Appendix B
Section R

TRICHLOROETHYLENE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Trichloroethylene is a colorless liquid used extensively as a solvent in the vapor degreasing of fabricated metal parts. The major source of it in the environment is volatilization during production and use. The odor threshold of trichloroethylene in water is 0.5 mg/L. The evidence reviewed in this document for the carcinogenicity of trichloroethylene includes the increase of malignant liver tumors in both male and female B6C3F1 mice. The U.S.EPA classifies trichloroethylene as a probable human carcinogen (Group B2). The drinking water concentration associated with a lifetime excess risk of one in a million has been determined to be 1.2 ug per liter.

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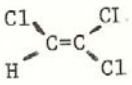
BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties:

Chemical Name:	Trichloroethylene
Synonyms:	1,1,2-Trichloroethylene, Trichloroethene
CAS #	79-01-6
Chemical formula	C_2HCl_3
Chemical structure	
Molecular weight	131.39
Physical state (room temperature)	colorless liquid
Melting point	-73 °C
Boiling point	86.7 °C
Vapor pressure, volatility	77 mm at 25 °C
Specific gravity, density	1.4 at 25 °C
Water solubility	0.1% w/v at 20 °C Log octanol/water
Partition coefficient	2.38
Taste threshold (water)	not available
Odor threshold (water)	0.5 mg/L
Odor threshold (air)	2.5-900 mg/m^3
Conversion factors	1 ppm = 5.45 mg/m^3 at 25 °C

Production and Use

Trichloroethylene is a synthetic halogenated hydrocarbon used extensively a a solvent in degreasing of fabricated metal parts and in industrial drycleaning Trichloroethylene may be found in printing inks, varnishes, paints, lacquers adhesives, spot removers, rug cleaners, and disinfectants. It is no longer use in food, drugs, or cosmetics. Most of the commercially produce trichloroethylene is derived from ethylene or dichloroethane.

Guidelines, Regulations, and Standards

The present Occupational Safety and Health Administration (OSHA) workplac standard for trichloroethylene is an 8-hour time-weighted-average (TWA) of 10 ppm.

An Ambient Water Quality Criteria Document for trichloroethylene was pub- lished by the U.S. Environmental Protection Agency (U.S.EPA, 1980). Assumin consumption of 2 liters of water and 6.5 grams of fish per day by a 70 kg adult a trichloroethylene level of 2.7 ug/L was estimated to limit excess lifetim cancer risk to one in a million.

The U.S.EPA under the Safe Drinking Water Act promulgated Recommende Maximum Contaminant Levels (RMCLs) and proposed Maximum Contaminant Levels (MCLs) (U.S.EPA, 1985b). The RMCL and MCL for trichloroethylene are zero and 5 ug/L, respectively.

The World Health Organization (WHO) recommended a tentative guideline valu of 30 ug trichloroethylene per liter of drinking water (WHO, 1984). This valu was based on a 70-kg adult consuming 2 L of water per day and on an acceptable risk level of less than one additional case of cancer per 100,000 population for a lifetime of exposure.

ENVIRONMENTAL EXPOSURE

Fate and Transport

Volatilization of trichloroethylene into the air during production and use is its major source in the environment. Trichloroethylene is routinely found in the aquatic environment. The half-life of trichloroethylene in surface waters is estimated to range from a few hours to ten days or longer depending on water turbulence and temperature. The major degradation products via photoxidation include phosgene and dichloroacetyl chloride (U.S.EPA, 1985a).

Ambient Levels

Federal surveys of trichloroethylene in public water supply systems indicat- ed that levels of this compound range from 0.06-4 and 0.11-53 ug/L in surface water and groundwater, respectively. The U.S.EPA used the Federal Reporting Data Systems survey of United States populations served by primary water supply systems to estimate exposure to trichloroethylene through drinking water (U.S.EPA, 1984). Potentially 1,844,000 individuals are exposed to levels of trichloroethylene in drinking water at or above 5 ug/L (Table I).

During the period 1978 thorugh 1981 the Office of Science and Research, New Jersey Department of Environmental Protection, sampled public water supplies statewide for over 100 substances. Trichloroethylene was detected in 19% of the samples at a mean level of 13 ug/L.

The New Jersey Assembly Bill A280 listed chemicals were recently monitored by New Jersey potable water purveyors. Trichloroethylene was found in 5 precent of the samples. The concentration levels ranged from 0.3 to 24.0 ug/L.

Table I

Estimated Drinking Water Intake of Trichloroethylene

Exposure Level(ug/l)	Population	Intake* (ug/kg/day)
≥ 0.5	25,131,000	≥0.014
≥ 5.0	1,844,000	>0.14
>10.0	1,417,000	>0.29
>50.0	212,000	>1.4
>100.0	42,000	>2.9

*Intake estimates assume 70 kg adult consumes 2 L of water per day.

Source: U.S.EPA, 1984

METABOLISM AND PHARMACOKINETICS

Absorption

Trichloroethylene is an uncharged, nonpolar, and highly lipophilic compound that can be expected to readily cross the gastrointestinal mucosal barrier. Virtually complete absorption by the oral route has been demonstrated in rats and mice. Dekant et al. (1984) dosed by gavage both rats and mice with 200 mg/kg (^{14}C)-trichloroethylene in corn oil vehicle, and recovered 93 to 98% of the radioactivity in expired air and urine. Prout et al. (1985) administered radiolabeled trichloroethylene in corn oil vehicle by mouth in doses of 10, 500, 1000, and 2000 mg/kg. For both rats and mice, 91 to 98% of the doses were recovered in expired air and urine. Peak blood levels occurred at about 1 hour in mice and 3 hours in rats, indicating rapid absorption from the gastrointestinal tract.

Distribution

Trichloroethylene distributes to all body tissues. Zenick et al. (1984) administered by gavage doses of 0, 10, 100, or 1000 mg/kg trichloroethylene to rats 5 days per week for 6 weeks. Trichloroethylene was found in all tissues examined with the highest concentrations noted in the fat, kidney, lung, adrenals, vas deferens, epididymis, brain, and liver.

Metabolism

A number of researchers have speculated that the metabolism of trichloroethylene is central to its hepatotoxic and carcinogenic effects (Green and Prout, 1985; Miller and Guengerich, 1983; Stott et al., 1982). Trichloroethylene is metabolized by the cytochrome P-450 monooxygenase system to trichloroacetaldehyde (Miller and Guengerich, 1982). Demonstrated trichloroethylene metabolites include trichloroethylene oxide, trichloracetaldehyde, trichloroacetic acid, monochloroacetic acid, trichloroethanol and trichloroethanol glucuronide (U.S.EPA, 1985a). Carbon dioxide is a major metabolite accounting for up to 10% of a single oral dose (Green and Prout, 1985).

Excretion

Trichloroethylene and its metabolites are eliminated primarily by exhalation and in urine. Trichloroethylene is lost from the human body with a half-life of about 1.5 hours (Stewart et al., 1962). Green and Prout (1985) studied in detail the elimination of trichloroethylene in Osborne-Mendel rats, Wistar rats, B6C3F1 mice, and Swiss mice. Analysis of expired air following a single dose by mouth of radioactive trichloroethylene (10 to 2000 mg/kg) identified two major radioactive components: carbon dioxide and unchanged trichloroethylene. Trace amounts of trichloroethanol and carbon monoxide were also detected. Urine from the rats and mice contained trichloroacetic acid, trichloroethanol glucuronide, and small amounts of free trichloroethanol.

Human Exposure and Body Burden

Monitoring trichloroethylene levels in blood or expired air and measuring urinary metabolites are common methods for determining trichloroethylene body burden (Stewart et al., 1962).

HEALTH EFFECTS

Overview

The principal adverse effects of trichloroethylene are central nervous system dysfunction and liver injury. Symptoms of liver injury include: degeneration of parenchymal cells, fatty infiltration, altered liver function, glycogen depletion, cellular necrosis, and increased liver weight. Trichloroethylene induced liver cancer in both sexes of B6C3F1 mice.

Human

Oral exposure of humans to 15 to 25 mL (21 to 35g) trichloroethylene resulted in vomiting, abdominal pain and unconsciousness (Stephens, 1945).

Animal

The oral LD_{50} of trichloroethylene in female and male CD-1 mice is 2.4 g/kg body weight (Tucker et al., 1982). Rats exposed to 300 mg/m^3 (55 ppm) trichloroethylene 5 days per week for 14 weeks had elevated liver weights (Kimmerle and Eben, 1973).

Behavorial and Central Nervous System

Short-term inhalation of high levels of trichloroethylene can lead to dizziness, headache, nausea, confusion and unconsciousness (Longley and Jones, 1963; Steinberg, 1981). Psychotic symptoms resulted from ingestion of trichloroethylene and alcohol.

Reproductive, Embryotoxic, and Teratogenic

It has not been demonstrated that trichloroethylene influences the reproductive system of rats and mice (Manson et al., 1984; Slacik-Erben et al., 1980; Zenick et al., 1984). Slacik-Erben et al. (1980) exposed male mice to 0, 50, 202, or 405 ppm for 24 hours with 50 mice per dose level. Each male was then mated with a new untreated female every 4 days, 12 times altogether. There were no biologically significant effects on pregnancy rates or pre- or post-implementation at any dose level.

Long-Evans hooded male rats were intubated at 100 days of age with 0, 10, 100, or 1000 mg/kg trichloroethylene in corn oil (10 males per group) for 5 days per week for 6 weeks (Zenick et al., 1984). The male rats were allowed to copulate with ovariectomized, hormonally primed females. The rats in the 10 and 100 mg/kg trichloroethylene treatment groups did not suffer impaired copulatory performance, semen quality, or plasma testosterone level.

Female Long-Evans hooded rats were exposed to vehicle-control (corn oil), 10, 100, or 1000 mg/kg per day trichloroethylene (23 per group) by gavage for 2 weeks before mating and throughout mating to day 21 of pregnancy (Manson et al., 1984). Maternal toxicity was noted in the 1000 mg/kg per day group. Oral exposure to trichloroethylene at levels below those causing maternal toxicity had no influence on mating performance, female fertility, pregnancy outcome, and neonatal survival. No major malformations were observed by gross examination of pups.

Genetic

In studies conducted by the National Toxicology Program (NTP) (Table II), trichloroethylene did not cause mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation by Arochlor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 fractions by a liquid-incubation procedure. Trichloroethylene did not induce chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activitation; the results for sister-chromatid exchange were considered equivocal. Trichloroethylene was mutagenic to mouse lymphoma L5178Y/TK cells only with activation by Aroclor 1254-induced male F344 rat liver S9.

Carcinogenicity

The carcinogenic potential of trichloroethylene has been adequately reviewe (IARC, 1979; Kimbrough et al., 1985; U.S. EPA, 1985a; WHO, 1985) Trichloroethylene administered by the oral exposure route induced hepatocellula carcinoma in both sexes of B6C3F1 mice (NTP, 1984; NCI, 1976). Trichloroethylen is classified as a probable human carcinogen (EPA Group B2).

Table II

Genetic Toxicology of Trichloroethylene

Process	End Point	Test System	Conclusion	References
Gene mutation	Base-pair substitution, Frameshift	Ames Salmonella battery with and without metabolic activation.	Negative	NTP unpublished results
		Mouse lymphoma K5178Y/TK^{+-} cells with metabolic anti-vation.	Positive	NTP unpublished results
		Mouse lymphoma L5178Y/TK^{+-}	Negative	NTP unpublished results
Chromosomal rearrangement homologuous	Sister chromatid exchange	Chinese hamster ovary cells in vitro with and without metabolic activation	Positive/Equivocal	NTP unpublished results
Chromosomal rearrangement non-homologous recombination	Chromosomal aberrations	Chinese hamster ovary cells in vitro with and without metabolic activation	Negative	NTP unpublished results
Chromosomal rearrangement ploidy change	Hypodiploidy	Human occupational study	Positive	Konietzko et al., 1978

Animal Laboratory Bioassays

The experimental induction of cancer by trichloroethylene has been demonstrated in mice (NTP, 1984; NCI, 1976). In a two-year study conducted by the National Toxicology Program (NTP, 1984), 8-week old F344/N rats and B6C3F1 mice of both sexes were given trichloroethylene by gavage. The trichloroethylene was dissolved in corn oil and administered 5 days per week for 103 weeks. Dosages (in milligrams of trichloroethylene per kilogram of body weight) were 0, 500, or 1000 mg/kg for rats, and 0 or 1000 mg/kg for mice. Both rats and mice were randomly distributed so that there were 50 animals per sex per treatment group. Food and water were freely available.

Animals were killed when moribund or at the conclusion of the study (103-107 weeks). A complete necropsy was performed on each animal unless precluded by cannibalism or autolysis. Selected results are presented in Table III. The National Toxicology Program concluded the following:

> Under the conditions of these studies, epichlorohydrin-free trichloroethylene caused renal tubular-cell neoplasms in male F344/N rats, produced toxic nephrosis in both sexes, and shortened the survival time of males. This experiment in male F344/N rats was considered to be inadequate to evaluate the presence or absence of a carcinogenic response to trichloroethylene. For female F344/N rats receiving trichloroethylene, containing no epichlorohydrin, there was no evidence of carcinogenicity. Trichloroethylene (without epichlorohydrin) was carcinogenic for B6C3F1 mice, causing increased incidences of hepatocellular carcinomas in males and females and of hepatocellular adenomas in females.

Trichloroethylene was administered to male and female Osborne-Mendel rats and B6C3F1 mice by gavage 5 days per week for 78 weeks (NCI, 1976). The animals were then observed for an additional period (32 weeks for rats; 12 weeks for mice) at the end of which time all surviving animals were sacrificed. Rats were started on the test at the age of 7 weeks, and mice at 5 weeks, with 50 animals in each group and 20 matched vehicle-controls for both sexes of both species.

Original doses were the maximum tolerated dose (MTD) and one-half the MTD (as determined in earlier, subchronic studies). For both the male and female rats, dosages were adjusted according to survival and body weights to give time-weighted-average (TWA) doses of 549 mg/kg, 5 days per week (650 mg/kg for 7 weeks, 750 mg/kg for 9 weeks, 500 mg/kg for 14 weeks, and 500 mg/kg on a 4-weeks on, 1-week-off cycle, for 48 weeks) and 1097 mg/kg, 5 days per week (1300 mg/kg for 7 weeks, 1500 mg/kg for 9 weeks, 1000 mg/kg for 14 weeks, and 1000 mg/kg on a 4-weeks-on, 1-week-off cycle, for 48 weeks). Time-weighted-average doses for male mice were 1169 mg/kg, 5 days per week (1000 mg/kg for 12 weeks, and 1200 mg/kg for 66 weeks) and 2339 mg/kg, 5 days per week (2000 mg/kg for 12 weeks, and 2400 mg/kg for 66 weeks). The doses for female mice were 869 mg/kg, 5 days per week (700 mg/kg per day for 12 weeks, and 900 mg/kg for 66 weeks) and 1739 mg/kg, 5 days per week (1400 mg/kg for 12 weeks, and 1800 mg/kg for 66 weeks). Food and water were provided ad libitum.

Animals were observed daily for mortality and were killed when moribund. A complete necropsy was performed on each animal, whether it died, was killed when moribund, or sacrificed at the termination of the experiment.

Table III

Incidence of Tumors in B6C3F1 Mice Induced by Trichloroethylene

Dose Levels		Responses	
Experimental	Adjusted	(# animals with tumor/ # animals at risk)	
mg/kg	mg/kg/day	Male	Female
	NTP-Hepatocellular Carcinoma		
0	0	8/48	2/48
1000	714.3	30/50	13/49
	NCI-Hepatocellular Carcinoma		
0	0	1/20	
1169	468	26/50	
2339	937	31/48	
0	0		0/20
869	348		4/50
1739	694		11/47

Rats treated with trichloroethylene showed no significant increase in tumor incidences over controls. Trichloroethylene treated mice, however, did show a significantly increased ($p<0.05$) incidence of hepatocellular carcinomas as compared to control animals (Table III). The incidence of hepatocellular carcinomas in male mice in the low dose groups was 26/50 (number of mice with tumor per number of mice examined), with the first tumor appearing at week 81 of the experimental period. The first tumor to appear in the high dose group was recorded at 27 weeks, with an overall incidence of 31/48. The single tumor recorded in the control group appeared at week 72. No hepatocellular carcinomas occurred in the control female mice, while the incidence for the high- and low-dose groups was 11/47 and 4/50, with latency periods of 91 and 90 weeks, respectively. The National Cancer Institute (NCI) concluded that:

> The results of this carcinogenesis test of trichloroethylene clearly indicate that trichloroethylene induced a hepatocellular carcinoma response in mice. While the absence of a similar effect in rats appears most likely attributable to a difference in sensitivity between the Osborne-Mendel rat and the B6C3F1 mouse, the early mortality of rats due to toxicity must also be considered.

Trichloroethylene (more than 99% pure, stabilized with 8 ppm diisopropylamine) was studied in 4 strains of rats (ACI, August, Marshall, and Osborne-Mendel) for 2 years (NTP, 1985). Six- to 8-week old rats were administered 0, 500, or 1000 mg/kg trichloroethylene in corn oil, by gavage, 5 days per week, for 103 weeks. Rats were randomly distributed so that there were 50 animals per strain per sex per treatment group. Both corn oil vehicle control and untreated control groups were used. Food and water were freely available.

Animals were killed when moribund or at the conclusion of the study. A complete necropsy was performed on each animal unless precluded by cannibalism or autolysis. The experimental data for these 2-year carcinogenesis studies of trichloroethylene were audited. The results of the audit revealed insufficient documentation of animal breeding, clinical observations, environmental conditions, and chemical analytical data. In addition, individual animal identification was uncertain in many instances.
The National Toxicology Program (NTP) stated that:

> These two year gavage studies of trichloroethylene in male and female CI, August, Marshall, and Osborne-Mendell rats are considered to be inadequate studies of carcinogenicity because of insufficient survival in dosed animals, and inadequate documentation of the conduct of the studies. However, under the conditions of these studies trichloroethylene administration was strongly associated with renal tubular cell cytomegaly and karyomegaly, and toxic nephropathy in both sexes of the four strains. In addition, an increased incidence of renal tubular cell neoplasms in male Osborne-Mendell rats, and possibly in female ACI and female August rats, and an increased incidence of testicular interstitial cell tumors in male Marshall rats may have been associated with the administration of trichloroethylene.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Animal bioassay data (NTP, 1984) was used for the trichloroethylene risk assessment. The rationale applied for the selection of animal laboratory studies for quantitative risk assessment was based upon the guidelines set forth be Crump and Howe (1980). The experimental study design judged to be most suitable involved trichloroethylene treatment of these animals for at least 85% of their expected lifespan and observation of animals for at least 90% of their lifespan. The highest dose level should maximize malignant response without causing overt chronic toxicity. The oral exposure route was considered relevant to setting drinking water criteria.

The NCI (1976) and NTP (1984) studies tested trichloroethylene exposure in rats and mice by the oral route. In the NCI study, mice were treated and observed for 80 to 90% of their average lifespan, respectively. The mice in the NTP study were treated and observed for 100% of their average lifespan. Trichloroethylene significantly increased the incidence of hepatocellular carcinoma (NCI, 1976) and hepatocellular adenomas and carcinomas (NTP, 1984) in B6C3F1 mice. Male mice were more sensitive to trichloroethylene than female mice. The quantitative risk assessment for trichloroethylene will consider the incidence of hepatocellular carcinoma and adenomas in male mice from the NTP (1984) studies.

Calculation of the Health-Based Maximum Contaminant Level

The dose-response relationships obtained from the NCI (1976) and NTP (1984) study were modeled by using regression techniques. The multistage model was used in this for low dose extrapolation with quantal data. The multistage model is given by:

$$P(d) = 1 - \exp(-q_o - q_1 d - \ldots - q_k d^k), \quad q_i \geq 0, \; i = 0, 1, \ldots, k,$$

where P (d) is the lifetime probability of cancer at dose d and k is set to the number of dose groups less one.

The multistage model was implemented using an updated version of the computer program GLOBAL82. All calculations were provided by K.S. Crump and Company (Crump, 1986).

Risk has been defined as "extra risk", i.e.,

$$[P(d) - P(0)/[1 - P(0)],$$

where P(d) is the lifetime probability of dying of liver cancer when exposed to trichloroethylene dose d and P(0) is the lifetime probability of dying of liver cancer when not exposed to trichloroethylene.

A risk level of one in a million was selected for use in establishing an MCL for a lifetime exposure scenario. The 95% upper confidence limit on risk is linear at low doses and will be considered a plausible upper bound on risk.

Animal-to-human extrapolation was based on the assumption that both animals and humans are equally susceptible (in terms of extra risk) to the carcinogen when dose is measured in the same unit for both species (Crump and Howe, 1980). The units of mg/m^2 body surface area per day will be used for animal-to-human extrapolation. If D_A represents animal dose in milligram per kilogram per day, then the human dose (D_H) is given by $D_H = D_A (W_A/W_H)^{1/3}$, where W_A and W_H are the weights of animals and humans, respectively.

Experimental dose levels are adjusted from milligrams per kilogram to milligrams per kilogram per day by a factor of 5/7 to account for trichloroethylene administration 5 days per week. A factor of $(90/104)^4 = 0.5608$ is further applied for the NCI study because the experiment was ended before the animals lived out their full lifespans.

The results of fitting the multistage model to the male B6C3F1 mice hepatocellular carcinoma or adenoma is provided in Table IV. The standard assumption is that a 70 kg adult consumes 2 L of water per day. The human dose (micrograms per liter) is calculated as follows:

= human dose (mg/kg/day) x 1,000 ug/mg) x (70kg) / (2 L/day)

= animal dose (mg/kg/day) x $(W_A/W_H)^{1/3}$ x 35,000

= animal dose (mg/kg/day) x $(0.03 \text{ kg}/70 \text{ kg})^{1/3}$ x 35,000

= animal dose (mg/kg/day) x 35,000/13

= (4.34×10^{-4}) x 35,000/13

= 1.2 ug/L.

A drinking water concentration of 1.2 ug trichloroethylene per liter is associated with a lifetime excess cancer risk of one in a million.

Assumptions and Uncertainty

The extrapolation of liver cancer risk from bioassay data to human liver cancer risk was carried out by assuming that animals and humans were equally sensitive to a particular measure of dose. The interspecies conversion factor applied was mg/m^2 surface area per day. This is equivalent to (mouse weight/human weight)$^{1/3}$. Mouse and human weights used are 0.03 and 70 kg, respectively.

A 70 kg adult was assumed to consume two L of drinking water per day for life. The derived MCL corresponds to a 95% upper bound excess risk. The 95% upper confidence level was considered a plausible upper bound on risk.

Conclusions

Trichloroethylene is classified as a probable human carcinogen (EPA Group B2). Trichloroethylene induced liver neoplasms in both sexes of B6C3F1 mice. The quantitative estimation of risk is based on the NTP (1984) mouse bioassay. A drinking water level of 1.2 ug trichloroethylene per liter was associated with a lifetime excess cancer risk of one in a million.

Table IV

Trichloroethylene Quantitative Risk Assessment

Study	Species	Sex	Organ	Histology	Animal Dose (mg/kg/day)
NCI	B6C3F1 mice	Male	Liver	Hepatocellular carcinoma	6.54×10^{-4}
NTP	B6C3F1 mice	Male	Liver	Hepatocellular carcinoma or adenoma	4.34×10^{-4}

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