. 1,1,1-Trichloroethane has been

successfully used as an anesthetic, therefore it would not be unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for this solvent.

4.4.3. Concentration-Response Relationship

When data are lacking for desired exposure times, scaling across time may be based on the relationship between acute toxicity (concentration) and exposure durations (ten Berge et al., 1986). The observations of Mullin and Krivanek (1982) were used to derive the time-scaling relationship used for the development of AEGL-2 values where an endpoint of the EC_{50} for ataxia in the rat was used. From the rat ataxia data the EC_{50} time points of 30 minutes and 1, 2, and 4 hours were analyzed to determine the least-squares linear curve fit of the graph log time vs log EC_{50} (Figure 1, Appendix A). The equation for the resulting line was y = 4.2823 - 0.3004; since n = -1/slope, n = 3.3.

For the derivation of n used for AEGL-3 values, the rat LC_{50} data were used because the rat seems to be slightly more sensitive than the mouse to 1,1,1-trichloroethane vapor exposure. The 15-minute LC_{50} calculated by Clark and Tinston, (1982), the 3- and 7-hour values by Adams et al. (1950), the 4-hour value by Calhoun et al. (1988), and the 6-hour value by Bonnet et al. (1980) were used to determine the least-squares linear curve fit of the graph (Figure 2, Appendix A), log time vs log LC_{50}. The resulting equation for the line was y = 4.98 - 0.33 x and n = -1/slope, therefore, the value of the exponent n is 3.0.

Values scaled for the derivation of the 10 minute, 30 minute, 1, 4, and 8 hour time points were calculated from the equation $C^n \times t = k$ (ten Berge et al., 1986) where n = 3.3 (AEGL-2) or 3 (AEGL-3). An n value of 3 or 3.3 indicates that concentration is more important than duration of exposure, i.e., effects at a specific concentrations do not vary greatly with increasing durations of exposure.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Several controlled human studies have been conducted which describe the threshold level for eye irritation and CNS effects following acute inhalation exposure to 1,1,1-trichloroethane. Humans begin to experience some eye irritation, slight dizziness, mild impairment of the Romberg test, and mild sleepiness after exposure to concentrations at or above 450 ppm for 4 hours (Stewart et al., 1969 and Salvini et al. 1971). The best human data relevant to AEGL-1 is that of Salvini et al. (1971). In this study, six healthy male students were exposed to average vapor concentrations of 450 ppm (TWA, range of 400-500 ppm) for two 4-hour intervals separated by a 1.5 hour break. A battery of psychophysiological tests was performed prior to and after the exposures. Performance on these tests was decreased slightly but a statistically significant decline was not produced by 1,1,1-trichloroethane exposure. However, mental fatigue as measured by a qualitative and quantitative decline in perceptual acuity was perceived by the authors as an effect of 1,1,1-trichloroethane on these subjects. Subjective complaints including eye irritation and slight dizziness were made during the first 4 hour exposure and did not increase in severity after the second exposure session (Salvini et al. 1971).

In a study conducted by Stewart et al. (1969), eleven healthy subjects were subjected to an average measured concentration of 500 ppm for 6.5 - 7 hr/day for 5 days in order to simulate a work week. Sporadic complaints of eye irritation and headache were made along with consistent complaints of mild sleepiness. Two subjects also responded to the test atmosphere conditions with a positive Romberg test during the exposure, a normal performance was elicited by both individuals within 10 minutes after leaving the chamber. It should be noted that these individuals had trouble performing the Romberg prior to the exposure.

Torkelson et al. (1958) found that four human subjects exhibited no untoward effects after inhalation of 450-710 ppm (TWA 546 ppm) for 1.5 hours and were all able to perform a normal Romberg test. When subjects were exposed on another occasion to 415-590 ppm (TWA 506 ppm) for 7.5 hours an odor that dissipated was reported and all subjects were able to perform a normal Romberg test. When Stewart et al. (1961) exposed 6 human subjects to 500 ppm for 1.3 hours 3/6 subjects reported eye irritation, however when these subjects were exposed to 500 ppm for 3.1 hours, no subjective symptoms were reported and all performed normal Romberg tests.

5.2. Summary of Animal Data Relevant to AEGL-1

The most appropriate study relevant to the derivation of AEGL-1 was that of Geller et al. (1982). Baboons were exposed to 700, 1400, 1800, or 2100 ppm for 4 hours in an atmosphere controlled chamber. These animals had been trained to perform neurobehavioral tasks previous to these exposure sessions. Accuracy of the responses in these tasks was not affected by the exposures, however, exposure to 1800 and 2100 ppm produced a 29 and 33% decrease in trials, respectively. This is indicative of a slight CNS depressant effect.

5.3. Derivation of AEGL-1

The data of Salvini et al. (1971) were used for derivation of AEGL-1 values. At a concentration of 450 ppm and a duration of exposure of 4 hours eye irritation and slight dizziness were reported by healthy human subjects. This study along with the studies of Stewart et al. (1961), Stewart et al.(1969) and Torkelson et al. (1958) support this concentration-duration relationship as the threshold for AEGL-1 level effects in humans. The value of 450 ppm was used as the reference point for the lowest concentration at which irritation or other effects were observed. An uncertainty factor of 2 was applied based on the observation by Salvini et al. (1971) that the severity of eye irritation and slight dizziness produced by 1,1,1-trichloroethane did not increase with time of exposure and the complaints were sporadic. The eye irritation experienced by humans is usually characterized as "slight" even at much higher exposure concentrations than the proposed AEGL-1 values. Among humans the MAC for volatile anesthetics typically varies by about 2-3 fold as shown by the experimental use of 1,1,1-trichloroethane as an anesthetic in the cases reported by Dornette and Jones (1960). Mild CNS effects like slight dizziness would be expected to occur within a similar range of variation.

AEGL-1 values are listed in Table 5. Calculations are presented in Appendix B.

TABLE 5. AEGL-1 Values for 1,1,1-Trichloroethane [ppm (mg/m^3)]

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
230 (1255)	230 (1255)	230 (1255)	230 (1255)	230 (1255)

The AEGL-1 values are considered conservative and should be protective of the toxic effects of 1,1,1-trichloroethane outside those expected as defined under AEGL-1. This confidence is based on several chamber exposure studies using similar exposure concentrations with similar outcomes among human subjects. Stewart et al. (1969) exposed healthy humans to a TWA concentration of 500 ppm/ 7 hr/5 days and observed an increase in mild sleepiness as the only untoward effect. Kramer et al. 1978 established a NOAEL of 249 ppm for chronic occupational exposure to 1,1,1-trichloroethane. In the baboon study (Geller et al. 1982), a slight decrement in attempted trials was produced by exposure to 1800 ppm for 4 hours. Because only mild untoward effects were observed at concentrations that were 2 times the proposed value and the severity did not increase with time, this AEGL-1 value is considered appropriate.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

The best human data for use in derivation of AEGL-2 values are those of Torkelson et al. (1958) and Stewart et al. (1961). Torkelson et al. (1958) exposed human subjects to 920 ppm for 1.3 hours and observed loss of equilibrium and feelings of lightheadedness in from 3 of 4 subjects. In this same study, 3 subjects were exposed for 5 minutes to rapidly increasing concentrations of 1,1,1-trichloroethane starting with 1740 ppm and ending with 2180 ppm. Loss of equilibrium was evident in all subjects and one subject was unable to stand. Stewart et al. (1961) exposed human subjects to concentrations up to 955 ppm for up to 1.3 hours with only 1 of 3 subjects exhibiting a positive Romberg test.

6.2. Summary of Animal Data Relevant to AEGL-2

The neurobehavioral data based on 1,1,1-trichloroethane exposures in rats reported by Mullin and Krivanek (1982) are the most appropriate animal data for use in the development of AEGL-2 values. In this study, groups of six rats were exposed to nominal concentrations of 0, 1500, 3000, 6000, and 12,000 ppm for 4 hours and behavioral screenings to determine the EC_{50} values for loss of righting reflex, ataxia, and loss of conditioned and unconditioned reflexes were performed at 30 minutes, 1, 2, and 4 hours from the start of the exposure. The EC_{50} values for ataxia were 6740, 6000, 4240, and 3780 ppm for the 30-minute and 1-, 2-, and 4-hour time points. The EC_{50} values for failure of the inverted screen test in mice were calculated by Moser and Balster (1985) for 10, 30, and 60 minute exposure durations as 7807, 5216, and 5674 ppm, respectively.

6.3. Derivation of AEGL-2

The human data available for the derivation of AEGL-2 values will not be used because of the unreliable methods used to generate exposure atmospheres in these studies, and the variability of the effects observed at various exposure-concentration durations. The rat EC_{50} values for ataxia calculated by Mullin and Krivanek (1982) will be used for derivation of AEGL-2 values. This study establishes the loss of equilibrium with the observation of EC_{50} values for ataxia in rats for exposure periods of 30 minutes, 1, 2, and 4 hours at 6740, 6000, 4240, and 3780 ppm. These values were used for the 30 minute, 1, and 4 hour AEGL-2 values with an uncertainty factor of 10 applied, 3 each for intra- and inter-species variability for a total of 10. Extrapolation was made to the 10-minute and 8-hour time points using the equation $C^n \times t = k$ where n = 3.3, based on least squares fit of this data (see Appendix A, Figure 1) and $k = 6.4 \times 10^{10}$ $ppm^{3.3}$·minutes for the 10-minute value and 7.8×10^{10} $ppm^{3.3}$·minutes for the 8-hour value. The intra-species uncertainty factor of 3 is 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 4.2). The interspecies uncertainty factor of 3 is supported by the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants. A factor of 3-fold should provide more than adequate protection based on the similarity of toxic effects, metabolism and excretion observed for 1,1,1-trichloroethane in rodents compared to humans. However, with a difference of 2 to 5 fold in the blood:air partition coefficient, humans would have a lower blood concentration than rodents under similar exposure conditions. These values are supported by the findings of Torkelson et al. (1958) and Stewart et al. (1961) which show that human exposures to concentrations of up to 955 ppm for 1.3 hours are well tolerated with minimal CNS effects. The 1-hour mouse EC_{50} for failure of the inverted screen test is approximately 6000 ppm, this is the same concentration calculated by Mullin and Krivanek (1982) for the 1-hour EC_{50} for ataxia in rats.

The values for AEGL-2 are listed in Table 6. Calculations are presented in Appendix B.

TABLE 6. AEGL-2 Values for 1,1,1-Trichloroethane [ppm (mg/m^3)]

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
930 (5074)	670 (3656)	600 (3274)	380 (2073)	310 (1691)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to the derivation of AEGL-3 values were identified. Concentration-duration exposure relationships were not reliably reported in human exposures where death occurred.

7.2. Summary of Animal Data Relevant to AEGL-3

Based on the 6-hour LC_{50} values calculated in rats and mice, the rat is slightly more sensitive to the effects of 1,1,1-trichloroethane than the mouse. Bonnet et al. (1980) reported a 6-hour LC_{50} value of 10,305 ppm and the LC_{50} in the mouse for the same time point was calculated as 13,414 ppm by Gradiski et al. (1978).

7.3. Derivation of AEGL-3

Estimation of the concentration causing no deaths from the 6-hour exposure-concentration graph presented by Bonnet et al. (1980) was used to derive the AEGL-3 values. The concentration-response curve crosses the X-axis between 7000 and 8000 ppm. Therefore, as a conservative estimate, a value of 7000 ppm for a duration of 6 hours was used for the derivation of AEGL-3 values. Extrapolation was made to the 30 minute and 1-, 4- and 8-hour time points using the equation $C^n \times t = k$ where n = 3, based on the rat lethality data (see Appendix A, Figure 2) and $k = 4.57 \times 10^{12}$ $ppm^3 \cdot$minutes. An intraspecies uncertainty factor of 3 and an interspecies uncertainty factor of 1 were applied for a total uncertainty factor of 3. The intraspecies uncertainty factor of 3 is based on the previously described argument that the MAC for volatile anesthetics should not vary by more than a factor of 2-3 fold. A variation of 3- fold among individuals was observed with the experimental use of 1,1,1-trichloroethane as an anesthetic in the cases reported by Dornette and Jones (1960). The interspecies uncertainty factor of 1 is supported by the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants and by the observed 2 to 5-fold greater blood:air partition coefficient for 1,1,1-trichloroethane in rodents compared to humans. This principle determines the relative blood concentration for a vapor and because it is higher for rats, a higher blood concentration is achieved at lower exposure concentrations among rodents compared to humans. The 1-hour value was also used for the 10- and 30-minute values so as not to exceed the threshold for cardiac sensitization (5000 ppm) observed in a study with dogs by Reinhardt et al. (1973). AEGL-3 values are listed in Table 7. Calculations are presented in Appendix B.

TABLE 7. AEGL-3 Values for 1,1,1-Trichloroethane [ppm mg/m^3)]				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
4200[a] (22,915)	4200 (22,915)	4200 (22,915)	2700 (14,731)	2100 (11,458)

[a]The 1-hour value was used as the 10- and 30-minute values so as not to exceed the threshold for cardiac sensitization observed in dogs (Reinhardt et al., 1973).

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 8.

TABLE 8. Summary of AEGL Values [ppm (mg/m^3)]					
AEGL Level	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	230 (1255)	230 (1255)	230 (1255)	230 (1255)	230 (1255)
AEGL-2	930 (5074)	670 (3656)	600 (3274)	380 (2073)	310 (1691)
AEGL-3[a]	4200 (22,915)	4200 (22,915)	4200 (22,915)	2700 (14,731)	2100 (11,458)

[a]The 1-hour value was used as the 10- and 30-minute values so as not to exceed the threshold for cardiac sensitization observed in dogs (Reinhardt et al., 1973).

AEGL-1 values were based on eye irritation and mental fatigue. The AEGL-2 values were based on the EC_{50} for ataxia observed in rats which would be analogous to CNS effects in humans that might impede escape in an acute exposure situation. The basis for the AEGL-3 was estimation of a concentration causing no deaths in rats during a 6-hour exposure. The data on which the AEGLs are based and the AEGL values are graphed in Figure 1.

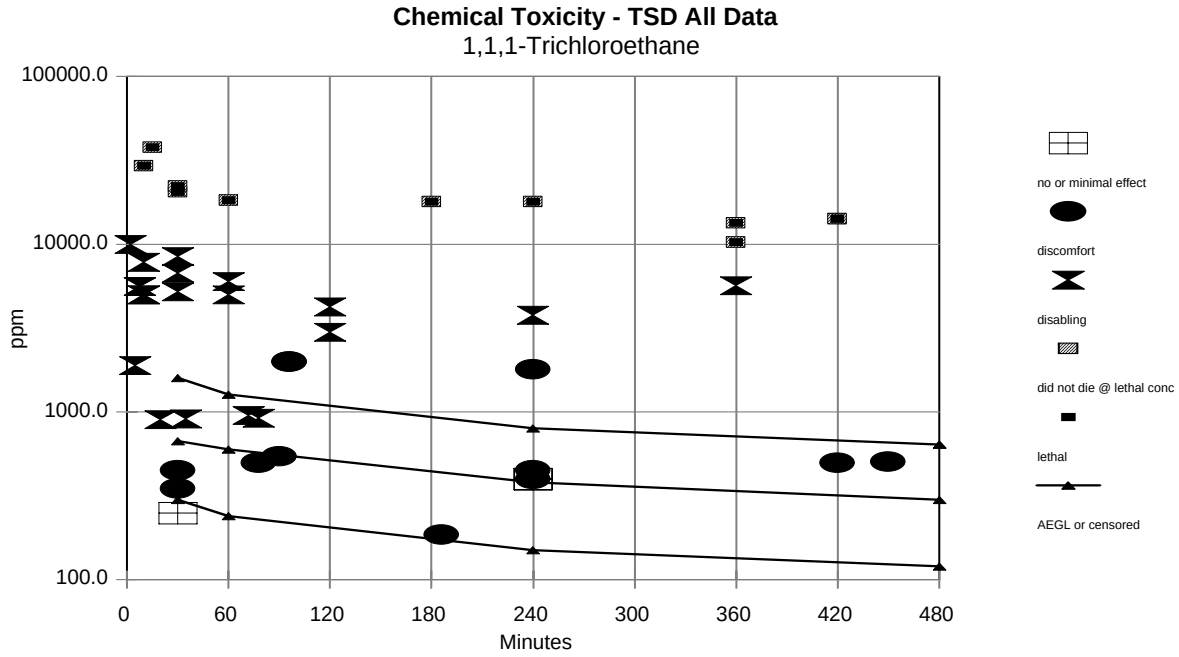

Figure 1. AEGL Values and Support Data for 1,1,1-Trichloroethane

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 9. The 1-hour AEGL-1 and -2 values are similar to but slightly lower than the respective ERPG-1 and -2 values (AIHA, 1999) whereas the 1-hour AEGL-3 value is slightly higher than the ERPG-3. The 30-minute NIOSH IDLH of 700 ppm is close to the 30-minute AEGL-2 of 670 ppm. The 8-hour AEGL-1, considered a safe value for the population, is slightly lower than the 8-hour ACGIH (1999) and OSHA PEL no-effect value for healthy workers of 350 ppm. The ACGIH STEL is 450 ppm. NIOSH (1997) recommends a ceiling value (not to be exceeded at any time) for 1,1,1-trichloroethane of 350 ppm because of its structural similarity to other chloroethanes that are potential occupational carcinogens.

TABLE 9. Extant Standards and Guidelines for 1,1,1-Trichloroethane

Guideline	Exposure Duration					
	10 Minutes	15 Minutes	30 Minutes	1 Hour	4 Hours	8 Hours
AEGL-1	230 ppm		230 ppm	230 ppm	230 ppm	230 ppm
AEGL-2	930 ppm		670 ppm	600 ppm	380 ppm	310 ppm
AEGL-3	4200 ppm		4200 ppm	4200 ppm	2700 ppm	2100 ppm
ERPG-1[a]				350 ppm		
ERPG-2				700 ppm		
ERPG-3				3500 ppm		
NIOSH IDLH[b,c]			700 ppm			
NIOSH REL-TWA						
NIOSH Ceiling[c]		350 ppm				
OSHA PEL[c]						350 ppm
ACGIH TLV-TWA[d]						350 ppm
ACGIH TLV-STEL		450 ppm				
MAK (German)[e]						200 ppm
MAC (Dutch)[f]						100 ppm

[a]AIHA, 1999.
[b]NIOSH, 1994.
[c]NIOSH, 1997.
[d]ACGIH, 1999.
[e]German Reasearch Association, 1999.
[f]Ministry of Social Affairs and Employment, 1999.

8.3. Data Quality and Research Needs

The data base for 1,1,1-trichloroethane is extensive and contains studies on both humans and animals. The majority of these studies support the CNS as being the primary target of exposure. Although deaths of humans have occurred during exposures to unknown concentrations in solvent abuse situations, the combination of occupational exposures, carefully controlled human studies, and its use as an experimental anesthetic (Dornette and Jones, 1960) all with no or minimal untoward effects attest to the safety of this chemical during routine exposures. The age of the subjects in the anesthetic study ranged from 0 to 70 years and the concentrations, up to 26,000 ppm, are far above the 10-minute AEGL-3 of 4800 ppm. An epidemiologic study indicated that ~250 ppm was a NOAEL for CNS effects in workers (Kramer et al., 1978). Several of the seven experimental studies with humans were well designed, well conducted and well documented and used a range of concentrations (220-1900 ppm) and exposure durations (5 minutes at 1900 ppm to 7 hours at 500 ppm) (Torkelson et al., 1958; Stewart et al., 1961;

Stewart et al., 1969; Salvini et al., 1971; Savolainen et al., 1982; Laine et al., 1996). These studies were used to derive and support the AEGL-1 values.

There is considerable information on the concentrations of halogenated hydrocarbon solvents that induce anesthesia and it has been shown that the MAC, the concentration causing lack of movement in 50% of subjects, varies 2-3 fold among all age groups. Cardiac arrhythmias caused by high concentrations usually occur in abuse situations, but may also occur during anesthesia with other anesthetics such as halothane. The human data were used to establish the AEGL-1 level and to support the AEGL-2 level which was based on animal data.

Studies conducted with animals involved six mammalian species and a wide range of exposure durations and concentrations. Exposure durations of 10-minutes to 7 hours are within the range of exposure durations addressed by the AEGLs. Endpoints ranged from no effect to death. The key reference for deriving the AEGL-2 values addressed neurobehavioral effects such as ataxia in rats at several concentrations and at exposure durations of 30 minutes to 4 hours (Mullin and Krivanek, 1982). Two studies with human subjects, Torkelson et al. (1958) and Stewart et al. (1961) support the 10-minute AEGL-2 of 930 ppm as human subjects suffered effects on equilibrium only during exposures to this concentration that were of durations up to seven times the 10-minute value.

AEGL-3 values were derived from animal data that correlates with the mechanism of death observed in humans. The effects observed in human lethalities support the animal data for the CNS being the target system of acute inhalation exposure. As noted, humans have been exposed to short-term concentrations up to 26,000 ppm during experimental anesthesia administration (Dornette and Jones, 1960). This value is far above the 10-minute AEGL-3 of 4800 ppm.

Two of the studies show that for anesthetics such as 1,1,1-trichloroethane, concentration is more important than time when considering a single endpoint. Thus, the n exponents of 3.3 for ataxia in the rat and 3 for death in the rat, applied to the concentration in time scaling ($C^n \times t = k$), are relatively high.

Although human epidemiological data addressing possible reproductive, developmental, teratogenic, and carcinogenic effects of this compound were not available, the animals data addressed these endpoints and indicated that 1,1,1-trichloroethane is not a reproductive or developmental toxicant and is not carcinogenic.

9. REFERENCES

ACGIH. 1999. American Conference of Governmental Industrial Hygienists, Inc. 1,1,1-trichloroethane. In: Threshold Limit Values for Chemical Substances and Physical Agents Biological Exposure Indicies. ACGIH, Cincinnati, OH.

Adams, E.M., H.C. Spencer, V.K. Rowe, and D.D. Irish. 1950. Vapor toxicity of 1,1,1-trichloroethane (methyl chloroform) determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 1:225-36.

AIHA. 1989. American Industrial Hygiene Association. Odor Thresholds for Chemicals with Established Occupational Health Standards. American Industrial Hygiene Association. Fairfax, VA.

AIHA. 1999. The AIHA 1999 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. American Industrial Hygiene Association. Fairfax, VA.

Anderson, H.R., B. Dick, R.S. Macnair, J.C. Palmer, and J.D. Ramsey. 1982. An investigation of 140 deaths associated with volatile substance abuse in the United Kingdom (1971-1981). Human Toxicol. 1:207-221.

Aoki, N., K. Soma, H. Katagiri, Y. Aizawa, T. Kadowaki, and T. Ohwada. 1997. The pulmonary hemodynamic effects of 1,1,1-trichloroethane inhalation. Ind. Health 35:451-455.

Astrand, I., A. Kilbom, I. Wahlberg, et al. 1973. Methylchloroform exposure: I. Concentration in alveolar air and blood at rest and during exercise. Work Environ. Health. 10:69-81.

ATSDR (Agency for Toxic Substances and Disease Registry). 1995. Toxicological Profile for 1,1,1-Trichloroethane (Update). Prepared by Research Triangle Institute under Contract No. 205-93-0606. U.S. Department of Health and Human Services. Public Health Service.

Aviado, D.M. and Belej, M.A. 1974. Toxicity of aerosol propellants on the respiratory and circulatory systems I. Cardiac arrhythmia in the mouse. Toxicology 2:31-42.

Bass, M. 1970. Sudden sniffing death. JAMA 212:2075-2079.

Belej, M.A., D.G. Smith, and D.M. Aviado. 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems IV. Cardiotoxicity in the monkey. Toxicology 2:381-395.

Bonnet, P., J.M. Francin, D. Gradiski, G. Raoult, and D. Zissu. 1980. Determination of the median lethal concentration of principle chlorinated aliphatic hydrocarbons in the rat. Arch. Mal. Prof. 41:317-321.

Bonventre, J., O. Brennan, D. Jason. 1977. Two deaths following accidental inhalation of dichloromethane and 1,1,1-trichloroethane. J. Anal. Toxicol. 1:158-160.

Bowen, S.E. and R.L. Balster. 1996. Effects of Inhaled 1,1,1-trichloroethane on locomotor activity in mice. Neurotoxicol. Teratol. 18:77-81.

Bowen, S.E., J.L. Wiley, E.B. Evans, M.E. Tokarz, R.L. Balster. 1996. Functional observational battery comparing effects of ethanol, 1,1,1-trichloroethane, ether, and flurothyl. Neurotoxicol. Teratol. 18:577-585.

BRRC. (Bushy Run Research Center). 1987a. Developmental toxicity study of inhaled 1,1,1-trichloroethane in CD (Sprague-Dawley) rats. Project report 50-517. Bushy Run Research Center, Export PA.

BRRC. (Bushy Run Research Center). 1987b. Developmental toxicity study of inhaled 1,1,1-trichloroethane in New Zealand white rabbits. Project report 50-514. Bushy Run Research Center, Export PA.

Caplan, Y.H., R.C. Backer, and J.Q. Whitaker. 1976. 1,1,1-trichloroethane Report of a fatal intoxication. Clinical Toxicol. 9:69-74.

Calhoun, L.L., L.G. Lomax, and J.E. Phillips. 1988. Aerothene tt: An acute vapor inhalation study in Fischer 344 rats. EPA/OTS, Doc # 86-880000173.

Carlson, G.P. 1981. Effect of alterations in drug metabolism on epinephrine-induced cardiac arrhythmias in rabbits exposed to methylchloroform. Toxicol. Lett. 9:307-313.

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

Chemfinder.com. 1999. <http://www.chemfinder.com>. Cambridge Soft Corporation. Cambridge, MA. Retrieved online, 8-12-99.

Clark, D.G., and D.J. Tinston. 1982. Acute inhalation toxicity of some halogenated and non-halogenated hydrocarbons. Human Toxicol. 1:239-247.

Coleman, C.N., T. Mason, E.P. Hooker, and S.E. Robinson. 1999. Developmental effects of intermittent prenatal exposure to 1,1,1-trichloroethane in the rat. Neurotox. Teratol. 21:699-708.

Danielson, B.R.G., H. Ghantous, L. Dencker. 1986. Distribution of chloroform and methyl chloroform and their metabolites in pregnant mice. Biol. Res. Preg. Perinatol. 7:77-83.

Dick, R.B. 1988. Short duration exposures to organic solvents: The relationship between neurobehavioral test results and other indicators. Neurotoxicol. Teratol. 10:39-50.

Dornette, W.H.L. and J.P. Jones. 1960. Clinical experiences with 1,1,1-trichloroethane: A preliminary report of 50 anesthetic administrations. Anesth. Analg. 39:249-252.

Droz, P.O., C. Nicole, and E.Guberan. 1982. Sniffing 1,1,1-trichloroethane: Simulation of two fatal cases. In: Collings A.J, Luxon S.G., eds. Safe Use of Solvents. Academic Press, Inc. 153-9.

Franks, N.P. and W.R. Lieb. 1994. Molecular and cellular mechanisms of general anesthesia. Nature 367:607-614.

Gamberale, F., M. Hultengren. 1973. Methylchloroform exposure. II. Psychophysiological functions. Work Environ. Health 10:82-92.

Geller, I., V. Mendez, R.J. Hartmann, E. Gause, W.J. Rippstein Jr. 1982. Effects of 1,1,1-trichloroethane on a match-to-sample discrimination task in the baboon. J. Toxicol. Environ. Health. 9:783-795.

German Research Association (Deutsche Forschungsgemeinschaft). 1999. List of MAK and BAT Values, 1999. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 35. Federal Republic of Germany: Wiley-VCH.

Gocke E., M.T. King, K. Eckhardt, et al. 1981. Mutagenicity of cosmetics ingredients licensed by the European communities. Mutat. Res. 90:91-109.

Gowitt, G.T., and R.L. Hanzlick. 1992. Atypical autoerotic deaths. Am. J. Forensic Med. Pathol. 13:115-119.

Gradiski, D., P. Bonnet, G. Raoult, et al. 1978. Comparative acute inhalation toxicity of the principal chlorinated aliphatic solvents. Arch. Mal. Prof. 39:249-57.

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

Guzelian, P.S. 1991. 1,1,1-Trichloroethane and the liver [letter to the editor]. Arch. Intern. Med. 151:2321-2322.

Halevy J., S. Pitlik, J. Rosenfeld, B-D. Eitan. 1980. 1,1,1-trichloroethane intoxication: a case report with transient liver and renal damage review. Clin. Toxicol. 16:467-472.

Hall, F.B. and C.H. Hine. 1966. Trichloroethane intoxication: A report of two cases. J. Forensic Science 11:404-413.

Hazelton Laboratories. 1989. Four acute inhalation toxicity studies of 1,1,1-trichloroethane in the rat with cover letter dated 032889. EPA/OTS Doc # 89-890000141.

Herd, P.A., M. Lipsky, H.F. Martin. 1974. Cardiovascular effects of 1,1,1-trichloroethane. Arch. Environ. Health 28:227-233.

Hobara, T., H. Kobayashi, E. Higashihara, T. Kawamoto, and T. Sakai. 1984. Acute effects of 1,1,1-trichloroethane, trichloroethylene, and toluene on the hematologic parameters in dogs. Arch. Environ. Contam. Toxicol. 13:589-593.

Hodgson, M.J., A.E. Heyl, D.H. Van Thiel. 1989. Liver disease associated with exposure to 1,1,1-trichloroethane. Arch. Intern. Med. 149:1793-1798.

Hodgson, M.J. and D.H. Van Thiel. 1991. 1,1,1-Trichloroethane and the liver [letter to the editor]. Arch. Intern. Med. 151:2322, 2326.

House, R.A., G.M. Liss, and M.C. Wills. 1994. Peripheral sensory neuropathy associated with 1,1,1-trichloroethane. Arch. Environ. Health 49:196-199.

HSDB (Hazardous Substance Data Base). 1999. MEDLARS Online Information Retrieval System, National Library of Medicine, retrieved 3/8/99.

Ingber, A. 1991. Occupational allergic contact dermatitis from methyl chloroform (1,1,1-trichloroethane). Contact Dermat. 25:193.

IHFA. (Industrial Hygiene Foundation of America, Inc.). 1965. A comparison of the subacute vapor toxicity of chlorotene nu, tri-ethane, type 314, and tri-ethane, type 324. OTS 84003A.

Jones, R.D., and D.P. Winter. 1983. Two case reports of deaths on industrial premises attributed to 1,1,1-trichloroethane. Arch. Environ. Health 38:59-61.

Jones, H.E., P.M. Kunko, S.E. Robinson, and R.L. Balster. 1996. Developmental consequences of intermittent and continuous prenatal exposure to 1,1,1-trichloroethane in mice. Pharmacol. Biochem. Behav. 55:635-646.

Katoh, T. and K. Ikeda. 1992. Minimum alveolar concentration of seroflurane in children. Brit. J. Anaesth. 68:139-41.

Katz M., J.A. Heddle, M .F. Salamone. 1981. Mutagenic activity of polycyclic aromatic hydrocarbons and other environmental pollutants. Chem. Anal. Biol. Fate: Polynucl. Aromat. Hydrocarbons, Int. Sym. 5:519-528.

Kirk-Othmer. 1991. Solvents, Industrial. In Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed., Vol. 21.

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

Kjellstrand, P., L. Maansson, B. Holmquist, I. Jonsson. 1990. Tolerance during inhalation of organic solvents. Pharmacol. Toxicol. 66:409-14.

Koob, G.F. and F.E. Bloom. 1988. Cellular and molecular mechanisms of drug dependence. Science 242:715-723.

Kramer, C., M. Ott, J. Fulkerson, N. Hicks, H. Imbus. 1978. Health of workers exposed to 1,1,1-trichloroethane: A matched-pair study. Arch. Environ. Health 33:331-342.

Laine, A., A.M. Seppalainen, K. Savolainen, and V. Riihimaki. 1996. Acute effects of 1,1,1-trichloroethane inhalation on the human central nervous system. Int. Arch. Occup. Environ. Health 63:53-61.

Landry, T.D., L.L. Calhoun, L.G. Lomax, and J.E. Phillips. 1988. An acute inhalation study of aerosolized 1,1,1-trichloroethane in rats (final report). EPA/OTS, Doc # 86-880000312.

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

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

Lindbohm, M.-L., H.Taskinen, M. Sallmen, and K. Hemminki. 1990. Spontaneous abortions among women exposed to organic solvents. Am. J. Ind. Med. 17:449-463.

Liss, G.M. 1988. Peripheral neuropathy in two workers exposed to 1,1,1-trichloroethane. JAMA 60:2217.

Mackay, C.J., L. Campbell, A.M. Samuel, K.J. Alderman, C. Idzikowski, H.K. Wilson, and D. Gompertz. 1987. Behavioral changes during exposure to 1,1,1-trichloroethane: time-course and relationship to blood solvent levels. Am. J. Indust. Med. 11:223-239.

Mackay. 1990. 1,1,1-trichloroethane : An evaluation in the mouse micronucleus test (final report) with attachments and cover letter dated 10/22/90. Submitted by Halogenated Solvents Industry. U.S. EPA/opts Public Files, Washington, D.C. Fiche #OTS0533133. [Unpublished study].

Maroni, M., C. Bulgheroni, C.M. Grazia. 1977. A clinical, neurophysiological and behavioral study of female workers exposed to 1,1,1-trichloroethane. Scand. J. Work. Environ. Health 3:16-22.

McCarthy, T.B., R.D. Jones. 1983. Industrial gassing poisonings due to trichloroethylene, perchlorethylene, and 1,1,1-trichloroethane. Brit. J. Indust. Med. 40:450-455.

McLeod, A.A., R. Marjot, M.J. Monaghan, P. Hugh-Jones, and G. Jackson. 1987. Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. Brit. Med. J. (Clin. Res. Ed.) 294: 727-729.

Ministry of Social Affairs and Employment (SDU Uitgevers). 1999. Nationale MAC list, 1999. The Hague, The Netherlands.

Monster, A.C., G. Boersma G., and H. Steenweg. 1979. Kinetics of 1,1,1-trichloroethane in volunteers; influence of exposure concentration and work load. Int Arch. Occup. Environ. Health 42:293-300.

Maroni, M., C. Bulgheroni, M.G. Cassitto, F. Merluzzi, R. Gilioli, and V. Foa. 1977. A clinical, neurophysiological and behavioral study of female workers exposed to 1,1,1-trichloroethane. Scand. J. Work Environ. Health 3:16-22.

Moser, V.C., R.L. Balster. 1985. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. Toxicol. Appl. Pharmacol. 77:285-91.

Mullin, L.S., and Krivanek, N.D. 1982. Comparison of unconditioned avoidance tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, and toluene or ethanol. Neurotoxicol. 3:126-137.

Mutti, A., and I. Franchini. Toxicity of metabolites to dopaminergic systems and the behavioural effects of organic solvents. Brit. J. Ind. Med. 44:721-723.

Nilsson, K.B. 1986b. Actions of 1,1,1-trichloroethane on the cAMP metabolism in the mouse brain. Acta Pharmaol. Toxicol. 59:362-369.

Nilsson, K.B. 1986a. Effects of 1,1,1-trichloroethane on the cGMP metabolism in mouse brain. Acta Pharmacol. Toxicol. 58:318-326.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard.... Occupation Exposure to 1,1,1-Trichloroethane (Methyl Chloroform) DHEW Publication No. (NIOSH) 76-184.

NIOSH (National Institute for Occupational Safety and Health). 1997. NIOSH Pocket Guide to Chemical Hazards. NIOSH, Cincinnati, OH, p. 202.

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs). NIOSH, Cincinnati, OH, pp. 313-314.

NIOSH (National Institute for Occupational Safety and Health). 1986. Fatal accident circumstances and epidemiology (FACE) report: Foundry worker dies in Indiana. FACE-86-23. Division of Safety Research, NIOSH, U.S. Department of Health and Human Services, Morgantown, WV.

Nolan, R.J., N.L. Freshour, D.L. Rick. 1984. Kinetics and metabolism of inhaled methyl chloroform (1,1,1-trichloroethane) in male volunteers. Fundam. Appl. Toxicol. 4:654-662.

NTP (National Toxicology Program). 1992. Initial Submission: NTP (DRAFT) Technical Report: Carcinogenesis Bioassay with 1,1,1-trichloroethane in rats and mice via gavage with cover letter dated 080392. EPA/OTS Doc # 88-920005715.

OSHA (Occupational Safety and Health Administration). 1995. Table Z-1. Limits for Air Contaminants. 29 CFR 1900.1000, p. 17.

Paa, G.L., E.A., Emerson, and C.H. Hine. 1958. Relative hepatotoxicity of seven halogenated hydrocarbons. J. Pharmacol. Exp. Ther. 123:225.

Pearson, C.R. 1982. C1 and C2 halocarbons. In: Hutzinger, O., ed. The Handbook of Environmental Chemistry, Berlin, Heidelberg, New York, Springer-Verlag, Vol. 3, Part B, pp. 69-88.

Peoples R.W. and F.F. Weight. 1994. Trichloroethanol potentiation of α-aminobutyric acid-activated chloride current in the mouse hippocampal neurons. Brit. J. Pharmacol. 113:555-563.

Peoples R.W., D.M. Lovinger, and F.F. Weight. 1990. Inhibition of excitatory amino acid currents by general anesthetic agents. Soc. Neurosci. Abstr. 16:1017.

Prendergast, J.A., R.A. Jones, L.J. Jenkins, Jr., and J. Siegel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10:270-289.

Quast, J.F., L.L. Calhoun, L.E. Frauson. 1988. 1,1,1-Trichloroethane formulation: A chronic inhalation toxicity and oncogenicity study in Fischer 344 rats and B6C3F1 mice. Fundam. Appl. Toxicol. 11:611-625.

Reinhardt, C.F., L.S. Mullin, M.E. Maxfield. 1973. Epinephrine-induced cardiac arrhythmia potential of some common industrial solvents. J. Occup. Med. 15:953-5.

Reitz, R.H., J.N. McKougal, M.W. Himmelstein, et al. 1988. Physiologically based pharmacokinetic modeling with methylchloroform: Implications for interspecies, high dose/low dose, and dose route extrapolations. Toxicol. Appl. Pharmacol. 95:185-199.

Salamone, M.F., J.A. Heddle, M. Katz. 1981. Mutagenic activity of 41 compounds in the in vivo micronucleus assay. Prog. Mutat. Res. 1:686-697.

Salvini, M., S. Binaschi, M. Riva. 1971. Evaluation of the psychophysiological functions in humans exposed to the threshold limit value of 1,1,1-trichloroethane. Brit. J. Ind. Med. 28:286-292.

Savolainen H. 1977. Some aspects of the mechanisms by which industrial solvents produce neurotoxic effects. Chem-Bio Interact. 18:1-10.

Savolainen, K. 1981. Pharmacokinetics, pharmacodynamics, and aspects of neurotoxic effects of four inhaled aliphatic chlorohydrocarbon solvents as relevant to man. Eur. J. Drug Metab. Pharmacokinet. 6:85-90.

Savolainen, K., V. Riihimaki, A. Laine. 1982. Biphasic effects of inhaled solvents on human equilibrium. Acta Pharmacol. Toxicol. 51:237-242.

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

Seppalainen, A.M., T. Salmi, K. Savolainen, V. Riihimake. 1983. Visual evoked potentials in short-term exposure of human subjects to m-xylene and 1,1,1-trichloroethane. Zbenden, G.

et al. (ed.). Application of Behavioral Pharmacology in Toxicology, Meeting, Capri, April, 1982. 91p. Raven Press: New York, N.Y., USA. pp. 349-352.

Siegel, J., R.A. Jones, R.A. Coon, and J.P. Lyon. 1971. Effects on experimental animals of acute, repeated and continuous inhalation exposures to dichloroacetylene mixtures. Toxicol. Appl. Pharmacol. 18:168-174.

Silverstein, M.A. 1983. Occupational fatality attributed to 1,1,1-trichloroethane [letter]. Arch. Environ. Health. 38:252.

Stahl, C.J., Fatteh, A.V., and Dominguez, A.M. 1969. Trichloroethane poisoning. Observations on the pathology and toxicology of six fatal cases. J. Forensic Sci. 14:393-397.

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

Stewart, R.D., H.H. Gay, D.S. Erley, Hake, C.L., and Schaffer, A.W. 1961. Human exposure to 1,1,1-trichloroethane vapor: Relationship of expired air and blood concentrations to exposure and toxicity. Am. Ind. Hyg. Assoc. J. 22:252-62.

Stewart, R.D., J.T. Andrews. 1966. Acute toxication with methylchloroform. JAMA 195:904-906.

Stewart, R.D., H.H. Gay, A.W. Schaffer, D.S. Erley, and V.K. Rowe. 1969. Experimental human exposure to methyl chloroform vapor. Arch. Environ. Health 19:467-472.

Taningher, M., S. Parodi, S. Grilli, et al. 1991. Lack of correlation between alkaline DNA fragmentation and DNA covalent binding induced by polychlorethanes after in vivo administration. Problems related to the assessment of a carcinogenic hazard. Cancer Detect. Prev. 15:35-39.

Taylor, G. J., R.T. Drew, E.M. Lores Jr., T.A. Clemmer. 1976. Cardiac depression by haloalkane propellants, solvents, and inhalation anesthetic in rabbits. Toxicol. Appl. Pharmacol. 38:379-387.

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. Haz. Mat. 13:301-309.

Thiele, D.L., E.H. Eigenbrodt, and Ware, A.J. 1982. Cirrhosis after repeated trichloroethylene and 1,1,1-trichloroethane exposure. Gastroenterol. 83:926-929.

Torkelson, T.R. 1994. Halogenated aliphatic hydrocarbons containing chlorine, bromine, and iodine. In Patty's Industrial Hygiene and Toxicology, 4th ed., Volume II, Part E. New York: John Wiley & Sons, Inc., pp. 4007-4251.

Torkelson, T.R., F. Oyen, D.D.McCollister, and V.K. Rowe. 1958. Toxicity of 1,1,1-trichloroethane as determined on laboratory animals and human subjects. Am. Ind. Hyg. Assoc. J. 19:353-362.

Trochimowicz, H.J., C.F. Reinhardt, L.S. Mullin, A. Azar, B.W. Karrh. 1976. The effect of myocardial infarction on the cardiac sensitization potential of certain halocarbons. J. Occup. Med. 18:26-30.

Tsuchimoto, T., B.E. Matter. 1981. Activity of coded compounds in the micronucleus test. Prog Mutat. Res. 1:705-711.

Turina, M.P., A. Colacci, S. Grilli, et al. 1986. Short-term tests of genotoxicity for 1,1,1-trichloroethane. Res. Commun. Chem. Pathol. Pharmacol. 52:305-320.

Warren, D.A., T.G. Reigle, S. Muralidhara, and C.E. Dallas. 1998. Schedule-controlled operant behavior of rats during 1,1,1-trichloroethane inhalation: Relationship to blood and brain solvent concentrations. Neurotoxicol. Teratol. 20:143-153.

WHO. 1992. Health and Safety Guide for 1,1,1-trichloroethane. World Health Organization.

Weast, R.C. 1986. CRC handbook of chemistry and physics, 67th ed, Boca Raton, Florida, CRC Press.

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

Woolverton, W.L., R.L. Balster. 1981. Behavioral and lethal effects of combinations of oral ethanol and inhaled 1,1,1-trichloroethane in mice. Toxicol. Appl. Pharmacol. 59:1-7.

Wrensch, M., S. Swan, J. Lipscomb, D. Epstein, L. Fenster, K. Claxton, P.J. Murphy, D. Shusterman, and R. Neutra. 1990. Pregnancy outcomes in women potentially exposed to solvent-contaminated drinking water in San Jose, California. Am J Epidemiol. 131:283-300

York, R.G., B.M. Sowry, L. Hastings, and J.M. Manson. 1982. Evaluation of teratogenicity and neurotoxicity with maternal inhalation exposure to methyl chloroform. J. Toxicol. Environ. Health. 9:251-266.

APPENDIX A: Time-Scaling Calculations for 1,1,1-Trichloroethane

The data of Mullin and Krivanek (1982) - EC_{50} values for ataxia in rats at time points of 30 minutes and 1, 2, and 4 hours - were fit to a straight line by linear regression (Figure 1). The resulting time-scaling value of n is 3.3.

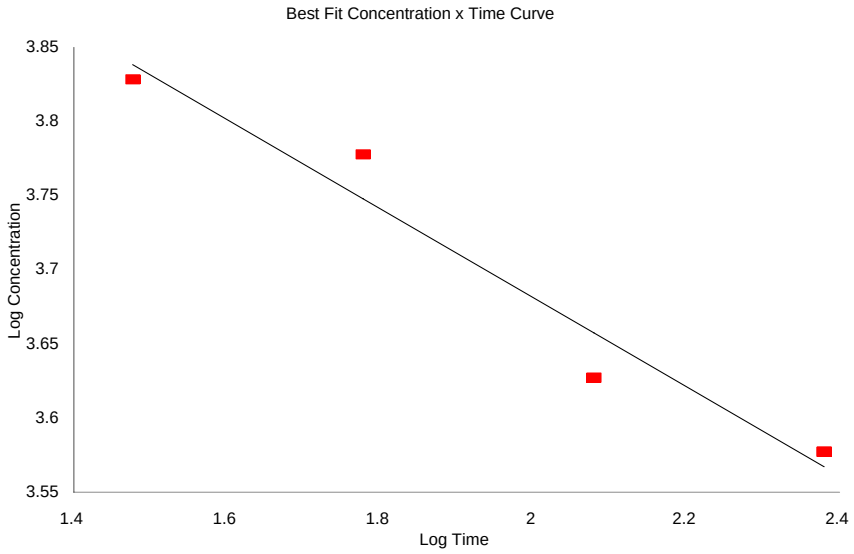

FIGURE 1. Regression curve for ataxia in the rat used for derivation of n.

The rat LC_{50} data of several investigators (Adams et al., 1950; Bonnet et al., 1980; Clark and Tinston, 1982; Calhoun et al., 1988) for the time points of 15 minutes and 3, 4, 6, and 7 hours were fit to a straight line by linear regression (Figure 2). The resulting time-scaling value of n is 3.

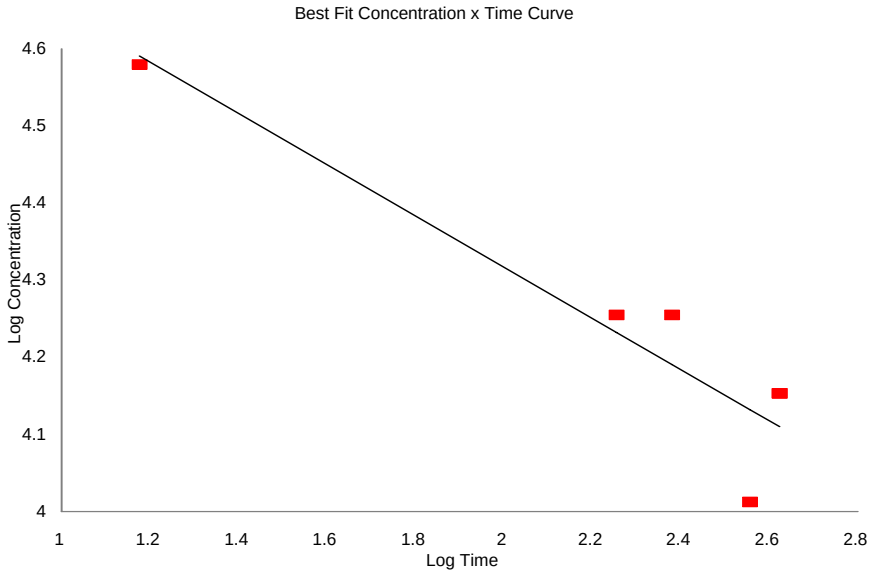

FIGURE 2. Regression curve for rat lethality data used for derivation of n.

APPENDIX B: Derivation of AEGL Values

DERIVATION OF AEGL-1 VALUES

Key study:	Salvini et al., 1971
Toxicity endpoint:	Eye irritation, mental fatigue during 4-hour exposure to 450 ppm
Scaling:	None
Uncertainty factors:	2 for intraspecies variability; subjects were healthy adult humans
10-minute AEGL-1:	230 ppm
30-minute AEGL-1:	230 ppm
1-hour AEGL-1:	230 ppm
4-hour AEGL-1:	230 ppm
8-hour AEGL-1:	230 ppm

DERIVATION OF AEGL-2 VALUES

Key study:	Mullin and Krivanek (1982)
Toxicity endpoint:	Ataxia in rats
Scaling:	$C^{3.3} \times t = k$ based on the EC_{50} for ataxia in rats: 0.5 hours, 6740 ppm; 1 hour, 6000 ppm; 2 hours, 4240 ppm; and 4 hours, 3780 ppm.
Uncertainty factors:	3 for intraspecies variability and 3 for interspecies variability for a total of 10
	The closest experimental exposure duration was used 10 and 30 minutes: 6740 ppm/10 = 670 ppm 1 hour: 6000 ppm/10 = 600 ppm 4 and 8 hour: 3780 ppm/10 = 380 ppm

Calculations

10-minute AEGL-2 : $(670 \text{ ppm})^{3.3} \times 30 \text{ minutes} = 6.4 \times 10^{10} \text{ ppm}^{3.3}\cdot\text{min}$
Divide k by 10 and take 3.3 route
C = 930 ppm

30-minute AEGL-2: C = 670 ppm

1-hour AEGL-2: C = 600 ppm

4-hour AEGL-2: C = 380 ppm

8-hour AEGL-2: $(380 \text{ ppm})^{3.3} \times 240 \text{ minutes} = 7.8 \times 10^{10} \text{ ppm}^{3.3}\cdot\text{min}$
C = 310 ppm

DERIVATION OF AEGL-3 LEVELS

Key study:	Bonnet et al. (1980)
Toxicity endpoint:	The concentration resulting in no deaths (7000 ppm) was estimated from the concentration-lethality curve for several 6-hour exposures.
Uncertainty factors:	1 for interspecies 3 for intraspecies
Scaling:	$C^3 \times t = k$ (based on LC_{50} values of several studies $(7000 \text{ ppm}/3)^3 \times 360 \text{ minutes} = 4.57 \times 10^{12} \text{ ppm}^3\cdot\text{minutes}$
Calculations	
10-minute AEGL-3:	4200 (same as 1-hour value to protect against cardiac sensitization (Reinhardt et al., 1973)
30-minute AEGL-3:	4200 (same as 1-hour value to protect against cardiac sensitization (Reinhardt et al., 1973)
1-hour AEGL-3:	$C^3 \times 60 \text{ minutes} = 4.57 \times 10^{12} \text{ ppm}^3\cdot\text{minutes}$ $C^3 = 7.6 \times 10^{10} \text{ ppm}$ $C = 4240 \text{ ppm}$
4-hour AEGL-3:	$C^3 \times 240 \text{ minutes} = 4.57 \times 10^{12} \text{ ppm}^3\cdot\text{minutes}$ $C^3 = 1.91 \times 10^{10} \text{ ppm}$ $C = 2670 \text{ ppm}$
8-hour AEGL-3:	$C^3 \times 480 \text{ minutes} = 4.57 \times 10^{12} \text{ ppm}^3\cdot\text{minutes}$ $C^3 = 9.5 \times 10^{9} \text{ ppm}$ $C = 2119 \text{ ppm}$

APPENDIX C: Derivation Summary for 1,1,1-Trichloroethane AEGLs

ACUTE EXPOSURE GUIDELINES FOR 1,1,1-TRICHLOROETHANE (CAS NO. 71-55-6) DERIVATION SUMMARY

AEGL-1 VALUES				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
230 ppm	**230 ppm**	**230 ppm**	**230 ppm**	**230 ppm**

Key Reference: Salvini, M., S. Binaschi, and M. Riva. 1971. Evaluation of the psychophysiological functions in humans exposed to the threshold limit value of 1,1,1-trichloroethane. Brit. J. Ind. Med. 28(3):286-92.

Test Species/Strain/Number: Human/6

Exposure Route/Concentrations/Durations: Inhalation/450 ppm/4 hours

Effects: Eye irritation, slight dizziness, mental fatigue (450 ppm for 4 hour was determinant for AEGL-1)

Endpoint/Concentration/Rationale: Threshold for eye irritation and mild CNS effects.

Uncertainty Factors/Rationale:
Interspecies = 1: subjects were human
Intraspecies = 2: threshold for CNS effects does not vary by more than 2-3 fold among humans

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: None

Data Adequacy: A well-conducted study in a human population was available and the database consisting of several similar studies supports this endpoint and level.

AEGL-2 VALUES				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
930 ppm	**670 ppm**	**600 ppm**	**380 ppm**	**310 ppm**

Key Reference: Mullin, L.S., and N.D. Krivanek. 1982. Comparison of unconditioned avoidance tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, and toluene or ethanol. Neurotoxicol. 3(1):126-37.

Test Species/Strain/Number: Rat/Charles River-CD/groups of six, males

Exposure Route/Concentrations/Durations: Inhalation/0, 1500, 3000, 6000, or 12,000 ppm/0.5, 1, 2, and 4 hours

Effects: EC_{50} for ataxia at 6740, 6000, 4240, and 3780 ppm after 0.5, 1, 2, 4, and 8 hour exposures, respectively

Endpoint/Concentration/Rationale: Ataxia indicates loss of equilibrium that might impede escape.

Uncertainty Factors/Rationale:
Interspecies = 3: Similar metabolism and toxicity in rats and humans; higher blood:air partition coefficient in rodents than in humans
Intraspecies = 3: MAC for volatile anesthetics varies by 2-3 fold among humans

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied; insufficient data

Time Scaling: $C^n \times t = k$ where n = 3.3, value derived from EC_{50} data for ataxia in the rat ranging from 30 minutes to 4 hours. Data point used for AEGL-2 derivation were 0.5, 1, and 4 hours. Other time points were based on extrapolation. Extrapolation to 10-minute values based on $k = 6.4 \times 10^{10}$ $ppm^{3.3} \cdot$minutes. Extrapolation to 8-hour values based on $k = 7.8 \times 10^{10}$ $ppm^{3.3} \cdot$minutes.

Data Adequacy: The key study with rats was well designed, conducted and reported. Several human studies that report similar effects at the derived AEGL-2 values support the AEGL-2 values.

AEGL-3 VALUES				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
4200 ppm	**4200**	**4200 ppm**	**2700 ppm**	**2100 ppm**

Key Reference: Bonnet, P., J.M. Francin, D. Gradiski, G. Raoult, and D. Zissu. 1980. Determination of the median lethal concentration of principle chlorinated aliphatic hydrocarbons in the rat. Arch. Mal. Prof. 41:317-21.

Test Species/Strain/Sex/Number: Rat/Sprague-Dawley/12/males/concentration

Exposure Route/Concentrations/Durations: Inhalation: 6 hour exposures to several concentrations presented graphically. Concentration causing no deaths estimated from graph (7000 ppm)

Endpoint/Concentration/Rationale: 7000 ppm/ threshold for death for 6-hour exposure in rats

Effects: LC_{50} of 10,305 ppm for 6-hour exposure; concentration resulting in no deaths (7000 ppm) estimated from concentration-effect curve.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies = 1: human and rat data suggest little interspecies variability; higher blood:air partition coefficient in rodents than in humans
Intraspecies = 3: MAC for volatile anesthetics varies by 2-3 fold among humans

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applied; insufficient data

Time Scaling: $C^n \times t = k$ where $n = 3$ and $k = 4.57 \times 10^{12}$ $ppm^3 \cdot$minutes; value derived from rat lethality data ranging from 15 minutes to 7 hours. Data point used for AEGL-3 derivation was 6 hours. Other time points were based on extrapolation. Ten- and 30-minute values were flatlined to the 1-hour value so as not to exceed the threshold for cardiac sensitization of 5000 ppm in the dog.

Data Adequacy: The study was well designed and conducted, but the concentration resulting in no deaths had to be estimated from a graph. The endpoint is appropriate for deriving AEGL-3 values. Studies with another species would result in higher values. The values are supported by the safe use of this chemical at concentrations of 10,000 to 26,000 ppm as an anesthetic for humans. The exposure durations during the anesthesia studies are unknown.