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# Trichloroethylene

HSIA White Paper

## Introduction

Trichloroethylene (TCE) is a solvent used widely by industry as a metal degreaser. It is especially valuable because of its cleansing properties, low flammability, and lack of measurable flashpoint. TCE also is used to a much lesser extent in adhesive, paint, and coating formulations and as a chemical process intermediate in the polyvinyl chloride (PVC) industry. It has been in use for about 50 years and is employed worldwide.

TCE is a colorless, volatile liquid and is a member of the family of unsaturated aliphatic halogenated hydrocarbons. In the United States, it is currently produced by Dow Chemical U.S.A. and PPG Industries, Inc. The 1985 demand was 81,600 metric tons, of which 18,100 tons were imported.

The health effects of TCE have been studied extensively and new data are constantly being developed. The most significant finding to come out of the many long-term animal carcinogenicity studies of TCE is that it produces liver cancer in mice, but not in rats or hamsters. Detailed metabolic studies have shown that these tumors arise by a mechanism specific to the mouse; thus, humans are unlikely to be at risk from trichloroethylene-induced liver cancer.

Scientists from the Centers for Disease Control (CDC) in Atlanta have reviewed the available data on trichloroethylene and have concluded that "[t]he risk associated with exposure to trace amount (parts per billion) concentrations of TCE in water appears to be minimal or perhaps negligible." The CDC scientists recommended a re-examination of the risks attributed to TCE in the past.

The scientific questions concerning the relevance of animal data, and the absence of a carcinogenic response in a number of human health and mortality studies, indicate that trichloroethylene does not pose a carcinogenic or reproductive risk to humans under normal use conditions.

The U.S. Occupational Safety and Health Administration has established a permissible exposure limit (PEL) of 100 parts per million for an 8-hour time-weighted average (TWA). The American Conference of Governmental Industrial Hygienists (ACGIH) currently recommends a threshold limit value (TLV) of 50 ppm for workplace exposure.

## Uses

For 1985, the industrial uses of trichloroethylene can be broken down in the following manner:

| | |
|---|---|
| metal cleaning/degreasing | 85% |
| PVC production | 7% |
| adhesives | 1% |
| paint removal/stripping | 1% |
| miscellaneous | 6% |

### ■ METAL CLEANING/DEGREASING

Among the properties that have contributed to trichloroethylene's wide acceptance as a metal cleaner and degreaser are the following:

- high solvency
- low flammability
- non-corrosiveness
- high stability
- low specific heat
- low boiling point
- low latent heat of vaporization

Commerical TCE formulations include a stablizer system to help prevent solvent breakdown caused by contaminants such as acids, alkalies, metal chips and fines, and exposure to oxygen, light, and heat. Trichloroethylene is the primary solvent for degreasing aluminum and is second to alkalies for cleaning sheet and strip steel prior to galvanizing.

Trichloroethylene's advantages for metal cleaning include the ability to degrease more thoroughly and several times faster than alkaline cleaners and its compatibility with smaller equipment that consumes less energy.

### ■ MISCELLANEOUS

The miscellaneous applications of trichloroethylene include the following:

- Low temperature heat-transfer medium
- Solvent in textile dyeing and finishing
- Critical electronic component cleaner
- Solvent for liquid oxygen and hydrogen tank flushing

## Health Effects

### ■ GENERAL

Acute (single) overexposure to trichloroethylene vapor can cause central nervous system effects (e.g., light-headedness, drowsiness, headache, giddiness) which may lead to unconsciousness or prove fatal in extreme circumstances. Also, at very high exposure levels, trichloroethylene can sensitize the heart to the effects of adrenaline and similar agents, which may lead to sudden cardiac arrest. In addition, trichloroethylene may irritate the respiratory tract at high vapor pressures. Repeated or lengthy contact with TCE in liquid form can cause irritation of the skin and eyes.

Chronic (repeated) overexposure has been associated with damage to the liver and kidneys, although this is less well documented in humans than in animals.

### ■ MUTAGENICITY

Trichloroethylene has been tested for its mutagenicity (genotoxicity) in a number of different assays including bacterial and mammalian systems, both in vivo (animal experiments) and in vitro (test tube experiments). Several of these assays have

been complicated by the presence of stabilizers which are known to cause positive responses. The general outcom of these many studies is that pure trichloroethylene either shows no mutagenic activity or only weak activity under certain conditions. Binding of trichloroethylene or its metabolites to protein, RNA, and DNA has been shown in vitro; only extremely low or no binding of metabolites to DNA has been reported in vivo. Hence, trichloroethylene does not show significant evidence of genotoxicity in these test systems.

## ■ CARCINOGENICITY

### Animal Studies

Trichloroethylene has been tested in a number of lifetime studies in laboratory rats, mice, and hamsters, with administration by inhalation, oral gavage (intubation), and dermal and subcutaneous (under the skin) application.

Administration of TCE via inhalation to Sprague-Dawley (SD) rats, Wistar rats, and Syrian hamsters at levels of up to 500 ppm showed no induction of tumors. Trichloroethylene administered to SD rats and Osborne-Mendel rats by oral gavage at doses of 50 to 2339 milligrams per kilogram (mg/kg) body weight per day also did not induce tumors.

Administration to B6C3F1 mice by oral gavage has produced liver tumors in two different studies at doses ranging from 50 to 2339 mg/kg per day. Administration to ICR mice by inhalation produced lung tumors at 150 and 450 ppm. A study of NMRI mice exposed via inhalation to up to 500 ppm showed increases in lymphomas in female mice, but the authors considered this finding to be due to viral/immune factors specific to the mouse. Another long-term study on Swiss mice exposed by oral, dermal, and subcutaneous application showed no increase in tumors.

In August 1986, the National Toxicology Program's Board of Scientific Counselors accepted a draft report of a two-year gavage study in ACI, August, Marshall, and Osborne-Mendel rats. Results showed some increases in renal and testicular tumors in rats exposed to 500 and 1000 mg/kg per day. However, the draft report concludes that "these studies are considered to be inadequate for assessing either the presence or absence of carcinogenicity because of chemically-induced toxicity, reduced survival, and deficiencies in the conduct of the studies as revealed by the data audit."

These numerous animal studies, taken together, indicate that trichloroethylene does not have a carcinogenic effect in the rat or the hamster. A carcinogenic response has been seen in the mouse, a species prone to a high spontaneous tumor incidence. In particular, high dosage regimens have led to an increased incidence of liver cancer in the B6C3F1 mouse.

### Significance of Animal Data

Following the observation that trichloroethylene produces liver cancers in mice but not in rats, industry commenced studies to investigate the reasons for this species difference and to establish whether or not the observations in mice are relevant to humans.

Results of this research show that the mechanism of action that produces liver tumors in mice exists in rats at levels too low to produce tumors and may not be present at all in humans. Oxidative metabolism of trichloroethylene produces a metabolite called trichloroacetic acid (TCA) which causes an increase in certain enzyme-containing organelles (known as peroxisomes) within the liver cells in rodents. This increase or proliferation of liver peroxisomes in rodents is associated with the formation of liver tumors.

Although TCA is known to cause peroxisome proliferation in rodents, it does not do so in human liver cells. Moreover, rat liver cells produce TCA at much lower levels than those of the mouse, and human liver cells produce even less than the rat.

In sum, this research not only explains why liver tumors are seen in mice but not in rats, but leads to the important conclusion that trichloroethylene is unlikely to produce tumors in the human liver.

## ■ HUMAN EPIDEMIOLOGY

A recent study has added considerably to the epidemiological data base on trichloroethylene. This study of over 2600 exposed workers with an average exposure of over six years found no increase in cancer-related deaths compared to the expected result among unexposed white males (the largest group used for purposes of comparison).

A number of other studies have been carried out with the specific objective of investigating any possible association between trichloroethylene exposure and human liver cancer. None of these studies show a correlation between trichloroethylene exposure and human liver cancer.

A number of more general studies have been reported on workers potentially exposed to trichloroethylene. Although most of these studies have limitations (e.g., insufficient information on levels of TCE exposure), none present evidence to suggest that exposure to trichloroethylene is associated with an increased incidence of cancer in humans.

## ■ REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Trichloroethylene has been evaluated in several studies for its ability to adversely affect the reproductive process in animals. Inhalation studies in rats, mice, and rabbits at concentrations ranging from 300 ppm to 1800 ppm have shown no significant teratogenic (reproductive) effects. At 300 ppm, no significant maternal toxicity, embryotoxicity, or fetotoxicity was seen in SD rats or Swiss-Webster mice. Nor were significant effects observed in SD rats exposed to 500 ppm. A non-significant increased incidence of hydrocephalus was seen in New Zealand rabbits exposed to 500 ppm. Slight fetotoxicity and growth depression were seen in Long-Evans rat offspring at 1800 ppm. A dominant lethal study in mice suggests the absence of any adverse effect on the male reproductive system. This spectrum of negative data suggests that trichloroethylene is unlikely to have an adverse effect on human reproduction when handled in accordance with good occupational hygiene practice.

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# HSIA Perchloroethylene White Paper

## Introduction

Perchloroethylene is the primary solvent used in commercial and industrial dry cleaning. Since being introduced to the dry cleaning industry in the late 1930's, it has replaced carbon tetrachloride and most petroleum solvents because of its relatively low toxicity and nonflammability. Today, approximately 75 percent of the nation's dry cleaners use the chemical. Other major uses of perchloroethylene are as a metal cleaning and degreasing solvent and as a chemical intermediate in the production of several fluorocarbons.

Perchloroethylene, also known as tetrachloroethylene, is a member of a family of unsaturated aliphatic halogenated hydrocarbons. It is a colorless, volatile liquid that is essentially nonflammable and has no measurable flashpoint. In the United States, perchloroethylene is produced by Dow Chemical U.S.A., Occidental Chemical Corporation, PPG Industries, Inc., and Vulcan Materials Company. The 1985 production was about 218,000 metric tons. An additional 59,000 metric tons were imported.

Perchloroethylene has been used safely in industry for almost 50 years. Because of its widespread usage, the potential for adverse health effects resulting from exposure to perchloroethylene has undergone considerable study. Research on the mutagenic potential of the chemical has yielded no significant effects in microorganisms. Studies of genotoxicity in higher animals also failed to show any effects. Similarly, perchloroethylene did not produce adverse effects in reproduction and development studies in laboratory animals.

The National Toxicology Program (NTP) recently completed an animal testing program on perchloroethylene which found evidence of liver tumors in a particular strain of laboratory mice (B6C3F1), reproducing results of an earlier study by the National Cancer Institute in the same strain of mice. The relevance of these results to humans, however, has been questioned because of research which indicates that the mechanism of liver tumor induction in mice does not apply to humans. Further, the results of an epidemiology study of 615 dry cleaner workers occupationally exposed to only perchloroethylene found no evidence of an increased cancer mortality rate.

The U.S. Occupational Safety and Health Administration (OSHA) has established a workplace permissible exposure limit (PEL) of 100 parts per million (ppm) for an 8-hour time-weighted average (TWA). The American Conference of Governmental Industrial Hygienists (ACGIH) currently recommends a threshold limit value (TLV) of 50 ppm for workplace exposure. This 50 ppm concentration is the approximate odor threshold for the chemical.

## Uses

For 1985 the uses of perchloroethylene can be broken down in to the following categories:

| | |
|---|---|
| dry cleaning/textile processing | 56% |
| chemical intermediate | 29% |
| metal cleaning/degreasing | 11% |
| miscellaneous | 4% |

### ■ DRY CLEANING

Today, perchloroethylene is used by approximately 75% of all dry cleaners including industrial, commercial, and coin-operated establishments. It was introduced to the dry cleaning industry in the late 1930's and had replaced other synthetic solvents, such as carbon tetrachloride, by the mid-1940's. A gradual shift from petroleum derivatives to perchloroethylene began in the late 1940's. This shift in solvents increased in the 1950's and early 1960's. However, in the period before 1960, petroleum derivatives were still the dominant solvents.

In addition to its nonflammability and relatively low toxicity, perchloroethylene's popularity in the dry cleaning industry can be attributed to the following properties:

- Safe to use on all common textiles, fibers, and dyes
- Effective at removing fats, oils, and greases
- Free of residual odor
- Chemically stable under all common use conditions
- Non-corrosive to the metals and other materials in the dry cleaning machinery
- Easily removed from clothes by rapid, safe drying
- The most energy- and cost-efficient solvent (can be easily redistilled and reused)

### ■ CHEMICAL INTERMEDIATE

Perchloroethylene is used as a basic raw material in the manufacture of chlorofluorocarbons (CFC's), principally trichlorotrifluoroethane (CFC-113), which is used in the electronics industry, in metal cleaning, and in dry cleaning. The chemical also is used in the synthesis of CFC-114, CFC-115, and CFC-116.

### ■ METAL CLEANING/DEGREASING

Many industries, including aerospace, appliance, and automotive manufacturers, use perchloroethylene for vapor degreasing metal parts during various production stages. Its high boiling point and resultant longer cleaning cycle are advantageous in removing "difficult" soils such as waxes with high melting points. The ability of the chemical to remove water during vapor degreasing is of benefit to jewelry manufacturers and other metal finishers.

Perchloroethylene's nonflammability and low vapor pressure make it an effective cold (room temperature) metal cleaner,

ither alone or when blended with flammable solvents. Its low vapor pressure contributes to reduced emissions from cleaning operations where it is employed.

### ■ MISCELLANEOUS

Perchloroethylene also is used as a dielectric fluid in some electrical transformers and as a carrier for rubber coatings, solvent soaps, printing inks, aerosols, adhesives, sealants, polishes, lubricants, and silicones.

# H alth Effects

### ■ GENERAL

General health effects of overexposure to perchloroethylene have been reported involving the central nervous system (CNS) and liver in humans. CNS effects in humans are generally most noticeable following acute occupational exposure. Prolonged exposure to concentrations of 200 ppm or more has been associated with dizziness, confusion, headache, nausea, and irritation of the eyes and mucous tissue. At higher level exposures (>600 ppm) these symptoms are intensified. Prolong d exposure to sufficiently high levels (>1500 ppm) may lead to unconsciousness due to anesthesia and, in extreme cases, death from respiratory depression.

Reversible changes in the liver and kidney of laboratory animals have been reported following prolonged exposure to concentrations of 200 ppm or more. In humans, transient alterations in liver function also have been noted in persons exposed to high levels of perchloroethylene vapor for extended periods of time. No cause-effect relationship has been established between kidney effects and exposure to perchloroethylene in humans.

### ■ MUTAGENICITY

The ability of perchloroethylene to cause genetic mutations has been tested in bacteria, laboratory animals, and human tissue. The preponderance of these data indicate that the chemical is not mutagenic. Commercial formulations of the chemical have elicited weakly positive responses in some yeast and bacterial assays, but only when toxic concentrations of perchloroethylene were used. Moreover, no dose-response relationships were established. In the one mutagenicity study conducted using highly-purified perchloroethylene, no evidence of mutagenic effect was observed in the bacteria tested.

### ■ CARCINOGENICITY

#### Animal Studies

Three studies of the carcinogenic potential of perchloroethylene in laboratory animals have been conducted. Two of the studies found a significant increase in benign and malignant liver tumors in mice. The strain of mice used in these studies (B6C3F1) is prone to a high spontaneous tumor incidence that appears unique to the species.

The first study, conducted by the National Cancer Institute, exposed (by gavage) Osborne-Mendel rats and B6C3F1 mice to up to 949 milligrams of perchloroethylene per kilogram (mg/kg) body weight and up to 1072 mg/kg body weight, respectively, each day, 5 days a week for 78 weeks. The study found a significant increase in benign and malignant liver tumors in both sexes of mice. Low survival in the rats tested, believed to result from exposure to doses higher than the maximum tolerated dose, compromised the study's ability to detect a carcinogenic effect in this species.

The Dow Chemical Company conducted an inhalation study of the carcinogenic effect of perchloroethylene on Sprague-Dawley rats. The Dow study exposed male and female rats to 0, 300, and 600 ppm of the chemical for 6 hours per day, 5 days per week for 52 weeks (and observed for another 52 weeks) and found no significant differences between the exposed and control animals.

In 1985, the National Toxicology Program released the results of a 2-year inhalation study which found a significant increase in malignant liver tumors in male and female B6C3F1 mice. The study exposed the mice and Fischer 344 rats to perchloroethylene concentrations of 0, 100, and 200 ppm and 0, 200, and 400 ppm, respectively, for 6 hours per day, 5 days a week for the length of the study. NTP also reported an increased incidence in mononuclear cell leukemia in male and female rats and the occurrence of kidney tumors in male rats. NTP concluded that these data demonstrated "clear evidence" of carcinogenicity in mice and male rats and "some evidence" of carcinogenicity in female rats.

#### Science Advisory Board Review of the NTP Study

In May 1986, the EPA's Science Advisory Board reviewed the results of the NTP study and concluded that the study does not provide a basis for associating either the leukemias or the kidney tumors observed in the rats with exposure to perchloroethylene. The Board's conclusion was based on the high spontaneous background rate of leukemia in concurrent and historical controls in this particular rat strain and the low incidence of rat kidney tumors in the NTP study. In their analysis, the Board noted that "no human analogue is known for mononuclear cell leukemia of the rat" and that "the scientific community has a poor understanding of the pathology of monunuclear cell leukemia."

Consequently, the Board regarded the animal evidence for carcinogenicity to be "limited." This later conclusion is based on the existence of "positive results in only one strain of mouse of a type of tumor that is common and difficult to interpret."

#### Significance of the Mouse Liver Data

Following the observation that perchloroethylene produces liver tumors in mice, but not in rats, industry initiated studies to investigate the reasons for this species difference and to determine the significance of the mouse data to humans. This pharmacokinetic research indicates that perchloroethylene is not the proximal carcinogen in the mouse bioassays, but that a metabolite of perchloroethylene, trichloroacetic acid (TCA), is the likely cause of the mouse liver tumor response. Tumor induction in rodent liver cells has been associated with TCA and the TCA-induced production of enzyme-containing organelles (called peroxisomes) in the cells. Production of TCA occurs at a much higher rate in mice than in rats, a genetically similar organism, and at an even lower rate in humans than in mice or rats. Moreover, in vitro exposure of human liver cells to TCA did not result in peroxisome production.

This research not only explains why liver tumors are seen in mice, but not rats, but leads to the important conclusion that perchloroethylene is unlikely to produce tumors in the human liver.

#### Epidemiology Studies

A number of epidemiology studies have investigated the incidence of cancer mortality among dry cleaner workers. Only two of these, however, have attempted to identify persons exposed to only perchloroethylene. The first, conducted for the National Institute for Occupational Safety and Health (NIOSH) and completed in 1980, examined the health records of 1600 dry cleaner workers employed for at least one year prior to 1960 in metropolitan shops where perchloroethylene was the primary solvent. The study found no deaths caused by liver cancer, but did find a significant increase in mortality due to colon cancer. These results were confounded, however, by possible exposure to other substances and the lack of complete health records for a significant number of workers. Based on this study, EPA concluded that the overall epidemiological data for perchloroethylene was "inadequate" for purposes of interpreting possible human carcinogenicity.

In 1985, NIOSH subsequently completed a follow-up to the 1980 study which involved a more detailed examination of an increased number of dry cleaner workers (1690 workers). The new study found the overall cancer mortality rate to be higher than, but not significantly different from, that predicted using U.S. mortality rates. The relative number of cancer deaths among the workers studied was reduced when compared to the higher cancer mortality rates in the metropolitan areas investigated. Among the site-specific cancer mortalities, urinary tract cancer (particularly in the bladder) was the only one found to have a significant increase. To eliminate the possible effects of exposure to other dry cleaning solvents, the researchers identified a subcohort of 615 workers with no known exposure to these other solvents. Within this subcohort of workers exposed to only perchloroethylene, the incidence of mortality from urinary tract cancer (and from cancer, in general) was lower than that expected from overall U.S. mortality rates.

### ■ REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Several studies of the effects of perchloroethylene on mammalian reproduction have been performed on mice, rats, and rabbits. The results of these animal tests do not indicate any significant reproductive effects.

In studies of female Sprague-Dawley rats and Swiss-Webster mice exposed by inhalation to a perchloroethylene concentration of 300 ppm during gestation, no reproductive effects were observed. A similar result was observed in CD rats and New Zealand rabbits after females were exposed to 500 ppm of the chemical before and during gestation. An inhalation study of Long-Evans hooded female rats exposed to 1000 ppm of perchloroethylene prior to and during gestation found a significant reduction in body weight and excess variation in skeletal and soft tissue development. However, weight gain and survival of offspring followed up to 18 months of age were not influenced by exposure to perchloroethylene. Some changes in maternal body weight and liver and kidney weight were noted in these studies.

On the basis of this laboratory data, EPA concluded that "there is no evidence that suggest that the [fetus] is uniquely susceptible to the effects of [perchloroethylene]."

## Environmental Fate

Perchloroethylene has been detected in the ambient air of urban and rural areas of the United States at levels of 10 parts per billion (ppb) or less. It has been detected less frequently in surface and ground waters at levels between 1 and 2 ppb. Because of a short evaporation half life, any amount of the chemical present in surface water is rapidly transported into the atmosphere. There is no evidence for significant bioaccumulation of the chemical, and it appears to have low toxicity to aquatic organisms.

Perchloroethylene is widely regulated as a volatile organic compound (VOC) under state regulations implementing the national ambient air quality standard for ozone. Although EPA proposed that perchloroethylene be exempted from regulation as a VOC in 1983, final action has not yet been taken.

Perchloroethylene's short atmospheric residence time ($<$ 1 year) means it is unlikely to reach the upper atmosphere, or stratosphere, where it could react with the protective ozone layer. Perchloroethylene also is not likely to contribute to the "greenhouse effect," whereby certain atmospheric gases are believed to absorb heat radiating outward from the earth and cause global warming.