Appendix B
Section Q

1,1,1-TRICHLOROETHANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

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New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

1,1,1-Trichloroethane is a commonly used industrial solvent. Long-term exposure of experimental animals to 1,1,1-trichloroethane has been associated with liver damage. The odor threshold for 1,1,1-trichloroethane in water is 50 mg/L (Verschueren, 1983). A health-based maximum contaminant level (MCL) of 26 ug/L was derived for 1,1,1-trichloroethane to protect from liver damage.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties (1,1,1-Trichloroethane, 1986)

Chemical name	1,1,1-Trichloroethane
Synonym	Methyl chloroform
CAS number	71-55-6
Chemical formula	$C_2H_3Cl_3$
Chemical structure	CH_3-CCl_3
Physical state	Colorless liquid at room temperature
Molecular weight	133.4
Melting point	-30.4 ^{o}C
Boiling point	74.1 ^{o}C
Vapor pressure	127 mm Hg at 20 ^{o}C
Specific gravity, density	1.34 at 20 ^{o}C
Odor threshold (air)	40-100 ppm (Verschueren, 1983)
Odor threshold (water)	50 mg/mL (Verschueren, 1983)
Solubility	4,400 mg/L at 20 ^{o}C
Conversion factor	1 ppm = 5.46 mg/m^3 at 25 ^{o}C

Production and Use

In 1954, 1,1,1-trichloroethane was introduced commercially, and since then has gained widespread use largely because of its low toxicity compared to other chlorinated hydrocarbons (Stewart, 1968). It is produced from vinylidene chloride, vinyl chloride, or ethane. Commercial 1,1,1-trichloroethane contains 3 to 7% of stabilizers which are added to prevent degradation. These include 1,4-dioxane, 1,3-dioxolane, butylene oxide, methyl ethyl ketone, alchohols, nitromethane, and nitroethane (U.S. EPA, 1984).

Cold cleaning and vapor degreasing are the major commercial applications for 1,1,1-trichloroethane. Additionally, it is used as an intermediate in the synthesis of vinylidene chloride, as a spot remover, and as a component of adhesives, coatings, and aerosols (U.S. EPA, 1984).

Guidelines, Regulations and Standards

The current OSHA standard for industrial exposure to 1,1,1-trichloroethane is 350 ppm (OSHA, 1976).

The recommended maximum contaminant level (RMCL) finalized by U.S.EPA for this compound in drinking water is 200 ug/L (U.S.EPA, 1985b). The draft Health Advisory (U.S. EPA, 1985a) recommends the following maximum concentrations: one day based on 10 kg child, 140,000 ug/L; 10 day and longer term for 10-kg child, 35,000 ug/L; longer-term for 70-kg adult, 25,000 ug/L; and lifetime, 200 ug/L assuming 20% relative source contribution from drinking water.

ENVIRONMENTAL EXPOSURE

Fate and Transport

1,1,1-Trichloroethane is released both into the atmosphere and via solid waste and water. In 1978, it was estimated that 470 million pounds were released into the air and 63 million pounds as solid waste and water (Katz et al., 1980).

Atmospheric 1,1,1-trichloroethane can reach the stratosphere where it undergoes photodecomposition. The resulting free radical products may contribute to the depletion of the ozone layer. The lifetime of atmospheric 1,1,1-trichloroethane has been estimated to be five to ten years (World Meteorological Organization, 1982). Because of its volatility, 1,1,1-trichloroethane is not expected to persist in aquatic environments (U.S.EPA, 1984).

Ambient Levels

OSHA (1976) has estimated that 2.9 million workers are exposed to 1,1,1-trichloroethane dermally or by inhalation.

1,1,1-Trichloroethane was detected in 5.8% of a random national sample of 466 drinking water supplies in the Ground Water Supply Survey conducted by U.S.EPA in 1982 (U.S.EPA, 1985b).

In a recent survey in potable N.J. water of A280 chemicals, 1,1,1-trichloroethane was found in 5% of 566 samples. The median level was 2 mg/L and the range of detected value was 0.5 to 102 mg/L.

METABOLISM AND PHARMACOKINETICS

Absorption

1,1,1-Trichloroethane may be absorbed orally and dermally, as well as by inhalation, the most common route of exposure. Absorption through intact human skin is poor (Stewart and Dodd, 1964), while gastrointestinal absorption has been reported to be rapid and complete (Stewart, 1971).

The pulmonary absorption by human volunteers was 30% after exposure to 70 ppm for 4 hours (Monster, 1979) and was 25% after 6 hours of exposure to 35 or 350 ppm (Nolan et al., 1984). Reitz et al. (1985) have recently demonstrated that the pharmacokinetics for 1,1,1-trichloroethane are similar after exposure by inhalation and drinking water.

Distribution

1,1,1-Trichloroethane has a high lipid/water partition coefficient and distributes throughout the body tissues, particularly those high in fat. The compound crosses the blood/brain barrier (Savolainen et al., 1977), and high levels are found in adipose tissues (Savolainen et al., 1977, Schumann et al., 1982a).

Metabolism

Metabolism of 1,1,1-trichloroethane takes place to a limited extent and is a saturable process in both rodents and man; over 90% is exhaled unchanged (Schumann et al., 1982a). This limited metabolism has been postulated to contribute to the compound's low degree of toxicity as compared to related chemicals (U.S.EPA, 1984).

The major urinary metabolites in both man and experimental animals are trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid. Additionally, $^{14}CO_2$ has been detected in the breath after administration of [1-^{14}C]1,1,1-trichloroethane (Hake et al., 1960) and [2-^{14}C]

1,1,1-trichloroethane (Schumann et al., 1982a).

Trichloroethanol is produced from 1,1,1-trichloroethane by hepatic microsomal cytochrome P-450. Further oxidation to trichloroacetate is postulated to proceed by alcohol and/or aldehyde dehydrogenase (Ivanetich and Van Den Honert, 1981).

Metabolism to trichloroethane and chloral hydrate by nuclear cytochrome P-450 also occurs (Casciola and Ivanetich, 1984). In contrast to carbon tetrachloride and trichloroethylene, 1,1,1-trichloroethane did not covalently bind to DNA and RNA after bioactivation by rat hepatocytes (Cunningham, et al., 1981).

Conflicting reports exist as to the effect of 1,1,1-trichloroethane exposure on mixed function oxidase levels. Both induction and depression have been observed (U.S EPA, 1984). Of particular relevance, Schumann et al. (1982b) found that prior exposure of mice and rats to 1500 ppm for 6 hours per day, 5 days per week for 16 months did not affect the disposition of a dose of [^{14}C]1,1,1- trichloroethane.

Excretion

The principal route of excretion of 1,1,1-trichloroethane is via pulmonary exhalation, regardless of route of exposure (U.S. EPA, 1984). Excretion as urinary metabolites also occurs to a limited extent, as discussed above.

Human Exposure and Body Burden

Human exposure to 1,1,1-trichloroethane occurs principally in occupationally exposed workers (U.S.EPA, 1984).

A pharmacokinetic model recently developed by Reitz et al. (1985) predicts that the body burden in a 70-kg person consuming 2L of drinking water daily containing 0.3 ppm 1,1,1,-trichloroethane for 100 days would be only 2.7 times higher than the body burden after a single day of consumption.

HEALTH EFFECTS

Overview

Acute exposure to 1,1,1-trichloroethane causes eye irritation, central nervous system (CNS) depression, anaesthesia, and can sensitize the heart to catecholamines. Long-term exposure of experimental animals has been associated with liver damage. No epidemiological association has been made between occupational exposure and health effects. The evidence currently available does not warrant classification of 1,1,1-trichloroethane as a mutagen, teratogen, or carcinogen.

Human

Humans experimentally exposed to 900 to 1000 ppm 1,1,1-trichloroethane have been reported to experience loss of coordination as measured by the Romberg test (Stewart et al., 1961; Torkelson et al., 1958). Exposure to 450 ppm caused transient eye irritation (Salvini et al., 1971). Savolainen et al. (1982) found that exposure at 200 and 400 ppm caused a biphasic response on equilibrium.

Three studies of exposed workers did not reveal any adverse effects which could be statistically related to 1,1,1-trichloroethane exposure (Seki et al., 1975; Maroni et al., 1977; Kramer et al., 1978).

The most extensive of these studies was that of Kramer et al. (1978) in which 151 workers were exposed to an 8-hour time-weighted-average concentration of up to 249 ppm for 6 years were pair matched with unexposed workers. No statistically significant associations with exposure were observed; the parameters examined included hematology, blood chemistry, hepatic function, and cardiovascular function.

1,1,1-Trichloroethane has been employed as a human anaesthetic (Dornette and Jones, 1960) at concentrations from 6000 to 26,000 ppm. As is the case for other halogenated hydrocarbons, exposure to such high levels sensitizes the heart to catecholamines and increases susceptibility to ventricular arrhythmias.

Accidental or intentional exposure of humans to high concentrations of 1,1,1-trichloroethane can result in death due to CNS depression. While CNS depression is the major effect of such acute exposure, mild hepatic effects (fatty vacuolation) have also been observed (Caplan, 1976).

Animals

Acute. The LD_{50} values for uninhibited 1,1,1-trichloroethane administered by gavage to female rats, mice, and rabbits were 10,300, 11,200, and 570 mg/kg, respectively (Torkelson et al., 1958).

CNS effects are observed after acute exposure of mice to 4,000 ppm or above (Woolverton and Balster, 1981; Moser and Balster, 1982). Sensitization of the myocardium to catecholamines also occurs after exposure to near anaesthetic levels. This effect is believed to be due to the physical properties of the compound, with sensitizing potential related to vapor pressure (Clark and Tinston, 1973).

Hepatic effects in mice and dogs were observed only after acute exposure to near lethal doses (Klaassen and Plaa, 1966; Klaassen and Plaa, 1967; Gehring, 1968).

Subchronic and Chronic. Several investigators have examined the effects of repeated exposure to 1,1,1-trichloroethane. Exposure to 500 ppm, 7 hours per day, 5 days per week for 6 months caused no adverse effects on hematology, gross and microscopic histology, organ weight, body weight gain, or survival in rats (20 per sex per group), guinea pigs (8 per sex per group), rabbits (2 per sex per group), or monkeys (2 female). Exposure of guinea pigs (5 female) to 2000 ppm, 30 minutes per day, 5 days/week, for 3 months, resulted in lung irritation and fatty liver changes. Exposure of guinea pigs (5 females) to 1000 ppm, 5 days per week; 7 hours per day for 3 months, caused increased liver weight, lung inflammation, and fatty liver changes while no effects were seen at this dose with shorter exposure periods. The 1,1,1-trichloroethane used in this study contained 3 to 6% inhibitors. Controls were exposed to air in inhalation chambers. (Torkelson et al., 1958).

Eben and Kimmerle (1974) detected no effects on behavior, appearance, weight gain, hematology, organ histology, or liver and kidney function in male SPF-Wistar II rats (20 group) rats exposed to 200 ppm, 8 hours per day, 5 days per week, for 3 months.

Prendergast et al. (1967) subjected rats (15 per group), guinea pigs (15 per group), squirrel monkeys (3 per group), rabbits (3 per group) and beagle dogs (2 per group) to varying regimens of 1,1,1-trichloroethane containing 8% inhibitors. Exposure to 2200 ppm, 8 hours per day, 5 days per week, for 30 days caused no visible, gross, or histopathological effects except weight loss in dogs and rabbits. No effects attributable to treatment were observed after continuous exposure to 135 or 370 ppm for 90 days. Controls were exposed to air in inhalation chambers.

Male CF-1 mice (200 per group) were exposed to 0, 250, or 1000 ppm 1,1,1-trichloroethane containing 3% to 6% of inhibitors continuously for 14 weeks by McNutt et al. (1975). Serial sacrifice of 10 mice per exposure group occurred during each week of exposure, and at two week intervals post-exposure. Increased liver weight and liver triglyceride accumulation occurred after exposure to 1000 ppm. Necrosis and cytoplasmic alterations were observed in the 1000 ppm group, with mild to minimal cytoplasmic alterations in the 250 ppm group.

Calhoun et al. (1981) conducted a subchronic study in which mice and rats were exposed to 1000 or 2000 ppm of a commercial preparation of 1,1,1-trichloroethane for 90 days. At both exposure levels, microscopic changes were observed in the liver and upper respiratory tract.

In a subchronic oral study recently reported by Bruckner et al. (1985), male Sprague-Dawley rats were given 500, 2500, or 5000 mg/kg 1,1,1-trichloroethane (uninhibited, 99%) by gavage in corn oil for up to 12 weeks. Animals in the two higher dosage groups exhibited CNS depression, statistically significant decreased weight gain, and increased mortality. Minimal, statistically significant, changes in liver function as measured

by serum enzymes were detected at 6 weeks only in the 5000 mg/kg group. Animals ingesting 500 mg/kg did not differ from controls in weight gain, survival, liver function, or gross or microscopic pathology.

Four chronic studies have been reported (NCI, 1977; NCI, 1983; Quast et al., 1978; Quast et al., 1984). These are discussed in detail under Carcinogenicity below.

Behavioral and Central Nervous System

Like other organic solvents, 1,1,1-trichloroethane causes non-specific CNS depression; these effects were the only observed in some studies. These observations are discussed in detail above under Human Health, Acute Effects, Animal, and Subchronic and Chronic Effects, Animal.

Reproductive, Embryotoxic, and Teratogenic

York et al. (1982) assessed the effects of exposure to 2100 ppm, 6 hours per day, 5 days per week in female Long-Evans rats 2 weeks prior to mating, during pregnancy, or both. No treatment related malformations or maternal toxicity was observed, although exposure during pregnancy decreased fetal weight. A multigeneration study involving exposure of male and female Swiss ICR mice to concentrations up to 5.8 mg/mL in drinking water revealed no effects on a number of reproductive indices (Lane et al., 1982). No maternal, embryonal, or fetal effects were seen after exposure of Sprague-Dawley rats and Swiss-Webster mice to 875 ppm, 7 hours per day on days 6-15 of gestation (Schwetz et al., 1975).

Genetic

A number of investigators have reported that 1,1,1-trichloroethane is weakly mutagenic in bacterial systems (U.S. EPA, 1984). Additionally, a positive response has been reported for unscheduled DNA synthesis in mouse hepatocytes (Williams, 1983). However, commercially available formulations containing 3 to 7% inhibitors were used in these studies. Some of these compounds, such as butylene oxide, are known to be mutagenic. Therefore, it is uncertain whether the positive responses were due to 1,1,1-trichloroethane or to one or more additives. No definitive conclusions about the compound's mutagenic potential can be made at this time.

Carcinogenicity

NCI (1977) conducted a carcinogenesis bioassay of technical grade (95%) 1,1,1-trichloroethane in Osborne-Mendel rats and B6C3F1 mice. The animals (50 per group per sex) were dosed with 1,1,1-trichloroethane in corn oil by gavage for 78 weeks; 5 days per week. Controls were untreated; no vehicle controls were used. Rats were dosed at 750 or 1500 mg/kg from 7 weeks of age. Survivors were sacrificed at 117 weeks. Mice were given a time-weighted average dose of 2807 and 5615 mg/kg from 5 weeks of age and survivors were sacrificed at 96 weeks. No treatment-related malignant and

non-malignant lesions were observed in either species. This study was deficient in that survival was poor in both controls and treated animals with only 3% of animals surviving until the end of the study.

A repeat of this bioassay (NCI, 1983) involved exposure of Fischer 344/N rats and B6C3F1 mice to 1,1,1-trichloroethane (99.7%) by gavage in corn oil. Rats (50 per sex per group) were dosed with 375 or 750 mg/kg and mice (50 per sex per group) with 1500 or 3000 mg/kg 5 times per week for 103 weeks. Controls were given corn oil alone. A significant increase in the incidence of hepatocellular carcinomas was seen in female mice, while this effect was considered equivocal in male mice. No carcinogenic effect was seen in male rats and the study was judged inadequate for evaluation of carcinogenicity in female rats because of the number of accidental deaths. There are serious data discrepancies in this study, and it, along with a number of others conducted in the same laboratory, is currently undergoing audit by the National Toxicology Program (NTP) prior to final evaluation of results. At this time, the results of the audit have not been released by NTP.

The Dow Chemical Company has conducted two chronic inhalation studies with 1,1,1-trichloroethane. The first involved exposure of Sprague-Dawley rats (96 per sex per treated group, 192 per sex per control group) to 875 or 1750 ppm 6 hours per day, 5 days per week, for 12 months. Animals were held until sacrifice at 31 months. No carcinogenic response was observed; an increased incidence of focal hepatocellular changes occurred in female rats given 1750 ppm (Quast et al., 1978).

The second Dow study involved B6C3F1 and Fischer 344 rats. At this time, only the results of the mouse study have been released (Quast et al., 1984). Mice (80 per sex per group) were exposed to 150, 500, or 1500 ppm production grade 1,1,1-trichloroethane (94%) 6 hours per day, 5 days per week for two years. Interim sacrifices were made at 6, 12, and 18 months. No treatment-related effects or evidence of carcinogenicity was detected; parameters examined included hematology, blood chemistry, and gross and histologic pathology.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Non-Carcinogenic. The available oral studies were judged to be in appropriate for risk assessment. In 1977 NCI bioassay, only 3% of animals survived to the end of the study. Serious data discrepancies have raised questions about the reliability of the 1983 NCI bioassay and it has not yet been released in final form. The subchronic oral study conducted by Bruckner et al. (1985) was not used because the responses observed in the lowest affected dose group (2500 mg/kg) were CNS depression, weight loss, and death. In order for CNS depression to be used as an endpoint, more sensitive, objective measurements should be performed, since undetected CNS

effects may have occurred at the lowest (500 mg/kg) dose. The study of Quast et al. (1978) was not judged the most appropriate for risk assessment. Available evidence indicates that the drinking water concentration which would result in an equivalent human dose is higher for the no-observed-adverse-effect level (NOAEL) (875 ppm) in the Quast et al. study than for the lowest-observed-adverse-effect level (LOAEL) (250 ppm) in the McNutt (1975) study under the exposure condition of these experiments.

The subchronic inhalation study conducted by McNutt et al. (1975) was judged most appropriate for risk assessment with liver damage as the endpoint. A dose-response relationship was observed with mild to minimal liver changes at 250 ppm and more severe effects at 1000 ppm.

Carcinogenic. Several carcinogenesis bioassays either gave negative results (see above) or were deficient. The only positive response (hepatocellular carcinomas in female mice) occurred in a study in which serious data discrepancies raise questions as to the validity of the results (Dr. L. Birnbaum, NTP, personal communication). At this time, the results of the audit of this study have not been released, and the study can not be used for evaluating 1,1,1-trichloroethane's carcinogenic potential.

1,1,1-Trichloroethane has been ranked as Group D (not classified, inadequate evidence of carcinogenicity) by EPA, and as Group 3 (cannot be classified as to human carcinogenicity) by IARC. Based on these rankings, it was considered a non-carcinogen for determination of RMCL for drinking water by EPA (U.S.EPA, 1985b). Depending on the results of the audit of the NTP study, changes in the carcinogenicity status of 1,1,1-trichloroethane may occur in the future.

On the basis of this information, no carcinogenesis risk assessment was made for 1,1,1-trichloroethane at this time.

Calculation of the Health-based Maximum Contaminant Level

A LOAEL of 250 ppm (McNutt et al., 1975) was used to derive an MCL. Simple conversion factors cannot be used to calculate the oral dose which is equivalent to the dose received by continuous inhalation of a given air concentration. The equivalent dose can be found by using pharmacokinetic modeling to determine the drinking water concentration which would result in the same body burden as the inhalation exposure at steady-state.

The conversion of the dose received by continous inhalation of 250 ppm by mice to a drinking water level resulting in an equivalent body burden in humans (in mg/kg) at steady-state was performed by Dr. R. Reitz of Dow Chemical Company (personal communication), using the pharmacokinetic model developed for 1,1,1-trichloroethane (Reitz et al., 1985, 1986). This pharmacokinetic model takes into account four compartments and is based on physiological parameters, including: volumes of tissue compartments,

cardiac output, alveolar ventilation, blood flow to tissue groups, partition coefficients, and metabolic rates. It has been validated by comparison with data from humans, rats, and mice of different ages exposed by various routes. Steady-state levels in mice are achieved within 4 hours of exposure to 250 ppm; to be conservative, the value at 10 days of exposure was used in the calculation. In humans, steady-state is achieved within 4 days of exposure to drinking water; again, to be conservative, the value after 100 days was used.

The model was used to predict the drinking water concentration which results in the same body burden in humans as does continuous inhalation of 250 ppm by mice. The predictions of the model and resulting MCL are shown below:

Body burden in mouse continuously breathing 250 ppm at steady-state = 22.8 mg/kg.

Drinking water concentration resulting in equivalent body burden of 22.8 mg/kg (2L per day consumed) in man = 1,280,000 ug/L.

1000 = safety factor to extrapolate from subchronic oral study.

10 = additional uncertainty factor between 1 and 10 when using a LOAEL instead of a NOAEL.

0.2 = contribution from drinking water alone.

$$\text{MCL} = \frac{1{,}280{,}000 \text{ ug/L} \times 0.2}{(1000)\ (10)} = 26 \text{ ug/L}$$

MCL = 26 ug/L

Assumptions and Uncertainty

The pharmacokinetic model used for the dose conversion is based on physiologic parameters determined experimentally in humans (Nolan et al., 1984) and mice (Schumann et al., 1982a), and was found to accurately predict experimental data for 1,1,1-trichloroethane administered by inhalation or in drinking water (Reitz et al., 1985, 1986). The model involves four compartments (fat, liver, rapidly-perfused tissues, and slowly-perfused tissues) and takes into account absorption after various routes of administration, metabolism, distribution to and accumulation in the four compartments, and excretion via the lungs or as metabolites.

The mice were assumed to weigh 29 g, which was the average weight of the animals used by McNutt et al. (1975).

The weight of a human was assumed to be 83 kg. This was the average weight of the male volunteers in the study of Nolan et al. (1984).

CNS effects may be a more appropriate endpoint than liver damage. No appropriate studies utilizing sensitive measures of CNS function have been conducted, however.

The 1,1,1-trichloroethane used in the study contained 3 to 6% of several inhibitors (dioxane, 2.4 to 3.0%, butanol, 0.12 to 0.30%, ethylene dichloride, and other materials).

It is assumed that 2 L of drinking water is consumed daily, and that 20% of exposure is through drinking water.

Conclusions

A health-based MCL of 26 ug/L was derived for 1,1,1-trichloroethane, based on liver effects seen in mice exposed by inhalation.

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