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Dear Paul:

Enclosed is a copy of PPG's Toxicity Summary Report on Trichloroethylene for distribution to the HSIA Health Hazards Communications Committee members.

Respectfully submitted,

Beth Concoby

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/jh

Attachment

SL 038076

T R I C H L O R O E T H Y L E N E

CAS NO. 79-01-6

SL 038077

INTRODUCTION

Under the Hazard Communication Rule of the U.S. Occupational Safety and Health Administration, employers are responsible for obtaining or developing a Material Safety Data Sheet (MSDS) for each hazardous chemical used in the workplace. In assessing the hazards of workplace chemicals, physical, fire and explosion, reactivity, and health hazards must be evaluated. This document reviews and evaluates the data on trichloroethylene known to HSIA on three types of potential health hazards: carcinogenicity, mutagenicity, and reproductive toxicity.

SUMMARY

The potential adverse health effects of trichloroethylene have been extensively studied and evaluated. An extensive compilation of literature has been published. Trichloroethylene has been used in industry without any serious health effects when used according to recommended practices. The primary effects reported by individuals occupationally overexposed to trichloroethylene are related to its anesthetic properties.

Carcinogenicity

The carcinogenicity of trichloroethylene has been evaluated in a number of laboratory studies in various experimental animals and in epidemiology studies. There is no evidence to suggest that trichloroethylene exposure is associated with an increased incidence of cancer in humans. The only positive carcinogenic response has been in mice dosed with high levels of trichloroethylene. However, mechanistic studies indicate that these tumors are not predictive of the chemical's carcinogenic potential in humans.

Mutagenicity

The mutagenic potential of trichloroethylene has been evaluated in a number of animals and microbial short-term tests. The preponderance of the test results indicates that trichloroethylene *per se* does not present a mutagenic hazard in humans. A few tests have shown marginal positive results at high concentrations of commercial trichloroethylene.

Reproductive Toxicity

The teratogenic potential of trichloroethylene has been evaluated in a number of well-designed inhalation exposure studies. The results of these studies indicate that trichloroethylene does not present a reproductive hazard to humans at concentrations below the permissible exposure limit.

DISCUSSION

I. CARCINOGENICITY DATA

The carcinogenic potential of trichloroethylene has been investigated in a number of chronic animal tests and in human epidemiology studies.

Animal Studies

The carcinogenicity of trichloroethylene has been evaluated in long-term studies with rats, mice, and hamsters. The test compound was administered by inhalation, gavage, topical application, or by subcutaneous injection.

Wistar rats, NMRI mice, and Syrian hamsters were exposed by inhalation to 0, 100, or 500 ppm trichloroethylene 6 hours/day, 5 days/week, for 18 months followed by lifetime observation. No signs of toxicity were reported in rats and hamsters, but mortality was significantly greater for mice in both treatment groups compared to controls. No significant increase in tumor incidence was reported for rats, hamsters, and male mice. A significant increase in the incidence of lymphomas was reported in female mice at both doses (Henschler, et.al., 1980).

The National Cancer Institute (NCI) conducted a carcinogenicity bioassay in the rat and mouse. Osborne-Mendel rats were given by gavage 549 or 1,097 mg/kg trichloroethylene daily, 5 days/week, for 78 weeks. The survival of the treated rats was low in both doses and chronic kidney lesions were common in the treated animals. A carcinogenic effect of trichloroethylene was not found in these species.

B6C3F1 mice were given trichloroethylene by gavage, 5 days/week, for 78 weeks at levels of 1,169 or 2,339 mg/kg treatment in males, and 869 or 1,739 mg/kg treatment in females. Survival was decreased in both sexes and dose groups. Statistically significant increases in liver tumor incidence were observed in treated male and female mice. Spontaneous liver tumor formation is a characteristic of the B6C3F1 mouse strain (NCI, 1976).

A draft report has been prepared for a carcinogenicity bioassay in Fischer 344 rats and B6C3F1 mice completed for the National Toxicology Program (NTP). Mice were given orally 1,000 mg/kg of trichloroethylene 5 days/week, for 103 weeks. There was a statistically significant decrease in the survival of the male mice. The incidence of liver tumors in male and female mice was statistically significant. Rats were given by gavage 500 or 1,000 mg/kg of trichloroethylene 5 days/week, for 103 weeks. A statistically significant decrease in the survival of male rats was observed along with an increased incidence of non-tumor kidney lesions in both sexes, which indicates that the maximum tolerated dose was exceeded in this study. There was a small but statistically significant increase in the incidence of renal tubular-cell tumors in high-dose males rats. The NTP has concluded that the study was "inadequate to evaluate the presence or absence of a carcinogenic response to trichloroethylene in male F344/N rats" (NTP, 1982).

In an unpublished study by Maltoni (1979), Sprague-Dawley rats received trichloroethylene by gavage at dose levels of 50 or 250 mg/kg, 4 or 5 days/week for 52 weeks. There was no evidence of a carcinogenic response in either sex.

Van Duuren (1979), investigated the carcinogenicity of trichloroethylene in a series of studies with ICR/HA Swiss mice. The studies employed a variety of administration routes which included topical, subcutaneous, and gavage. An initiation-promotion study was also conducted with a single topical application of 1 mg trichloroethylene followed by repeated applications with the promoter phorbol myristate acetate. A carcinogenic response was reported in these studies.

A recent inhalation exposure study reported lung tumors in mice following inhalation exposure to 150 and 450 ppm trichloroethylene. A known respiratory tract carcinogen (epichlorohydrin) was present in the test material. Therefore, the interpretation of the involvement of trichloroethylene in the formation of these tumors is unclear. A carcinogen effect was not observed in rats similarly exposed to trichloroethylene in this study (Fukuda, et.al., 1983).

Human Epidemiology

A number of epidemiology studies have been conducted to evaluate the relationship of human exposure to trichloroethylene and the incidence of cancer. However, the trichloroethylene exposures were not identified in several of the studies.

The first study evaluated the cancer mortality of 518 Swedish male workers exposed to trichloroethylene. Workplace trichloroethylene exposure levels were not available. Urine trichloroacetic acid (a metabolite of TCE) levels were determined on each worker twice a year. The workers were divided into exposure groups based on their urine trichloroacetic acid levels. There were no significant differences between the observed and the expected number of cancer deaths in the total cohort (Axelson, et.al., 1978).

A similar mortality study is ongoing in Finland. There are plans to follow and analyze the cohort every five years. The cohort is comprised of 1,148 men and 969 women who had occupational exposure to trichloroethylene at some time between 1963 and 1976. Tola reported on the cohort in 1980. The observed number of all deaths and of cancer deaths were compared with those expected based on national mortality statistics for 1971. There was no indication of any increased risk of death from cancer or other causes in the exposed group (Tola, et.al., 1980).

Several studies examined the mortality of laundry and dry-cleaning workers. The dry-cleaning agents and exposure levels were not identified. There was an excess of cancer reported in two of the studies. Due to the possible confounding influence of other dry-cleaning agents and lack of demographic information, no conclusions could be drawn from these studies regarding carcinogenicity (Fielder, et.al., 1982; Katz and Jowett, 1981).

The animal data indicate that a carcinogenic response is only obtained in a species prone towards liver tumors and under excessive dosing regimens leading to increased mortalities or organ injuries. Other studies on TCE metabolism in different species indicated that mice, rats, and humans respond differently to trichloroethylene. Therefore, while there have been carcinogenic responses reported in mice exposed to trichloroethylene, there is strong evidence to indicate that this is not predictive of human response. The epidemiology studies support this conclusion.

II. MUTAGENICITY

Trichloroethylene has been evaluated in a number of short-term tests to determine its mutagenic potential. Tests have been performed on bacteria, yeast, and insects to evaluate trichloroethylene's ability to cause gene mutations. Trichloroethylene has also been evaluated for its effects on genetic material in insects, rodents, and occupationally exposed workers.

Several studies investigated the mutagenic potential of pure and commercial trichloroethylene in bacteria. Overall, pure trichloroethylene was not mutagenic and commercial trichloroethylene demonstrated only a very weak mutagenic response with metabolic activation. The response elicited by trichloroethylene was not typical of known mutagenic agents in that mutagenic activity was observed only at highly cytotoxic levels (Fielder, et.al., 1982; Henschler, et.al., 1977; Baden, et.al., 1979; Miyata, et.al., 1981).

The mutagenicity of trichloroethylene was also evaluated in several strains of yeast. Negative responses were obtained with tests on Schizosaccharomyces pombe. Commercial trichloroethylene was found to be weakly active in Saccharomyces cerevisiae when tested in the presence of a metabolizing system (Callen, et.al., 1980; Loprieno, 1979; Williams, et.al., 1982; Mondino, 1979).

Trichloroethylene was tested for its ability to induce sex-linked recessive lethal mutations in Drosophilia. The frequency of mutations was not significantly different than the control (Beliles, 1980).

The effects of trichloroethylene on animal chromosomes was examined in several studies. Beliles (1980), exposed rats by inhalation to 100 and 500 ppm of trichloroethylene and then examined the bone marrow cells for chromosomal aberrations or aneuploidy. There was no statistically significant increase in any parameter.

Slacik-Erben, et.al., (1980) performed a dominant lethal assay in mice. Male mice were exposed to 50, 200, or 450 ppm of trichloroethylene for 24 hours. There were no significant changes in the fertilization rate, or in the pre- or post-implantation losses. Another study exposed Chinese hamster ovary cells in vitro to 1700 ppm trichloroethylene. There was no increase in the number of sister chromatic exchanges in the exposed cells (White, 1979). Beliles (1980), also investigated the ability of trichloroethylene to cause X or Y chromosome loss in Drosophila. Exposure to 100 or 500 ppm trichloroethylene did not significantly increase the frequencies of X or Y chromosome loss.

The peripheral lymphocytes of 28 chemical workers potentially exposed to trichloroethylene were examined for chromosomal aberrations. As a result of poor study methodology, the results are inconclusive (Konietzko, et.al., 1978).

In summary, a substantial number of tests have been conducted on trichloroethylene to evaluate its genotoxic potential. Marginal positive responses have been reported, but in general were associated with high concentrations of commercial solvent which contained mutagenic stabilizers. The majority of the tests performed were negative for a genotoxic effect.

III. REPRODUCTIVE TOXICITY

Trichloroethylene has been evaluated in several studies for its ability to adversely affect the offspring of exposed laboratory animals. The teratology potential of trichloroethylene has been investigated in animal studies using dosings, which in some studies, produced slight signs of maternal toxicity. Inhalation studies in which mice and rats were exposed to 300 ppm trichloroethylene during gestation did not demonstrate any significant maternal toxicity, embryo toxicity, fetal toxicity, or teratogenicity (Schwetz, et.al., 1975; Bell, 1977). Pre-gestational exposures in combination with gestational exposures of trichloroethylene were evaluated in two inhalation studies in rats. Exposures of 500 ppm and 1,800 ppm provided no indication of maternal toxicity, embryotoxicity, teratogenicity, or postnatal behavioral effects (Beliles, et.al., 1980; Dorfmueller, et.al., 1979). There was no indication of embryo or maternal toxicity in rabbits exposed to 500 ppm trichloroethylene. There was an increased incidence of hydrocephalus in one group that was not exposed pre-gestationally. However, the increase was not statistically significant.

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