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**Item 4937**

**United States Environmental Protection Agency  
Office of Pollution Prevention and Toxics**

**1,1,1-TRICHLOROETHANE**  
**CAS Reg. No. 71-55-6**

**PROPOSED ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)**

**“PUBLIC DRAFT”**

## PREFACE

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

AEGLs represent ceiling exposure values for the general public and are applicable to emergency exposure periods ranging from less than 1 hour to 8 hours. Three AEGLs will be developed for each of four exposure periods (30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. The three AEGLs have been defined as follows:

**AEGL-1** is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but not necessarily “hypersusceptible” individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.

**AEGL-2** is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but not necessarily “hypersusceptible” individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below AEGL-2 but at or above AEGL-1 represent exposure levels which may cause notable discomfort.

**AEGL-3** is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but not necessarily “hypersusceptible” individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

## 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 (Nolan et al., 1984). 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 involve effects on the 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 does not seem to be a developmental toxin although reliable epidemiological data for humans are unavailable. 1,1,1-Trichloroethane does not seem to have 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  $n = 3.3$  or  $3$ .

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 hr sessions separated by a 1.5 hr interval (Salvini et al., 1971). Stewart et al. (1969) exposed human subjects to TWA concentration of 500 ppm for 7 hr repeatedly for 5 days, the only consistent complaint was mild sleepiness and failure of the Romberg test by two of the subjects which had trouble with this test initially. Torkelson et al. (1958) reported a NOAEL for the Romberg test in humans after exposure to a TWA of 506 ppm for 7.5 hr. For derivation of the AEGL-1, the observations of Salvini et al. (1971) were used as the starting point for the threshold of eye irritation and very subtle CNS effects in humans at a concentration of 450 ppm for 4 hr. An uncertainty factor of 2 was chosen 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 which should be protective of sensitive individuals. The resulting figure of 230 ppm was used at all 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.

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 min, 1, 2, and 4 hr exposures to be 6740, 6000, 4240, and 3780 ppm. These values were used as the basis for AEGL-2 derivation using an uncertainty factor of 10 and extrapolations were made to the 10-minute and 8 hr time points using the equation  $C^n \times t = k$ , where  $n = 3.3$  based on the data presented by Mullin and Krivanek (1982). An uncertainty factor of 10 was applied which 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 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 the concentration exposure-durations applied in experimental human studies which resulting in effects that could impede escape i.e., CNS intoxication.

The AEGL-3 values were derived from a lethality concentration-effect curve in the mouse for a 6 hr exposure-duration (Bonnet et al., 1980). The  $LC_0$  was conservatively estimated from this curve as a concentration of about 7000 ppm for a 6 hr exposure-duration. An extrapolation was made to the 30 min, 1, 4, and 8 hr time points using the equation  $C^n \times t = k$ , where  $n = 3$  based on the rat lethality data. An uncertainty factor of 10 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 3 was used because of the similarities in toxicity, metabolism, and excretion of 1,1,1-trichloroethane in rats compared to humans. The resulting concentrations were multiplied by a modifying factor of 3 in order to achieve a reasonable concentration at which humans might experience life-threatening toxic effects. This factor is justified by the existence of a higher blood:air partition coefficient for rats 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.

| SUMMARY OF PROPOSED AEGL VALUES (ppm [mg/m <sup>3</sup> ]) |                              |                 |                 |                 |                 |   |
|--|------------------------------|-----------------|-----------------|-----------------|-----------------|---|
| Classification   | 10-minute                    | 30-minute       | 1-hour          | 4-hour          | 8-hour          | Endpoint (Reference)  |
| AEGL-1   | 230<br>(1252)                | 230<br>(1252)   | 230<br>(1252)   | 230<br>(1252)   | 230<br>(1252)   | Eye irritation and slight dizziness in humans observed by Salvini et al. (1971) |
| AEGL-2   | 930<br>(5064)                | 670<br>(3650)   | 600<br>(3270)   | 380<br>(2070)   | 300<br>(1633)   | EC <sub>50</sub> for ataxia in rats, Mullin and Krivanek, (1982)                |
| AEGL-3   | 4800 <sup>a</sup><br>(26135) | 4800<br>(26135) | 3800<br>(20690) | 2400<br>(13067) | 1900<br>(10345) | LC <sub>0</sub> extrapolated from Bonnet et al. (1980)                          |

<sup>a</sup> The 30-minute value was used as the 10-minute value so as not to exceed the threshold for cardiac sensitization observed in dogs (Reinhardt et al., 1973).

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## 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 reportedly 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 the general population and for occupationally exposed individuals. Workers have been chronically exposed to concentrations up to 249 ppm with no untoward effects (Kramer 1978). Concentrations of up to 16 ppb have been determined in air sampled near industries producing or handling this chemical (USEPA, 1984).

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 hr, and greater than 95% is eliminated within 50 hr (Astrand et al., 1973; Monster et al., 1979; Nolan et al., 1984). The biological half-life in human urine is  $8.7 \pm 1.8$  hr (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 volatile carbon dioxide (ATSDR, 1995; Nolan et al., 1984). These metabolites have much longer half-lives than 1,1,1-trichloroethane itself (27 and 76 hr, 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 physicochemical properties of 1,1,1-trichloroethane are given in Table 1.

| TABLE 1. PHYSICOCHEMICAL DATA FOR 1,1,1-TRICHLOROETHANE |  |                            |
|---|--|----------------------------|
| Parameter   | Value  | Reference                  |
| Common name   | Methylchloroform   | –                          |
| Synonyms  | Chloroethene; chlorotene; chloroethene; Methyltrichloromethane; trichloroethane; $\alpha$ -trichloroethane | ATSDR (1995)               |
| CAS registry no.  | 71-55-6  | www.chemfinder.com         |
| Chemical formula  | C <sub>2</sub> H <sub>3</sub> Cl <sub>3</sub>  | www.chemfinder.com         |
| Molecular weight  | 133.4  | www.chemfinder.com         |
| Physical state  | clear liquid   | www.chemfinder.com         |
| Vapor pressure  | 103 mm at 20°C   | Weast (1986)               |
| Vapor density (air = 1)                                 | 4.6  | USEPA (1984)               |
| Specific gravity  | 1.3249 (26/4°C)  | Clayton and Clayton (1994) |
| Boiling/flash point                                     | 74.1°C   | Clayton and Clayton (1994) |
| Melting point   | -30.4°C  | HSDB                       |
| log Kow   | 2.49   | HSDB                       |
| Solubility in water                                     | 0.480 g/L at 20 °C   | Pearson (1982)             |
| Conversion factors in air                               | 1 ppm in air = 5.4 mg/m <sup>3</sup>   | ATSDR (1995)               |
| Odor threshold  | 390 ppm detection, 710 ppm recognition (range 16-714 ppm)  | AIHA (1989)                |

## 2. HUMAN TOXICITY DATA

### 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. Unfortunately, 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 14000 ppm, and in the second case, the young man exposed himself to concentrations between 10000 and 20000 ppm. Other situations of intentional intoxications which resulted in fatalities have been reported by Gowitt et al. (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 hr 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 sequela 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**

Ingerber (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 yrs 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 hepatotoxicity 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-yr-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 extrasystoles, 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 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 Romberg test for example is a measure of equilibrium with the eyes closed, 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 hr 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. (1981) examined the effects of 200 and 400 ppm (TWA) 4 hr inhalation exposures 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.

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 subjec-

tive 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. 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 min 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 min after the exposure. In the next experiment, 6 male volunteers were exposed to 500 ppm for 186 min with no untoward effects reported. When three subjects were exposed to 955 ppm for 73 min, 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 min after the exposure had ended. Two subjects were exposed to 910 ppm for 35 min, 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 min, 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 min period. At concentrations ranging from 0 - 1000 ppm subjects stated that they were aware of a sweet odor, from 1000 - 1100 ppm, 6/7 subjects reported mild eye irritation, 1900 - 2000 ppm produced mild throat irritation in 6/7 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.

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 min, 415 - 590 ppm for 450 min, or 890 - 1190 ppm for 30 min. Subjects did report noticing a definite odor at these concentrations. When subjects were exposed to concentrations ranging between 900 - 1000 ppm for 70 min, 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 min experienced a noticeable odor as well as obvious disturbances of equilibrium.

Subjective and objective psychophysiological functions were evaluated after 30 min exposures to increasing measured concentrations of 1,1,1-trichloroethane (Gambarale and Hultengren, 1973). Twelve healthy male subjects were repeatedly tested during exposure to 250, 350, 450, and 550 ppm with a five min. 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 min). This means the blood concentrations were increasing during the 2 hr exposure and were not reflective of actual solvent concentrations administered during each 0.5 hr exposure period.

Stewart et al. (1969) conducted a similar study with eleven healthy subjects 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 hr, and 50% were unable to detect the odor after 6 hr. 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's test in two of the subjects during the exposure; within ten minutes following cessation, both subjects were able to perform this test normally.

Six healthy male students were exposed to average vapor concentrations of 450 ppm (TWA range 400-500 ppm) for two periods of 4hr separated by a 1.5 hr 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 hr 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 hr 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 9-70 yr 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 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 min after discontinuation of the anesthetic.

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 BUN. Also, no CNS effects were reported for even the highest exposure group. Therefore, 249 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 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.

**TABLE 2: EFFECTS OF EXPOSURE TO 1,1,1-TRICHLOROETHANE IN HUMANS**

| <b>Concentration (ppm)</b> | <b>Duration</b>                    | <b>Effect</b>   | <b>Reference</b>               |
|----------------------------|------------------------------------|---|--------------------------------|
| 250                        | 0.5 hr                             | NOAEL for reaction time and perceptual speed  | Gamberale and Hultengren, 1973 |
| 350                        | 0.5 hr                             | subtle but statistically significant changes in perceptual speed  | Gamberale and Hultengren, 1973 |
| 400 TWA                    | 4 hr                               | NOAEL for body sway, reaction time and critical flicker fusion  | Savolainen et al. 1982         |
| 400                        | 4 hr                               | ↓ latency of cortical response for Visually Evoked Potentials   | Seppalainen et al. 1983        |
| 450                        | 0.5 hr                             | subtle but statistically significant changes in perceptual speed, reaction time, manual dexterity                     | Gamberale and Hultengren, 1973 |
| 450                        | 4 hr ,2 sessions w/1.5 hr interval | eye irritation, slight dizziness and mental fatigue (symptoms did not increase in severity during the second session) | Salvini et al. 1971            |
| 440-561 (500)              | 6.5 - 7 hr, 5/d                    | mild sleepiness, abnormal Romberg test  | Stewart et al. 1969            |
| 450-710 (546)              | 1.5 hr                             | NOAEL subjective and Romberg test   | Torkelson et al. 1958          |
| 415-590 (506)              | 7.5 hr                             | Odor detection that dissipated, NOAEL Romberg   | Torkelson et al. 1958          |
| 500                        | 1.3 hr                             | eye irritation in 3/6 subjects  | Stewart et al. 1961            |
| 500                        | 3.1 hr                             | No effects reported   | Stewart et al. 1961            |
| 900                        | 20 min                             | lightheadedness, 1/2 positive Romberg test  | Stewart et al. 1961            |
| 910                        | 35 min                             | 1/2 lightheadedness, Romberg more difficult   | Stewart et al. 1961            |
| 955                        | 1.2 hr                             | 1/3 positive Romberg test   | Stewart et al. 1961            |
| 900-1000 (920)             | 1.3 hr                             | strong odor, loss of equilibrium, 3/4 lightheadedness   | Torkelson et al. 1958          |
| 1740-2180 (1900)           | 5 min                              | Equilibrium loss  | Torkelson et al. 1958          |
| 10,000 - 26,000            | 2 min                              | induction of light plane anesthesia   | Dornette and Jones 1960        |
| 6000 - 22,500              | –                                  | maintenance of light anesthesia during surgical procedures  | Dornette and Jones 1960        |

## **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 or hypoxic anoxia as a result of anesthetic hypotension and hemorrhage. 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 hr. Based on the available data, a NOAEL for the threshold of subtle CNS effects seems to be about 350 ppm for durations up to 8 hr, the established TLV. Concentrations above 900 ppm for periods of 70-75 min appeared 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 min 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 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<sub>50</sub> data for rats and mice are summarized in Table 3 (Section 3.6).

#### **3.1.1 Rats**

Clark and Tinston (1982) determined a 15 min LC<sub>50</sub> 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 min LC<sub>50</sub> was determined to be 38,000 ppm. Death was characterized by slight ataxia, loss of righting reflex, prostration, shallow respiration, and death eventually from respiratory depression.

Adams et al. (1950) reported measured inhalation LC<sub>50</sub> values of 18000 ppm and 14250 ppm for 3 and 7 hr exposures, respectively in five Wistar rats/sex/group. At 5000 ppm a narcotic effect was noticed within 1 hr characterized by hypoactivity and increased ease of handling. After exposure to 10000 ppm, decreased activity was noticeable initially, followed by ataxia and prostration; after 3 hr, 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 hr. At 15000 and 18000 ppm effects were the same but with a more rapid onset.

A measured inhalation LC<sub>50</sub> value for a six hour exposure in 12 male Sprague-Dawley rats/group was reported by Bonnet et al. (1980) as 10305 ppm. Intoxication was characterized by hypoactivity followed by unconsciousness 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 15523, 18425, or 21063 ppm. All rats exposed to 21063 ppm died during exposure as well as 3 females that were exposed to 18425 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-wk observation period had no gross exposure-related abnormalities. An LC<sub>50</sub> of between 18425 and 21033 ppm was reported for males, and 18000 ppm was reported for female rats (Calhoun et al., 1988). Similar results were obtained in a 4-hr acute inhalation exposure conducted by Seigel et al. (1971). In this experiment, an LC<sub>50</sub> of 18400 ppm was obtained using Sprague-Dawley rats.

In another acute inhalation toxicity study conducted at Hazelton Labs (1989) five Sprague-Dawley rats/sex/group were exposed to measured concentrations between 12564 and 16017 ppm for four hours. In this study, LC<sub>50</sub> values were calculated to be 13268 ppm, 13426, and 13338 for males, females, and combined, respectively. Clinical signs included observations of neuromuscular dysfunction, increased secretory responses, as well as general “poor condition”. Increased incidence of rough/pitted/granular spleens was observed in the 14-day survivors.

### **3.1.2 Mice**

Moser and Balster (1985) calculated LC<sub>50</sub> values for CD-1 male albino mice at 10, 30, and 60 min 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<sub>50</sub> values obtained were 29492, 20616, and 18358 for the 10, 30, and 60 min 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<sub>50</sub> 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 min LC<sub>50</sub> of 22241 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.

### **3.1.3 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 hr/day, 5 days/wk for 4 wk. 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 wk observation period.

## **3.2 Nonlethal Toxicity**

### **3.2.1 Monkeys and Baboons**

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-hr in an atmosphere controlled chamber (Geller et al., 1982). Behavioral tasks were carried out during the 3<sup>rd</sup> and 4<sup>th</sup> hr 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 hr. The animal displayed ataxia after about 1 hr, and after about 5 hr, 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.

### 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 hr; an additional group of five dogs was exposed to a concentration of 700 ppm for four hours. Hematological parameters were analyzed to determine possible effects of this solvent. A transient decrease in leukocytes was observed after 1 hr at 700 ppm where a decrease of 60-70% was evident 30 min 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 10000 ppm for ten minutes via a one-way face mask then were given two pharmacologic doses of epinephrine (8  $\mu\text{g}/\text{kg}$ ) in the cephalic vein with a ten min 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.

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.

### 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 min  $\text{EC}_{50}$  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 min  $\text{EC}_{50}$  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 min. 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 hr 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 hr during exposure and 18 hr after exposure. The  $\text{EC}_{50}$  values for loss of righting reflex and ataxia are presented in Table 3. Rats began to fail the unconditioned reflex tests after 2 hr at 3000 ppm, while conditioned avoidance responses became impaired at 6000 ppm.

### 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/responding then a decrease followed by an anesthetic-like effect characterized by hypoactivity and loss of consciousness at higher concentrations.

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 min exposure periods by Moser and Balster (1985). These concentrations were 7807, 5216, and 5674 ppm for the 10, 30, and 60 min time points, respectively. Woolverton and Balster (1981) determined the  $EC_{50}$  for a 30 min exposure to be 5173 ppm. Half the animals recovered within five minutes of the exposure and all recovered within 60 min even at the highest concentration tested (7000 ppm).

Kjellstrand et al. (1985) examined the effect of 1 hr exposures to measured concentrations of 2000, 1300, or 890 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 min. 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 under static or dynamic conditions (flow rates of 10 L/min). Under static conditions activity increased from the 1250 ppm up to a peak at 5000 ppm concentrations, then decreased rapidly at higher concentrations. Under dynamic conditions, the increase and decrease occurred at much lower concentrations such that the concentration-effect curve was shifted to the left about 4-fold.

Following a 20-min inhalation exposure to nominal concentrations of 1,1,1-trichloroethane at 0, 4000, 8000, 10000, 133000, or 180000 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 - 10000) ppm, produced excitement, while higher concentrations produced hypoactivity and an anesthetic effect. All the concentrations tested 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 min. This exposure produced 2<sup>nd</sup> degree block during all exposures and there was no difference in the arrhythmia when epinephrine (6

$\mu\text{g}/\text{kg}$ ) 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 min 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 ( $3 \mu\text{g}/\text{kg}$ ) induced premature ventricular contractions. These premature contractions occurred within 7.5 min of commencement of exposure, but were abolished with discontinuation of 1,1,1-trichloroethane exposure.

### 3.3 Developmental/Reproductive Toxicity

Four groups of female Long-Evans rats were exposed by inhalation to  $2100 \pm 200$  ppm 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, pregnant Sprague-Dawley rats were exposed to mean analytical concentrations of 0, 1017, 3122, or 5906 ppm during gestational days 6-15. Significant decreases in body weight gain among dams were observed in the 1000, 3000, and 6000 ppm groups. Significant decreases in food (3000 and 6000 ppm) and water (6000 ppm) 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 embryotoxicity or teratogenicity was observed at any exposure concentration (BRRC 1987a).

Schwetz et al. (1975) exposed pregnant Swiss-Webster mice and Sprague-Dawley rats to 1,1,1-trichloroethane vapor at a concentration of  $875 \pm 27$  ppm 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 6 hr/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).

### 3.4. Genotoxicity

*In vivo* assays to determine the genotoxic potential in various mouse cell 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 Tanningher 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<sub>1</sub> mice; 80/sex/group were exposed to vapor concentrations of 0, 150, 500, or 1500 ppm 1,1,1-trichloroethane 6 hr/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<sub>50</sub> data and the neurobehavioral data available in rats and mice is presented in Tables 3 and 4, respectively. 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 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 delays in rats and mice. Chronic inhalation studies in rats and mice indicate no carcinogenic potential of this compound in these species.

| <b>Species</b> | <b>Duration</b> | <b>Concentration</b> | <b>Reference</b>             |
|----------------|-----------------|----------------------|------------------------------|
| mouse          | 10 min          | 29492                | Moser and Balster, 1985      |
| rat            | 15 min          | 38,000               | Clark and Tinston, 1982      |
| mouse          | 30 min          | 20616                | Moser and Balster, 1985      |
| mouse          | 30 min          | 22241                | Woolverton and Balster, 1981 |

|       |        |       |                         |
|-------|--------|-------|-------------------------|
| mouse | 60 min | 18358 | Moser and Balster, 1985 |
| rat   | 3 hr   | 18000 | Adams et al., 1950      |
| rat   | 4 hr   | 18000 | Calhoun et al., 1988    |
| rat   | 6 hr   | 10305 | Bonnet et al., 1980     |
| mouse | 6 hr   | 13414 | Gradiski et al., 1978   |
| rat   | 7 hr   | 14250 | Adams et al., 1950      |

#### **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.

**TABLE 4: SUMMARY OF ANIMAL NEUROBEHAVIORAL TOXICITY  
DATA WITH 1,1,1-TRICHLOROETHANE**

| Species | Duration (hr)              | Concentration (ppm)          | Effect  | Reference                  |
|---------|----------------------------|------------------------------|---|----------------------------|
| Baboon  | 4 hr                       | 1800 and 2100                | no effect on correct responses, 29 & 33% fewer trials                           | Geller et al. (1982)       |
| Rat     | 10 min                     | 5000                         | EC <sub>50</sub> for loss of righting reflex                                    | Clark and Tinston (1982)   |
| Rat     | 1.6 hr                     | 2000, 3500, and 5000         | concentration-related decrease in responding in a schedule-controlled situation | Warren et al. (1988)       |
| Rat     | 2 hr                       | 3000                         | EC <sub>50</sub> failure of unconditioned responses                             | Mullin and Krivanek(1982)  |
| Rat     | 0.5, 1, 2, 4 hr            | 8480                         | EC <sub>50</sub> loss of righting reflex  | Mullin and Krivanek (1982) |
| Rat     | 0.5<br>1<br>2<br>4         | 6740<br>6000<br>4240<br>3780 | EC <sub>50</sub> Ataxia   | Mullin and Krivanek (1982) |
| Mouse   | 10 min<br>30 min<br>60 min | 7807<br>5216<br>5674         | EC <sub>50</sub> failure on inverted screen test                                | Moser and Balster (1985)   |

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, it is rapidly cleared from the body as evidenced by the rapid recovery rates observed after anesthetic concentrations were produced 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 hr, and greater than 95% is eliminated within 50 hr (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 volatile carbon dioxide (ATSDR, 1995; Nolan et al., 1984). These metabolites have much longer half-lives than 1,1,1-trichloroethane itself (27 and 76 hr, 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 exposures 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<sub>A</sub> 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 Intraspecies and Interspecies Variability**

Comparison of LC<sub>50</sub> values for the rat and mouse shows a slight difference in sensitivity between these species. The 6 hr LC<sub>50</sub> in rats was calculated by Bonnet et al. (1980) as 10,305 ppm and the LC<sub>50</sub> in mice for the same timepoint 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 the 1 hr mouse EC<sub>50</sub> 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 hr EC<sub>50</sub> for ataxia in rats.

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; Matthew, 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" (ie 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.

#### **4.4.2 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  $n$  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 min, 1, 2, and 4 hr were analyzed to determine the least-squares linear curve fit of the graph (Fig. 1), log time vs log  $EC_{50}$ . The equation for the resulting line was  $y = 4.2823 - 0.3004 x$ , since  $n = -1/\text{slope}$ ,  $n = 3.3$ .

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 min  $LC_{50}$  was calculated by Clark and Tinston, (1982), the 3 and 7 hr values by Adams et al. (1950), the 4 hr by Calhoun et al. (1988), and the 6 hr by Bonnet et al. (1980) were used to determine the least-squares linear curve fit of the graph (Fig. 2), log time vs log  $LC_{50}$ . The resulting equation for the line was  $y = 4.98 - 0.33 x$  and  $n = -1/\text{slope}$ , therefore, the value of the exponent  $n$  is 3.0.

Values scaled for the derivation of the 10 min, 30 min, 1, 4, and 8 hr timepoints 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. RATIONALE AND PROPOSED AEGL-1**

AEGL-1 is the airborne concentration (expressed as ppm or  $mg/m^3$ ) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.

#### **5.1 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 hr (Stewart et al.,

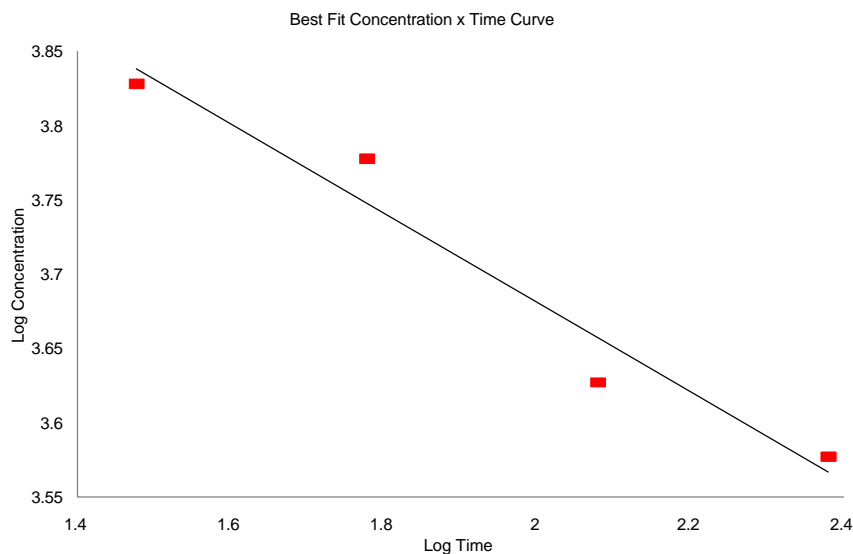


FIGURE 1. Regression curve for ataxia in the rat used for derivation of n.

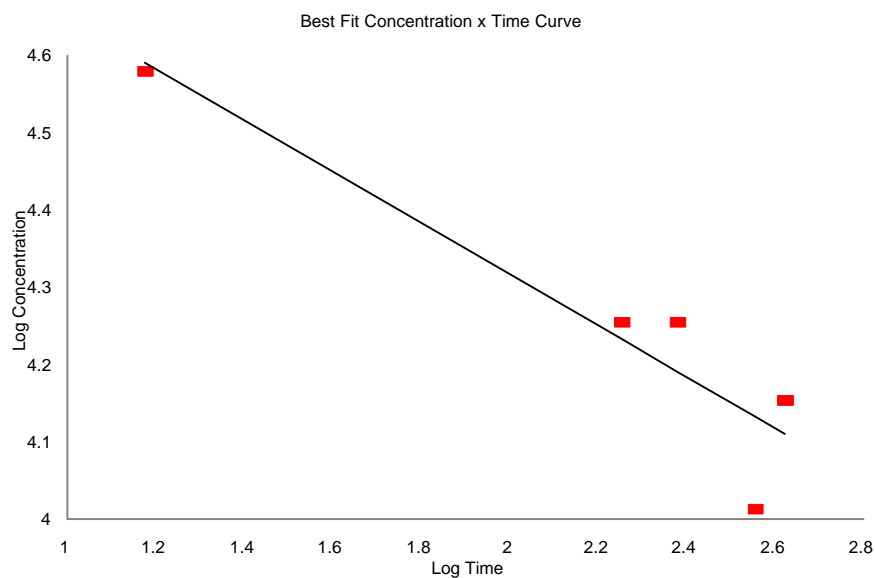


FIGURE 2. Regression curve for rat lethality data used for derivation of n.

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 hr 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 hr 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 min 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 hr 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 hr 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 hr 3/6 subjects reported eye irritation, however when these subjects were exposed to 500 ppm for 3.1 hr, no subjective symptoms were reported and all performed normal Romberg tests.

## **5.2 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 hr 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 hr 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 of 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 presented in Table 5. Calculations are presented in Appendix A.

| TABLE 5: AEGL-1 VALUES FOR 1,1,1-TRICHLOROETHANE (ppm [mg/m <sup>3</sup> ]) |               |               |               |               |               |
|---|---------------|---------------|---------------|---------------|---------------|
| AEGL level  | 10-min        | 30-min        | 1-hr          | 4-hr          | 8-hr          |
| AEGL-1  | 230<br>(1252) | 230<br>(1252) | 230<br>(1252) | 230<br>(1252) | 230<br>(1252) |

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. 1988), a slight decrement in attempted trials was produced by exposure to 1800 ppm for 4 hr. Since only mild untoward effects were observed at concentrations 2x the proposed value, and the severity did not increase with time, this AEGL-1 value seems quite appropriate.

## 6. RATIONALE AND PROPOSED AEGL-2

AEGL-2 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hyper-susceptible” individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below AEGL-2 but at or above AEGL-1 represent exposure levels which may cause notable discomfort.

### 6.1. 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 hr and observed loss of equilibrium and feelings of lightheadedness were reported from 3/4 subjects. In this same study, 3 subjects were exposed for 5 min 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 hr with only 1/3 subjects exhibiting a positive Romberg test.

### 6.2 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. The available human is not appropriate for use due to inconsistent responses among individuals and the lack of a clear concentration-response relationship. In this study, groups of six rats were exposed to nominal concentrations of 0, 1500, 3000, 6000, and 12,000 ppm for 4 hr and behavioral screenings to determine the EC<sub>50</sub> values for loss of righting reflex, ataxia, and loss of conditioned and unconditioned reflexes were performed at 30 min, 1, 2, and 4 hr from the start of the exposure. The EC<sub>50</sub> values for ataxia were 6740, 6000, 4240, and 3780 ppm for the 30 min, 1, 2, and 4 hr timepoints. The EC<sub>50</sub> values for failure of the inverted screen test in mice were calculated by Moser and Balster (1985) for 10, 30, and 60 min 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<sub>50</sub> 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<sub>50</sub> values for ataxia in rats for exposure periods of 30 min, 1, 2, and 4 hr at 6740, 6000, 4240, and 3780. These values were used for the 30 min, 1, and 4 hr AEGL-1 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 8 hr timepoint using the equation  $C^n \times t = k$  where  $n = 3.3$ , based on least squares fit of this data (see section 4.4.2). 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 hr are well tolerated with minimal CNS effects. The 1 hr mouse EC<sub>50</sub> 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 hr EC<sub>50</sub> for ataxia in rats.

The values for AEGL-2 are given in Table 6. Calculations are presented in Appendix A.

| <b>AEGL level</b> | <b>10-min</b> | <b>30-min</b> | <b>1-hr</b>   | <b>4-hr</b>   | <b>8-hr</b>   |
|-------------------|---------------|---------------|---------------|---------------|---------------|
| AEGL-2            | 930<br>(5064) | 670<br>(3650) | 600<br>(3270) | 380<br>(2070) | 300<br>(1633) |

## 7. RATIONALE AND PROPOSED AEGL-3

AEGL-3 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

### 7.1. Human Data Relevant to AEGL-3

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

## 7.2 Animal Data Relevant to AEGL-3

Based on the 6 hr LC<sub>50</sub> values calculated in rats and mice, the rat seems to be slightly more sensitive to the effects of 1,1,1-trichloroethane. Bonnet et al. (1980) reported a 6 hr LC<sub>50</sub> value of 10305 ppm and the LC<sub>50</sub> in the mouse for the same time point was calculated as 13414 ppm by Gradiski et al. (1978).

### 7.3 Derivation of AEGL-3

Estimation of the LC<sub>0</sub> from the 6 hr LC<sub>50</sub> concentration-effect curve for the rat presented by Bonnet et al. (1980) was used to derive the AEGL-3 values. Inspection of this curve provides the opportunity to estimate an LC<sub>0</sub> value between 7000 and 8000 ppm. Therefore, as a conservative estimate, a value of 7000 ppm for a duration of 6 hrs was used for the derivation of AEGL-3 values. Extrapolation was made to the 30 min, 1, 4, and 8 hr time points using the equation  $C^n \times t = k$  where  $n = 3$ , based on the rat lethality data (see section 4.4.2). A total uncertainty factor of 10 was used and the resulting concentrations were multiplied by a modifying factor of 3 in order to achieve a reasonable concentration at which humans might experience life-threatening effects. The 30-min value was also used for the 10-min value so as not to exceed the threshold for cardiac sensitization (5000 ppm) observed in dogs by Reihnhardt et al., (1973). 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. 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. The modifying factor of 3 is supported 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. 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). AEGL-3 values are given in Table 7. Calculations are presented in Appendix A.

| TABLE 7: AEGL-3 VALUES FOR 1,1,1-TRICHLOROETHANE (ppm [mg/m <sup>3</sup> ]) |                              |                 |                 |                 |                 |
|---|------------------------------|-----------------|-----------------|-----------------|-----------------|
| AEGL level  | 10-min                       | 30-min          | 1-hr            | 4-hr            | 8-hr            |
| AEGL-3  | 4800 <sup>a</sup><br>(26135) | 4800<br>(26135) | 3800<br>(20690) | 2400<br>(13067) | 1900<br>(10345) |

<sup>a</sup>The 30-min value was used as the 10-min value so as not to exceed the threshold for cardiac sensitization observed in dogs (Reihnhardt 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 <sup>3</sup> ]) |              |              |              |              |              |
|--|--------------|--------------|--------------|--------------|--------------|
| AEGL Level   | 10-min       | 30-min       | 1-hour       | 4-hour       | 8-hour       |
| AEGL-1   | 230 (1252)   | 230 (1252)   | 230 (1252)   | 230 (1252)   | 230 (1252)   |
| AEGL-2   | 930 (5064)   | 670 (3650)   | 600 (3270)   | 380 (1470)   | 300 (1633)   |
| AEGL-3   | 4800 (26135) | 4800 (26135) | 3800 (20690) | 2400 (13067) | 1900 (10345) |

AEGL-1 values were based on eye irritation and mental fatigue. The AEGL-2 values were based on the EC<sub>50</sub> 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 the LC<sub>0</sub> from an LC<sub>50</sub> concentration-effect curve in the rat.

## 8.2 Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 9.

|                             |          |
|-----------------------------|----------|
| ACGIH TLV-TWA (ACGIH 1998)  | 350 ppm  |
| ACGIH TLV-STEL (ACGIH 1998) | 450 ppm  |
| OSHA PEL-TWA (NIOSH 1997)   | 350 ppm  |
| OSHA Ceiling (NIOSH 1997)   | 350 ppm  |
| NIOSH REL-TWA (NIOSH 1997)  | 350 ppm  |
| NIOSH STEL (NIOSH 1997)     | 450 ppm  |
| NIOSH IDLH (NIOSH 1994)     | 700 ppm  |
| ERPG-1 (AIHA-ERPG, 1998)    | 350 ppm  |
| ERPG-2 (AIHA-ERPG, 1998)    | 700 ppm  |
| ERPG-3 (AIHA-ERPG, 1998)    | 3500 ppm |

## 8.3. Confidence in the Proposed AEGLs

Confidence in the proposed AEGL values is very high. Human data were available for establishing levels AEGL-1 and -2 and the supporting animal data were in good agreement with the values. The AEGL-3 values were derived from animal data that correlates with the mechanism of death observed in humans.

## 8.4. Data Deficiencies

The main deficiency in the data set is lack of human data for establishing AEGL-3 values. Lethal human scenarios support the animal data for the CNS being the target organ from acute inhalation exposure. However, reports of human deaths were not accompanied by good exposure-duration data.

The lack of human epidemiological data for possible reproductive, developmental, teratogenic, and carcinogenic effects of this compound was also particularly notable.

## 9. REFERENCES

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**APPENDIX**

**TIME SCALING CALCULATIONS FOR 1,1,1-TRICHLOROETHANE**

## DERIVATION OF AEGL-1 VALUES

|                      |  |
|----------------------|--|
| Key study:           | Salvini et al., 1971   |
| Toxicity endpoint:   | eye irritation, mental fatigue at 450 ppm                          |
| Scaling:             | none   |
| Uncertainty factors: | 2 for intraspecies variability; subjects were healthy adult humans |

$$\underline{10\text{-min AEGL-1}} = 230$$

$$\underline{30\text{-min AEGL-1}} = 230 \text{ ppm}$$

$$\underline{1\text{-hr AEGL-1}} = 230 \text{ ppm}$$

$$\underline{4\text{-hr AEGL-1}} = 230 \text{ ppm}$$

$$\underline{8\text{-hr AEGL-1}} = 230 \text{ ppm}$$

## DERIVATION OF AEGL-2 VALUES

|                      |   |
|----------------------|---|
| Key study:           | Mullin and Krivanek (1982)  |
| Toxicity endpoint:   | ataxia in rats  |
| Scaling:             | $C^3 \times t = k$ (ten Berge, 1986)<br>$(380)^{3.3} \times 4 = 2.2 \times 10^{11}$ ppm·hr              |
| Uncertainty factors: | 3 for intraspecies variability and 3 for interspecies variability for a total of 10; subjects were rats |

10-min AEGL-2 = 930 ppm

$$\begin{aligned}C^{3.3} \times 10\text{-min} &= 6.4 \times 10^{10} \text{ ppm}\cdot\text{min} \\C^{3.3} &= 6.4 \times 10^9 \text{ ppm} \\C &= 934 \text{ ppm} \\8\text{-hr AEGL-3} &= 930 \text{ ppm}\end{aligned}$$

30-min AEGL-2 = 670 ppm

$$\begin{aligned}C &= 6740 \text{ ppm} \\30\text{-min AEGL-2} &= 6740 \text{ ppm}/10 = 670 \text{ ppm}\end{aligned}$$

1-hr AEGL-2 = 600 ppm

$$\begin{aligned}C &= 6000 \text{ ppm} \\1\text{-hr AEGL-2} &= 6000 \text{ ppm}/10 = 600 \text{ ppm}\end{aligned}$$

4-hr AEGL-2 = 380 ppm

$$\begin{aligned}C &= 3780 \text{ ppm} \\4\text{-hr AEGL-3} &= 3780 \text{ ppm}/10 = 380 \text{ ppm}\end{aligned}$$

8-hr AEGL-2 = 300 ppm

$$\begin{aligned}C^3 \times 8 \text{ hrs} &= 2.2 \times 10^{11} \text{ ppm}\cdot\text{hr} \\C^3 &= 2.7 \times 10^{10} \text{ ppm} \\C &= 3016 \text{ ppm} \\8\text{-hr AEGL-3} &= 3016 \text{ ppm}/10 = 300 \text{ ppm}\end{aligned}$$

## DERIVATION OF AEGL-3 LEVELS

|            |                      |
|------------|----------------------|
| Key study: | Bonnet et al. (1980) |
|------------|----------------------|

Toxicity endpoint: The approximate LC<sub>0</sub> estimated from the concentration-effect curve for lethality after a 6 hr exposure to 1,1,1-trichloroethane.

Scaling:  $C^3 \times t = k$  (ten Berge, 1986)  
 $(7000 \text{ ppm})^3 \times 6 \text{ hr} = 2.058 \times 10^{12} \text{ ppm}\cdot\text{hr}$

Uncertainty factors: 10:  
3 for intraspecies variability and 3 for interspecies variability

Modifying factors: resulting concentrations were multiplied by 3.

10-min AEGL-3 = 4800 (same as 30-minute value to protect against cardiac sensitization)  
(Reinhardt et al., 1973)

30-min AEGL-3 = 4800

$$\begin{aligned}C^3 \times 0.5 \text{ hr} &= 2.1 \times 10^{12} \text{ ppm}\cdot\text{hr} \\C^3 &= 4.1 \times 10^{12} \text{ ppm} \\C &= 16025 \text{ ppm} \\30\text{-min AEGL-3} &= 16025 \text{ ppm}/10 * 3 = 4800 \text{ ppm}\end{aligned}$$

1-hr AEGL-3 = 3800 ppm

$$\begin{aligned}C^3 \times 1 \text{ hr} &= 2.1 \times 10^{12} \text{ ppm}\cdot\text{hr} \\C^3 &= 2.1 \times 10^{12} \text{ ppm} \\C &= 12719 \text{ ppm} \\1\text{-hr AEGL-3} &= 12719 \text{ ppm}/10 * 3 = 3800 \text{ ppm}\end{aligned}$$

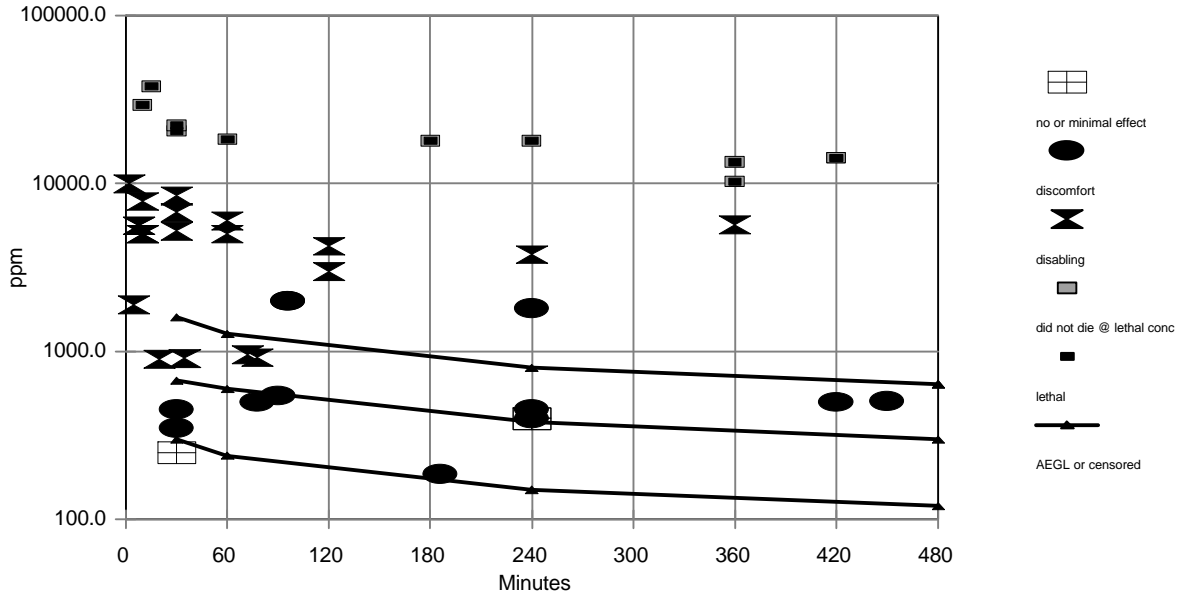
4-hr AEGL-3 = 2400 ppm

$$\begin{aligned}C^2 \times 4 \text{ hrs} &= 2.1 \times 10^{12} \text{ ppm}\cdot\text{hr} \\C^2 &= 5.1 \times 10^{11} \text{ ppm} \\C &= 8012 \text{ ppm} \\4\text{-hr AEGL-3} &= 8012 \text{ ppm}/10 * 3 = 2400 \text{ ppm}\end{aligned}$$

8-hr AEGL-3 = 1900 ppm

$$\begin{aligned}C^2 \times 8 \text{ hrs} &= 2.1 \times 10^{12} \text{ ppm}\cdot\text{hr} \\C^2 &= 2.6 \times 10^{11} \text{ ppm} \\C &= 6359 \text{ ppm} \\8\text{-hr AEGL-3} &= 6359 \text{ ppm}/10 * 3 = 1900 \text{ ppm}\end{aligned}$$

Chemical Toxicity - TSD All Data  
1,1,1-Trichloroethane



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

| <b>AEGL-1 VALUES</b>  |                   |                |                |                |
|---|-------------------|----------------|----------------|----------------|
| <b>10 minutes</b>   | <b>30 minutes</b> | <b>1 hour</b>  | <b>4 hours</b> | <b>8 hours</b> |
| <b>230 ppm</b>  | <b>230 ppm</b>    | <b>230 ppm</b> | <b>230 ppm</b> | <b>230 ppm</b> |
| Key Reference: 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(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:<br>Interspecies = 1: subjects were human<br>Intraspecies = 2: subjects were healthy humans   |                   |                |                |                |
| Modifying Factor: NA  |                   |                |                |                |
| Animal to Human Dosimetric Adjustment: NA   |                   |                |                |                |
| Time Scaling: None  |                   |                |                |                |
| Confidence and support for AEGL values: A well-conducted study in a human population was available and the database consisting of several similar studies supports this endpoint and level.                       |                   |                |                |                |

| <b>AEGL-2 VALUES</b>   |                   |                |                |                |
|--|-------------------|----------------|----------------|----------------|
| <b>10 minutes</b>  | <b>30 minutes</b> | <b>1 hour</b>  | <b>4 hours</b> | <b>8 hours</b> |
| <b>930 ppm</b>   | <b>670</b>        | <b>600 ppm</b> | <b>380 ppm</b> | <b>310 ppm</b> |
| Key References: 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(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 hr   |                   |                |                |                |
| Effects: EC <sub>50</sub> for ataxia at 6740, 6000, 4240, and 3780 ppm after 0.5, 1, 2, 4, and 8 hr exposures, respectively  |                   |                |                |                |
| Endpoint/Concentration/Rationale: Ataxia indicates loss of equilibrium that might impede escape.   |                   |                |                |                |
| Uncertainty Factors/Rationale:<br>Interspecies = 3: Rats were used<br>Interspecies = 3: MAC for volatile anesthetics varies by 2-3 fold  |                   |                |                |                |
| Modifying Factor: NA   |                   |                |                |                |
| Animal to Human Dosimetric Adjustment: NA  |                   |                |                |                |
| Time Scaling: C <sup>n</sup> x t = k where n = 3.3, value derived from EC <sub>50</sub> 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 hr. Other time points were based on extrapolation. |                   |                |                |                |
| Confidence and Support for AEGL values: Well conducted study in rats with several human studies that report similar effects at the derived AEGL-2 values.  |                   |                |                |                |

| <b>AEGL-3 VALUES</b>  |                   |                 |                 |                 |
|---|-------------------|-----------------|-----------------|-----------------|
| <b>10 minutes</b>   | <b>30 minutes</b> | <b>1 hour</b>   | <b>4 hours</b>  | <b>8 hours</b>  |
| <b>4800 ppm</b>   | <b>4800</b>       | <b>3800 ppm</b> | <b>2400 ppm</b> | <b>1900 ppm</b> |
| 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 hr (LC <sub>0</sub> estimated from concentration-effect curve 7000 ppm was determinant for AEGL-3)  |                   |                 |                 |                 |
| Endpoint/Concentration/Rationale: LC <sub>0</sub> / 7000 ppm/ threshold for death for 6 hr exposure in rats   |                   |                 |                 |                 |
| Effects:LC <sub>50</sub> 10,305 ppm for 6 hr exposure, LC <sub>0</sub> estimated from concentration-effect curve is 7000 ppm  |                   |                 |                 |                 |
| Uncertainty Factors/Rationale:<br>Total uncertainty factor: 10<br>Interspecies = 3: human and rat data suggest little interspecies variability<br>Intraspecies = 3: human data suggest variation of 2-3 fold                  |                   |                 |                 |                 |
| Modifying Factor: resulting concentrations were multiplied by 3.  |                   |                 |                 |                 |
| Animal to Human Dosimetric Adjustment: Insufficient data  |                   |                 |                 |                 |
| Time Scaling: C <sup>n</sup> x t = k where n = 3, value derived from rat lethality data ranging from 15 minutes to 7 hours. Data point used for AEGL-3 derivation was 6 hour. Other time points were based on extrapolation.  |                   |                 |                 |                 |
| Confidence and Support for AEGL values: Well-conducted study with appropriate endpoint for AEGL-3.  |                   |                 |                 |                 |