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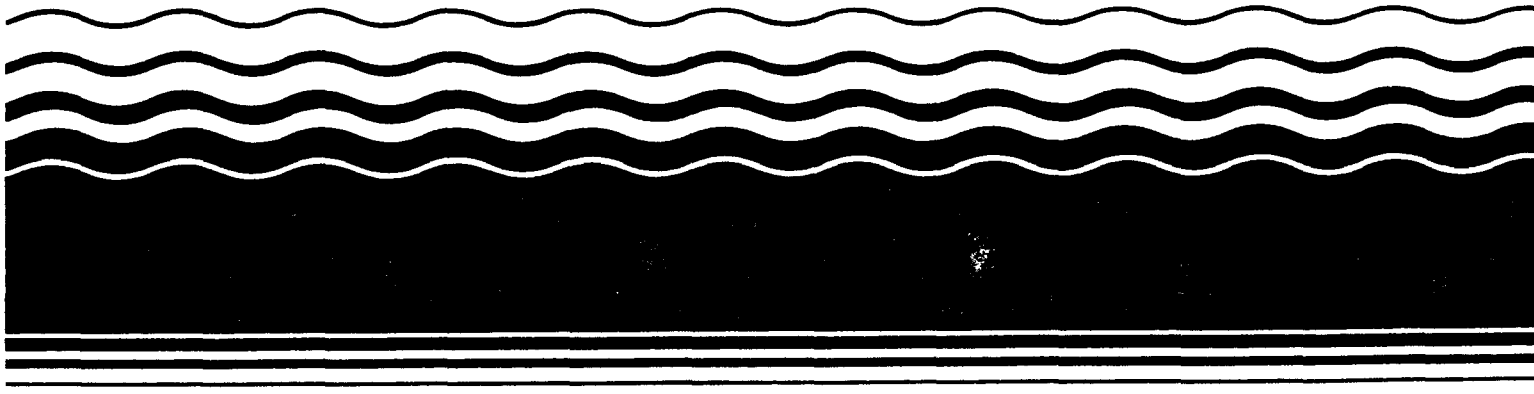
HEALTH EFFECTS ASSESSMENT FOR 1,1,1-TRICHLOROETHANE



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U.S. Environmental Protection Agency
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U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,1,1-Trichloroethane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Chlorinated Ethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-029. NTIS PB 81-117400.

U.S. EPA, 1982. Revision and update of hazard profile on 1,1,1-trichloroethane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Health Assessment Document for 1,1,1-Trichloroethane (Methyl Chloroform). EPA-600/8-82-003F. NTIS PB84-183565.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Several subchronic inhalation studies in a number of species have been conducted. An inhalation AIS of 756 mg/day was estimated based on a 90-day continuous inhalation exposure study in guinea pigs. This estimate may require revision when more complete human data are available.

Only one chronic inhalation study has been conducted (Quast et al., 1978). In this study, rats were exposed to 4765 mg/m^3 6 hours/day, 5 days/week. The AIC estimated from this study is 442 mg/day. This estimate may also require revision when more complete data are available. A CS of 2 was also calculated from this study based on mild hepatocellular lesions observed at 9549 mg/m^3.

Only one oral bioassay was located (NCI, 1977), in which rats in all exposure groups exhibited poor survival as a result of murine pneumonia. 1,1,1-Trichloroethane treated animals appeared to be more severely affected than controls. The low dose 750 mg/kg was used to estimate an AIC of 37.5 mg/day by applying an uncertainty factor of 1000. This is the same approach taken in the development of an ambient water quality criterion for this compound (U.S. EPA, 1980a).

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BSP	Sulfobromophthalein
BUN	Blood urea nitrogen
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxalacetic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 1,1,1-trichloroethane (CAS No. 71-55-6), also known as methyl chloroform, are given as follows:

Chemical class:	Halogenated aliphatic hydrocarbon
Molecular weight:	133.41
Vapor pressure:	123 mm Hg at 25°C (Mabey et al., 1981)
Water solubility:	1495 mg/ℓ at 25°C (Horvath, 1982) 1334 mg/ℓ at 25°C (Banerjee et al., 1980)
Octanol/water partition coefficient:	295 (Banerjee et al., 1980)
Bioconcentration factor:	9 in whole body of bluegill (Lepomis macrochirus) (U.S. EPA, 1980a)
Half-life in air:	2.2-4.8 years (Singh et al., 1981; Makide and Rowland, 1981)
Half-life in water:	20-25 minutes (Callahan et al., 1979) 1.5-7 days (estimated)

The estimated half-life of 2.2-4.8 years indicates that this compound may transport from troposphere to stratosphere, where it can contribute to depletion of the ozone layer. The estimated range for the half-life of 1,1,1-trichloroethane in water has been derived from the reaeration rate ratio of 0.533 (Mabey et al., 1981) and the oxygen reaeration rate range of 0.19-0.96 day^{-1} (Mabey et al., 1981).

No quantitative soil mobility value expressed as a retardation factor for 1,1,1-trichloroethane in soil could be located in the literature; however, since this compound is less water soluble and has a lower octanol/water partition coefficient (Mabey et al., 1981) than its isomer 1,1,2-trichloroethane, its soil retardation factor should be lower than that of 1,1,2-trichloroethane. For 1,1,2-trichloroethane, the soil retardation

factor for a soil depth of 140 cm and an organic carbon content of 0.087% has been estimated to be 1.2 (Wilson et al., 1981).

The half-life of 1,1,1-trichloroethane in soil could not be located in the literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface (Bouwer et al., 1981). In subsurface soil, biodegradation of 1,1,1-trichloroethane is probably a slow process (Tabak et al., 1981). Therefore, this compound is expected to remain significantly undegraded in subsurface soil and may leach into groundwater. Bouwer et al. (1981) studied the leachability of 1,1,1-trichloroethane from soil, and Page (1981) detected the presence of this compound in groundwater at high frequency (78%).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

The chloroethanes are likely to be absorbed easily following ingestion or inhalation (U.S. EPA, 1980a). Stewart (1971) concluded that 1,1,1-trichloroethane is "rapidly and completely" absorbed from the gastrointestinal tract of humans and rapidly and preferentially distributed to the CNS. Stewart and Andrews (1966) reported the case of acute (non-fatal) intoxication resulting from the accidental ingestion of 1 ounce of 1,1,1-trichloroethane. The concentration of the compound measured over a period of time in expired air was found to be equivalent to that resulting from inhalation exposure to 500 ppm in air. Absorption from the gastrointestinal tract appeared to be rapid and complete.

2.2. INHALATION

1,1,1-Trichloroethane has been investigated for use as an anesthetic because of its rapid pulmonary absorption and distribution to the CNS (U.S. EPA, 1984). It was considered to be a more potent anesthetic than trichloroethylene and somewhat safer than chloroform, which has a similar odor and physical properties.

The kinetics of the pulmonary uptake of 1,1,1-trichloroethane have been studied by a number of investigators (Monster et al.,. 1979; Humbert and Fernandez, 1977). These studies have been collectively summarized and interpreted by the U.S. EPA (1984).

Inhaled 1,1,1-trichloroethane rapidly equilibrates with alveolar capillary blood. The rate of absorption depends largely on the blood/air partition coefficient, which has been estimated at 3.3 (Sato and Nakajima, 1979). Pulmonary absorption, initially rapid, slows markedly until

eqilibrium is reached. The percent of 1,1,1-trichloroethane retained in the body during any given breath cycle is described by the formula $(C_I-C_A)/C_I \times 100$, where C_I is the concentration in inspired air and C_A is the concentration in alveolar air. Initially, a larger percentage of the concentration in inspired air is retained than when equilibrium has been reached. Monster et al. (1979) and Humbert and Fernandez (1977) exposed volunteers to 1,1,1-trichloroethane at 70 or 140 ppm for 4 and 8 hours. At equilibrium, which was reached in 4 hours, retention was estimated by Monster et al. (1979) to be 30% of the inhaled dose, but 40% less than that by Humbert and Fernandez (1977). These data were sufficient for the U.S. EPA (1984) to classify 1,1,1-trichloroethane as a poorly absorbed partially soluble vapor.

Although no toxicokinetic data could be found in the available literature concerning absorption after either oral or inhalation exposure, Stahl et al. (1969) reported levels of 60, 62 and 120 ppm, respectively, in the blood of three victims of fatal intoxication (ingested or inhaled), indicating rapid absorption by either route. Other quantitative data regarding the absorption of 1,1,1-trichloroethane could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the subchronic oral exposure of man or experimental animals to 1,1,1-trichloroethane could not be located in the available literature.

3.1.2. Inhalation. Adams et al. (1950) exposed animals to various concentrations (5000 ppm: guinea pigs, rats, rabbits; 3000 ppm: guinea pigs, rats, monkeys; 1500 ppm: guinea pigs; 650 ppm: guinea pigs) of 1,1,1-trichloroethane for 7 hours/day, 5 days/week for ~1-3 months. Body weights, relative organ weights and BUN were recorded, and histopathological examinations were performed on selected major organs. Guinea pigs had slight but significantly reduced growth rate at all exposure levels. BUN remained normal in all test groups. Slight fatty liver degeneration was observed in the 3000 ppm group, which had progressed to "slight to moderate" in the 5000 ppm group. Additionally, testicular degeneration of varying degrees was observed in the males of the 5000 ppm group.

Torkelson et al. (1958) subjected rats, rabbits, guinea pigs and monkeys to 500, 1000, 2000 or 10,000 ppm 1,1,1-trichloroethane in the air to establish safe conditions for repeated exposure. Animals were exposed to 500 ppm for 7 hours/day, 5 days/week for 6 months. From these preliminary studies, it was determined that the female guinea pig was the most sensitive species of those tested. Parameters of toxicity evaluated were growth rate, general appearance, mortality, hematology, organ weights and gross and microscopic pathology. Rats, guinea pigs, rabbits and monkeys appeared to be unaffected after exposure for 6 months. Female guinea pigs tolerated exposure to 1000 ppm for 0.6 hours/day, 5 days/week, with no observed effects and male rats tolerated 10,000 ppm for 0.5 hours/day, 5 days/week, presumably for 6

months, with no evidence of organ pathology. This study defined a NOEL of 500 ppm in rats, guinea pigs, rabbits and monkeys.

U.S. EPA (1982) discussed the study by Prendergast et al. (1967) that apparently defined a NOEL of 370 ppm in a variety of species. Groups of 15 Long-Evans or Sprague-Dawley rats, 15 Hartley guinea pigs, 3 squirrel monkeys, 3 New Zealand rabbits and 2 beagle dogs were exposed continuously to 1,1,1-trichloroethane for 90 days at either 135 or 370 ppm.

McNutt et al. (1975) exposed CF-1 mice to 1,1,1-trichloroethane concentrations of 5400 mg/m^3 and 1350 mg/m^3 continuously for up to 14 weeks. In the high-dose animals, cytoplasmic alterations were observed in the centrilobular hepatocytes upon electron microscopic evaluation. Necrosis of hepatocytes occurred in 40% of the high-dose group after 12 weeks of exposure. Moderate liver triglyceride accumulation was evident in this group. Triglyceride accumulation peaked following 7 weeks of exposure and declined during subsequent weeks. "Mild to minimal" cytoplasmic alterations were seen in the low-dose group. Necrosis and fat accumulation were not observed. Rats, dogs and monkeys were exposed to the same concentrations, but exposure-related effects were not demonstrated in these species.

Stewart et al. (1975) exposed 20 human subjects to 500 ppm 1,1,1-trichloroethane for 7.5 hours/day, 5 days/week for 3 weeks. No effects on clinical blood or urine chemistries or on measurements of pulmonary function were noted. The subjects did, however, complain of fatigue, irritation and headache.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic oral exposure of man to 1,1,1-trichloroethane could not be located in the available literature. The only report of chronic oral exposure of laboratory animals was the NCI (1977) carcinogenicity bioassay conducted with Osborne-Mendel rats.

Originally, doses of 3000 or 1500 mg/kg bw dissolved in corn oil were given by gavage 5 days/week to groups of 50 rats of each sex. Marked signs of intoxication in all treatment groups caused termination of the experiment after a few weeks. The experiment was restarted with new rats at dosages of 1500 or 750 mg/kg, 5 days/week for 78 weeks. During the second year, yellow discoloration of the fur of the lower abdomen, increased ocular and nasal discharge and dyspnea were noted. Typical signs of aging were noted in all groups of rats including controls, but seemed more severe in 1,1,1-trichloroethane-exposed rats. Survival data presented in Table 3-1 indicate a negative association with treatment which was significant ($p<0.04$) in treated male rats.

The NCI (1977) bioassay also included $B6C3F_1$ mice. Groups of 50 mice of each sex were administered 2000 or 4000 mg 1,1,1-trichloroethane in corn oil/kg bw by gavage 5 days/week for 78 weeks. Because no signs of toxicity were observed, the dosages were raised to 2500 and 5000 mg/kg after 10 weeks, and again to 3000 and 6000 mg/kg after another 10 weeks in the low- and high-dose groups, respectively. Resultant TWA doses, expanded to reflect treatment of 5 days/week, were 2005 and 4011 mg/kg/day in low- and high-dose groups, respectively. Untreated controls consisted of 20 mice of each sex; no vehicle control animals were used in these studies. A reduction of body weight gain, which appeared to be related directly to treatment, was observed in mice of both sexes. Survival data are presented in Table 3-2. For female mice, a significant ($p=0.02$) association between mortality and treatment level was noted. No specific lesions appeared to account for reduced survival.

TABLE 3-1

Comparison of Survival of Control Groups with 1,1,1-Trichloroethane-Treated Rats[a]

Dose Group	Initial No. of Animals	No. Alive at 78 Weeks	No. Alive at 110 Weeks[b]
Male:			
Control	20	7	0
Low-dose	50	1	0
High-dose	50	4	0
Female:			
Control	20	14	3
Low-dose	50	9	2
High-dose	50	12	1

[a]Source: NCI, 1977

[b]Time at last weighing

TABLE 3-2

Comparison of Survival of Control Groups with Survival of 1,1,1-Trichloroethane-Treated Mice*

Dose Group	Initial No. of Animals	No. Alive at 78 Weeks	No. Alive at 90 Weeks
Male:			
Control	20	6	2
Low-dose	50	21	15
High-dose	50	14	11
Female			
Control	20	12	11
Low-dose	50	28	23
High-dose	50	14	13

*Source: NCI, 1977

3.2.2. Inhalation. Acute exposure of humans to 1,1,1-trichloroethane resulted in disruption of CNS function as manifested by changes in reaction time, perceptual speed, manual dexterity and equilibrium following exposure to 350 ppm for 3 hours (U.S. EPA, 1980a). Inhalation of 450 ppm for 8 hours caused eye, nose and throat irritation, and impaired perceptive capabilities under stress conditions (U.S. EPA, 1980a).

Kramer et al. (1976) evaluated the cardiovascular and hepatic functions of employees exposed to an 8-hour TWA of 4-217 ppm for periods of ~6 years. Although the U.S. EPA (1980a) did not discuss what clinical parameters were measured, no statistically significant findings were reported regarding 1,1,1-trichloroethane. Weitbrecht (1965) reported irritation in nine women exposed to a "workroom concentration" of 10 ppm 1,1,1-trichloroethane. These women worked over open vats of 1,1,1-trichloroethane and occasionally had their hands immersed in it for varying lengths of time. Fukabori et al. (1976, 1977) determined that significant amounts of 1,1,1-trichloroethane can be absorbed through unbroken skin. Furthermore, it is suspected that air concentrations of such a volatile liquid directly above open vats were considerably greater than the levels found in workroom air. It is, therefore, impossible to relate the effects reported by this small sample to a specific level of exposure to 1,1,1-trichloroethane.

Seki et al. (1975) reported on 196 male workers exposed to 1,1,1-trichloroethane for $\geq$5 years at concentrations of 4, 25, 28 or 53 ppm. Routine clinical pathological blood and urine chemistries failed to reveal evidence of hepatic or renal malfunction. On the basis of these tests, the ability of workers to detect tuning fork vibrations and evaluation of answers from a questionaire, Seke et al. (1975) concluded that exposure to <53 ppm

1,1,1-trichloroethane resulted in no dose-related effects. There were no control subjects in this study and it was unclear how frequently the concentration data were obtained. It was suspected (U.S. EPA, 1980a) that actual concentrations experienced by these workers were in excess of those reported.

Maroni et al. (1977) studied a cohort of 21 women exposed for 6.5 years to an average concentration of 1,1,1-trichloroethane of 110-345 ppm. An evaluation of neurophysiological function (specific tests not reported) revealed no neurotoxicity in exposed workers compared with seven unexposed control subjects (U.S. EPA, 1980a).

Only one report of chronic animal exposure to 1,1,1-trichloroethane by inhalation was found in the available literature. Quast et al. (1978) exposed 96 rats of each sex to 875 or 1750 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 12 months, followed by an observation period of 19 months. Animals were monitored for decreased life span and changes in hematology, clinical chemistry, and gross and microscopic pathology. The only effect reported was focal hepatocellular change in high-dose females. The lower dose level of 875 ppm appeared to represent a NOEL in this study. This concentration, expanded to continuous exposure, assuming an inhalation rate of 0.26 m^3/day and a body weight of 0.35 kg for rats, corresponds to a dosage of 633 mg/kg/day.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. No reports of teratogenicity of 1,1,1-trichloroethane caused by oral exposure in humans, and no studies of teratogenicity of orally-administered 1,1,1-trichloroethane in animals could be located in the available literature.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity or fetotoxicity of 1,1,1-trichloroethane in humans could not be located in the available literature. Results of animal experiments in mice and rats were negative. Swetz et al. (1975) exposed Swiss-Webster mice to 875 ppm 1,1,1-trichloroethane for 7 hours/day on days 6-15 of gestation; day 0 was the day a vaginal plug was first observed. Control mice were maintained on filtered air. On day 18, fetuses were collected by Caesarean section. All fetuses were examined for external anomalies; half of the fetuses were examined for soft tissue malformations by free-hand sectioning, and half were cleared, stained and examined for skeletal malformations. From each litter, one fetus was subjected to complete histopathological examination. Exposure to 875 ppm 1,1,1-trichloroethane for 7 hours/day on days 6-15 of gestation was associated with slightly but not significantly reduced maternal body weights, but was not associated with fetoxicity or teratogenicity.

Schwetz et al. (1975) exposed pregnant rats on gestation days 6-15 to 875 ppm 1,1,1-trichloroethane using the same protocol that had been used with mice. Rats were terminated on gestational day 21; fetuses were collected by Caesarean section and were examined for external malformation. From each litter, 50% of the fetuses were examined for soft tissue malformation, and the other 50% were examined for skeletal malformation. A randomly selected fetus from each litter was serially sectioned for complete histological evaluation. There was no evidence of maternal or fetal toxicity or tertogenicity in any of the 23 litters examined.

3.4. TOXICANT INTERACTIONS

Traiger and Plaa (1974) examined the effects of pretreatment with acetone or isopropanol on the hepatotoxicity of selected chlorinated ethanes in mice as evaluated by SGOT activity. Pretreatment with acetone or isopropanol did not alter the toxicity of 1,1,1-trichloroethane in mice.

Pretreatment of mice for 3 days with 5 g ethanol/kg by gavage and administration of 2.75 mℓ 1,1,1-trichloroethane by intraperitoneal injection on the 4th day resulted in depressed liver function as evidenced by BSP retention. BSP was elevated from 0.91 mg/100 mℓ serum in nonpretreated mice to 3.76 mg/100 mℓ serum in ethanol-pretreated mice (Klaassen and Plaa, 1966). Cornish and Adefuin (1966) demonstrated that pretreatment of rats with ethanol enhanced the hepatotoxicity of 1,1,1-trichloroethane as evaluated by SGOT activity. Pretreatment with phenobarbital did not affect the hepatotoxicity of 1,1,1-trichloroethane as evaluated by SGOT levels (Cornish et al., 1973). No further details concerning these studies were available from U.S. EPA (1980a).

Exposure of rats to 3000 ppm 1,1,1-trichloroethane in the air for 24 hours decreased sleeping time induced by intraperitoneal injection of hexobarbital, meprobamate or zoxazolamine 24 hours post-exposure. Inhibitors of protein synthesis blocked the effect of 1,1,1-trichloroethane on hexobarbital induced sleeping time (Fuller et al., 1970). The hypothesis that hepatic microsomal enzymes were induced by the chlorinated hydrocarbon was supported by data showing in vitro stimulation of microsomal aniline hydroxylase activity by 1,1,1-trichloroethane (Van Dyke and Rikans, 1970). Potentiation of toxicity was not observed in extensive studies with a 3:1 mixture of 1,1,1-trichloroethane and tetrachloroethylene (by weight) in mice, rats, guinea pigs, rabbits, dogs and human subjects (Rowe et al., 1963).

4. CARCINOGENICITY

4.1. HUMAN DATA

No reports of cancer in humans associated with 1,1,1-trichloroethane could be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. The NCI (1977) sponsored a bioassay of the carcinogenicity of 1,1,1-trichloroethane in Osborne-Mendel rats and B6C3F$_1$ mice (see Section 3.2.1). Low survival of both male and female treated rats may have precluded significant development of tumors late in life. A variety of neoplasms were observed in both treated and matched control rats. These neoplasms were common to aged rats and were not significantly related to dosage. Malignancies found only in treated rats included papillary cystadenocarcinoma in the subcutis (1/50 high-dose females), urinary bladder transitional cell carcinoma (1/50 high-dose males), malignant glioma in the brain (1/48 low-dose males) and mesenteric metastatic osteosarcoma (1/50 high-dose females).

Similarly, mice suffered early heavy mortality that was significantly related to dosage level for females. A variety of neoplasms was observed in both treated and matched control mice. Although not statistically significant, malignant lymphoma was a relatively common finding in both treated and control mice. Other pathologic lesions found were those common to aging mice and were not significantly related to treatment. Malignancies found only in treated mice were fibrosarcoma (1/42 low-dose females) and sarcoma (1/50 high-dose females) in the skin, hepatocellular adenoma (3/49 high-dose males), hepatocellular carcinoma (1/49 high-dose males) and hemangiosarcoma (1/47 low-dose males).

NCI (1977) concluded that "these studies cannot be regarded as appropriate tests for the carcinogenicity of [1,1,1trichloroethane] in the test animals because of the abbreviated lifespans of both the rats and the mice."

4.2.2. Inhalation. A brief report of the investigation of 1,1,1-trichloroethane-induced carcinogenicity by inhalation was located in the literature. Quast et al. (1978) exposed 96 rats of both sexes to 875 or 1750 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 12 months, followed by an additional 19-month observation period. As discussed in Section 3.2.2., the only effect reported was a focal hepatocellular change in high-dose females. No significant dose-related neoplasms were reported.

4.3. OTHER RELEVANT DATA

Few reports of mutagenicity of 1,1,1-trichloroethane were located in the available literature. Positive results in Salmonella typhimurium strain TA100 were observed by several investigators (Simmon et al., 1977; Fishbein, 1979; Snow et al., 1979). Exogenous metabolic activation was not required to obtain a positive result, but did increase the number of revertants/plate. Henschler et al. (1977) and Taylor (1978) obtained negative results with S. typhimurium strain TA100. S. typhimurium strain TA1535 was positive with metabolic activation (Farber, 1977) and without activation (Nestmann et al., 1980). Negative results were obtained in an experiment in which precautions were not taken to prevent evaporation of the compound (Simmon et al., 1977). Negative results were obtained with S. typhimurium strains TA98, TA1537 and TA1538 (Farber, 1977; Simmon et al., 1977; Taylor, 1978; Nestmann et al., 1980). It was suggested that volatilization was responsible for the negative results in these tests (U.S. EPA, 1984).

1,1,1-Trichloroethane was not mutagenic in the gene conversion or mitotic recombination tests with Saccharomyces cerevisiae (Farber, 1977; Simmon et al., 1977) or the host-mediated forward mutation assay using Schizosaccharomyces pombe in mice. The chemical also failed to produce chromosomal aberrations in the bone marrow cells of rats (Rampy et al., 1977), but responded positively in the mammalian cell transformation test with rat embryo cells (Price et al., 1978).

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the risk to humans associated with oral or inhalation exposure to 1,1,1-trichloroethane. Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), 1,1,1-trichloroethane is most appropriately designated a Group D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1980) recommended a TLV of 350 ppm and an STEL of 450 ppm to protect against anesthetic effects and objections to odor, based primarily on the study by Kramer et al. (1978). Other countries, however, recommended much lower levels, as summarized in Table 5-1.

The Code of Federal Regulations (1981) standard for an 8-hour TWA exposure to 1,1,1-trichloroethane is 350 ppm in workplace air. According to U.S. EPA (1980a), NIOSH recommended a 10-hour TWA exposure criterion of 200 ppm to protect against CNS responses and cardiovascular and respiratory effects.

Based on extrapolations of data from the NCI (1977) bioassay, the U.S. EPA (1980a) set the ambient water quality criteria at 18.4 mg/ℓ.

When used as a solvent in pesticide formulations or as a post-harvest fumigant for citrus fruit, 1,1,1-trichloroethane is exempt from requirement of a tolerance for residues (IARC, 1979).

TABLE 5-1

Current Regulatory Standards and Criteria for 1,1,1-Trichloroethane

Standard or Criteria	Recommendation	Reference
TLV, U.S.	350 ppm (~1900 mg/m^3)	ACGIH, 1980
STEL, U.S.	450 ppm (~2450 mg/m^3)	ACGIH, 1980
TLV, E. Germany (1973)	90 ppm	ACGIH, 1980
TLV, W. Germany (1974)	200 ppm	ACGIH, 1980
TLV, Sweden (1978)	70 ppm	ACGIH, 1980
TLV, USSR (1972) TLV, Czechoslovakia (1969)	4 ppm 90 ppm	ACGIH, 1980
Ambient water quality criteria	18.4 mg/ℓ	U.S. EPA, 1980a
NIOSH (current)	350 ppm	IARC, 1979
NIOSH (proposed)	200 ppm	U.S. EPA, 1980a

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Since no pertinent data concerning subchronic oral exposure to 1,1,1-trichloroethane could be found in the available literature, no calculation of an AIS is possible.

6.1.2. Inhalation. The Adams et al. (1950) study (see Section 3.1.2.) defined a LOAEL in guinea pigs of 650 ppm 1,1,1-trichloroethane 7 hours/day, 5 days/week, associated with slight retardation of growth. Assuming an inhalation rate of 0.23 m^3/day and a body weight of 0.43 kg, this corresponds to a dosage of 395 mg/kg/day. The significance of the reported retardation of growth is questionable, however, because similar effects were not observed by Prendergast et al. (1967) in a study in which guinea pigs were exposed continuously to 370 ppm for 90 days. Applying the same assumptions mentioned above, this exposure corresponds to 1080 mg/kg/day.

Torkelson et al. (1958) defined a NOEL of 500 ppm in guinea pigs exposed to 1,1,1-trichloroethane for 7 hours/day, 5 days/week for 6 months. Using the same assumptions for inhalation rate and body weight of guinea pigs, this level corresponds to a dosage of 304 mg/kg/day. In this study guinea pigs were more sensitive than the other species tested.

The lowest exposure concentration which defined an effect level was the 14-week continuous exposure study conducted by McNutt et al. (1975) using mice. In this study, the lowest dose tested, 1350 mg/m^3, produced electron microscopically detectable cytoplasmic alterations in hepatocytes following continuous exposure and is appropriately designated a LOAEL.

Since the goal of the risk estimates in this document is to project acceptable exposure concentrations for continuous exposure situations, and since extrapolation from intermittent exposure regimens to projected contin

uous exposure conditions is subject to significant uncertainty, use of data generated using a continuous exposure protocol is preferable. Two continuous exposure, subchronic studies have been conducted. McNutt et al. (1975) established a LOAEL in mice exposed continuously for 14 weeks to 1350 mg/m^3 for electron microscopically detectable alterations in hepatocytes. The projected dose to the mice is 2250 mg/kg/day. The other continuous exposure protocol (Prendergast et al., 1967) established a NOEL for guinea pigs exposed to 2014 mg/m^3 for 90 days. The projected animal dose is 1080 mg/kg/day. An AIS can be calculated from the guinea pig NOEL by multiplying by 70 kg and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for interindividual variability). The resulting AIS is 756 mg/day.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The only report of chronic oral exposure to 1,1,1-trichloroethane is the NCI (1977) bioassay. Survival time in rats was reduced significantly in both dose groups. The low dose (750 mg/kg) is selected for derivation of an AIC. An uncertainty factor of 10 is used for interspecies extrapolation, a factor of 10 is used to afford greater protection to unusually sensitive populations and a final factor of 10 to extrapolate from a LOAEL to a NOEL. The general poor health of these rats was attributed primarily to chronic murine pneumonia, a common syndrome encountered in aging laboratory rodents. It is entirely possible that exposure to 1,1,1-trichloroethane may have accelerated this disease process, or that the disease process may have masked subtle manifestations of 1,1,1-trichloroethane-induced toxicity. From these data, an AIC is calculated as follows:

AIC = 750 mg/kg/dose x 70 kg/man x 5 days/7 days/week ÷ 1000

AIC = 37.5 mg/day

The term, 5 days/7 days/week, is applied to adjust for treatment on 5 days/week.

6.2.2. **Inhalation.** The sole chronic inhalation evaluation (Quast et al., 1978) reported a NOEL of 4765 mg/m³ for rats exposed 6 hours/day, 5 days/week. Assuming an inhalation rate of 0.26 m³/day and an average body weight of 0.35 kg for rats, this NOEL results in an animal dose of 632 mg/kg/day. A human AIC is calculated by multiplying the animal dose by 70 kg, the assumed average body weight of humans, and by applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to afford greater protection to unusually sensitive individuals). The resulting AIC is 442 mg/day for an average 70 kg human.

U.S. EPA (1983b) computed a CS for the hepatocellular histopathology observed by Quast et al. (1978) in rats exposed to 1750 ppm (9549 mg/m³) 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 1 year. A human MED was calculated by expanding this concentration to continuous exposure and assuming that an average human inhales 20 m³ of air/day and that absorption of the chemical is 50%. A human MED of 17,053 results, corresponding to an RV_d of 1. The minor histological hepatocellular changes observed are assigned an RV_e of 2. A CS of 2 is calculated by multiplying RV_d x RV_e.

6.3. **CARCINOGENIC POTENCY (q_1*)**

Neither the NCI (1977) bioassay nor the study by Quast et al. (1978) demonstrated evidence for carcinogenicity of 1,1,1-trichloroethane by oral or inhalation routes, respectively. It is not possible, therefore, to derive a q_1* for 1,1,1-trichloroethane for either the oral or inhalation exposure routes.

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APPENDIX

Summary Table for 1,1,1-Trichloroethane

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	guinea pig	2014 mg/m³ (continuous)	none	756 mg/day	Prendergast et al., 1971
AIC	rat	4765 mg/m³ (6 hours/day, 5 days/week	none	442 mg/day	Quast et al., 1978
Maximum CS	rat	1750 ppm (9549 mg/m³) 6 hours/day, 5 days/week for 1 year (RV_d = 1)	mild hepatocellular histopathologic lesions (RV_e = 2)	2	Quast et al., 1978; U.S. EPA, 1983b
Oral					
AIS	NA	NA	NA	ND	NA
AIC	rat	750 mg/kg/day	reduced survival	37.5 mg/day	NCI, 1977

NA = Not applicable; ND = not derived