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TRICHLOROETHYLENE: AN UPDATE

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The toxicity of tricholoroethylene (TCE) has been summarized in a number of reviews. In this particular update, only the more recent studies that deal with metabolism and carcinogenicity have been examined. In reviewing the more recent publications on metabolism of TCE, we determined that differences exist in its metabolism if low doses are compared with high doses in animals. There may also be a difference in the metabolism of TCE between different species—namely mice, rats, and humans. TCE has not been shown to be a potent carcinogen in rats and it only seems to be a potent carcinogen in one specific strain of mice, namely the B6C3F1 mouse. Epidemiology studies have been rather limited. The number of persons examined so far for chronic toxic effects is small, compared with the enormous size of the work force that is exposed to TCE over prolonged periods. On an empirical basis, the occupational experience with TCE does not suggest that this compound is a potent carcinogen. The risk associated with exposure to trace amount (ppb) concentrations of TCE in water appear to be minimal or perhaps negligible.

Because there are differences in metabolism of TCE, it is important that theoretical risks attributed to TCE in the past be reexamined. It is highly possible that in humans, the metabolic pathway leading to the formation of the proximate carcinogen is not activated at low doses, where TCE is excreted by first-order kinetics.

INTRODUCTION

Tricholoroethylene (TCE) is a solvent used extensively for vapor degreasing of fabricated metal parts. To a minor degree, it is used as a solvent in the textile industry, as a solvent for adhesives, as a lubricant, and as a low-temperature heat transfer fluid. It is a component in several consumer products such as spot removers and cleaning fluids for rugs. A pharmaceutical grade of TCE is used as a general anesthetic in surgical, dental, and obstetrical procedures, and as an analgesic in the treatment of trigeminal neurolgia. It has also been used as a disinfectant and detergent for skin, minor wounds, and surgical instruments. It has also been used on a variety of animals as a volatile anesthetic (IARC, 1979).

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Because of the extensive use of TCE and because it is slightly soluble in water (0.1 g/100 ml water at 20°C), surface water as well as ground water in many areas of the United States and other industrialized countries (IARC, 1979) may contain low concentrations of TCE. TCE has not been routinely measured in all water systems. TCE appears to be widely distributed in water at or below 1 μg/l. TCE concentrations of up to 47 μg/l have been found in finished surface drinking water. Groundwater concentrations as high as 22,000 μg/l have occasionally been recorded in localized areas. In other areas, peak ground water concentrations were 30 μg/l (Environmental Protection Agency, 1980). Levels in soil and sediment have ranged from 0 to more than 100 mg/kg soil. TCE in low concentrations may also be present in food, drink, and in marine organisms, as well as human tissues. An estimated 60,000 people are exposed annually to TCE as an anesthetic (IARC, 1979). Since TCE has been shown to produce tumors in rodents and because it also has some mutagenic activity, concern has been raised about the exposure of humans to trace amounts of TCE in drinking water on an on-going basis. In this update we review the more recent information on the carcinogenic effects of this compound, its metabolism in different species, and the human health effects. An attempt is made to determine what the risk and level of concern should be in relation to trace amounts of TCE in drinking water. This paper does not represent an exhaustive review of the available literature on TCE; only the more pertinent recent studies are summarized since there have already been a number of reviews on the subject in the literature (Environmental Protection Agency, 1984; Lyman, 1978; Mercier, 1977; National Institute for Occupational Safety and Health, 1973, 1978; Waters et al., 1977).

METABOLISM

Recently, a number of papers have been published reporting on the metabolism of trichloroethylene (TCE). Parchman and Magee (1982) gave a single interperitoneal dose of [1,2-^{14}C]—labeled trichloroethylene (TCE) to male Sprague-Dawley rats and B6C3F1 male mice. In these studies, it was determined that the interperitoneal LD50 was approximately 2.5g/kg. Mice excreted 5-15% of a dose of labeled trichloroethylene as [^{14}C]carbon dioxide within 24 h in exhaled air. The proportion of the dose excreted in CO_2 was greater in mice than in rats, but increased in the rats after starvation or pretreatment with phenobarbital. Labeling of liver protein was relatively high (10,000-23,000 cpm/mg) in the mouse, while DNA labeling was very low. No other adducts could be identified by high-pressure liquid chromatography in DNA. These authors concluded that the ability of TCE to interact with DNA in vivo was very slight.

Stott et al. (1982) compared the metabolism of TCE in male B6C3F1 mice and male Osborne-Mendel rats. When mice were exposed to

either 10 or 600 ppm of ^{14}C-labeled TCE by inhalation, almost all of the TCE was metabolized within 50 h. The primary rate of excretion in mice was urine. Approximately 9% of the ^{14}C-labeled TCE was biotransformed to ^{14}C-carbon dioxide. Very little intact TCE was excreted in the urine of mice at these dosage levels. On the other hand, in the rats, at the 600 ppm dose, TCE metabolism appeared saturated. The total metabolism of ^{14}C-labeled TCE was decreased in the rat at that dose to about 79%, whereas about 98% of the 10 ppm dose was metabolized. At the same time, exhalation of ^{14}C-labeled TCE increased 10-fold with increased ^{14}C-labeled TCE exposure. In the rat, ^{14}C-labeled TCE metabolites were excreted primarily via the kidneys, which accounted for about 62 and 55% of the body burden in low- and high-dose rats, respectively. Mice metabolized more ^{14}C-labeled TCE to a reactive intermediate capable of binding to macromolecules than did rats in both hepatic and renal tissues following the 600 ppm exposure, but the recovery for radioactivity in liver and kidney of rats and mice increased only modestly after the 10 ppm exposure. On a percentage basis it was similar for both species at the lower dose. In mice given an oral dose of 1200 mg/kg, the maximum estimate of the average DNA alkylation level of 0.62 ± 0.42 alkylation/10^6 nucleotides was observed in 3 of 4 treated mice. Mice appear to metabolize more inhaled TCE than rats at both low and high dosage levels. This may, in part, explain the differences in susceptibility to TCE toxicity and carcinogenicity between rats and mice.

Mueller et al. (1982) studied the metabolism of TCE in three species of subhuman primates (chimpanzees, baboons, and rhesus monkeys). TCE was given as a single intramuscular injection of 50 mg TCE/kg body weight. Forty to 60% of the administered dose was excreted in urine and feces of the chimpanzees, 11-28% in baboons, and 7-40% in the rhesus monkey. The chimpanzees excreted only 2-5% of the total dose in the feces whereas the baboons excreted 25-34% and the rhesus monkey excreted 18-23%. Apparently, a considerable portion of TCE is exhaled in subhuman primates. Trichloroacetic acid and trichloroethanol were identified in urine. In addition, trichloroethanol glucuronide and trichloroacetic acid glucuronide were present in urine.

Miller and Guengerich (1983) studied the metabolism of TCE in in vitro systems that consisted of purified rat cytochrome P-450, rat, human, and mouse liver microsomes, rat lung microsomes, and isolated rat and mouse hepatocytes. The authors postulate several pathways for the metabolism of TCE. One involves the "suicidal" P-450 heme destruction in vitro to the extent of 40% of the heme in a microsomal system. Second, chloral may be formed and then either reduced to trichloroethanol and conjugated or oxidized to trichloroacetic acid. Third, trichloroethanol oxide may be formed, decomposing to carbon monoxide and glyoxylate. Fourth, metabolites may be formed that bind irreversibly with protein, DNA and RNA. The contributions of these four major pathways depend on the isozymes of cytochrome P-450 that are

involved. The levels of protein adducts and particularly DNA adducts were substantially higher in isolated C57BL/6 × C3HF1 mouse hepatocytes than in isolated Osborne-Mendel rat hepatocytes. These results also support the idea that differences in metabolism may explain the previously reported differences in carcinogenic effect in mice and rats.

By using a modified neglect of diatomic overlap, Loew et al. (1983) calculated the properties of six chloroethylenes that could serve as indicators of the relative metabolic behavior and carcinogenic activity. It has been proposed that chloroaldehydes and acylchlorides are plausible active forms of ultimate carcinogens of the chloroethylenes. However, it is also possible that an epoxide can form the observed DNA adducts. None of these ultimate carcinogens have been isolated and identified. Results of the evaluation by Loew et al. (1983) indicate no correlation between calculated indicators of electrophilicity of the putative ultimate carcinogens and the tentative rank order of carcinogenic activity. This lack of correlation holds for all possible chloraldhydes or acylchlorides of the parent compound. This suggests that the carcinogenic activity is not genetic in origin and may rather be epigenetic as suggested by Stott et al. (1982). This epigenetic mechanism of carcinogenicity may be related to the cytotoxicity of TCE in the liver.

Bergman (1983) examined the covalent binding of ^{14}C-labeled TCE in various tissues of the mouse and found that the entire radioactivity in RNA from liver and kidney and in DNA from kidney, testes, lung, pancreas, and spleen was due to metabolic incorporation, particularly into guanine and adenine. In the liver DNA, the radioactivity was eluted in early fractions and the elution profile of radioactivity gave no direct evidence of the formation of TCE-DNA adducts in vivo. This investigator found that microsomal mediated metabolic activation is necessary for the binding to DNA. This is further emphasized by the fact that covalent binding in the in vitro studies was enhanced in the presence of microsomes from mice, particularly when these mice had been pretreated with phenobarbital. Similar findings were also reported by Miller and Guengerich (1983). Some strains of mice, such as the MMIR mice, are resistant to the carcinogenicity of TCE (Henschler et al., 1980). Similarly, male Osborne-Mendel rats are resistant to TCE induced hepatocellular carcinoma. On the other hand, C57 BL/6 × C3H/He F1 (also called B6C3F1) hybrid mice are susceptible to TCE-induced hepatocellular carcinoma. Species and strains that are resistant to the induction of liver tumors by TCE also seem to bind less TCE in the liver. Thus the binding of TCE to microsomal proteins of B6C3F1 mice was 46% higher than that of ^{14}CTCE to microsomal proteins from male Osborne-Mendel rats (Banerjee and Van Duuren, 1978). The binding reported from in vitro systems seems to be higher than if this is examined in the in vivo systems (Parchman and Magee, 1982; Magee et al., 1982).

Costa et al. (1980) determined that TCE was activated by the phenobarbital-induced form of cytochrome P-450 of hepatic micro-

somes from male Long-Evans rats to a reactive species that can chemically alter the heme protein of cytochrome P-450. In addition to in vivo and in vitro studies dealing primarily with reactive metabolites and binding to cellular constituents, a number of less reactive water-soluble metabolites have also been identified.

Ikeda et al. (1980) found that trichloroethylene was metabolized to chloral hydrate, trichloroethanol, and trichloroacetic acid in vitro when livers of male Wistar strain rats were used as the enzyme source. According to Filser and Bolt (1979), low doses of TCE are excreted by first-order kinetics in male Wistar rats; however, once metabolism is saturated with TCE, excretion occurs by zero-order kinetics. In addition to trichloroacetic acid, Hathaway (1980) identified in mice an additional metabolite, the dichloroacetic acid. This suggests that in mice the mutagenic and tumorogenic effects of TCE may be attributable to a rearrangement of the 2-haloalkene-derived haloepoxides into chloroacetyl chloride and dichloroacetyl chloride. On the other hand, in rats and humans, TCE is rearranged into chloral and further products of its metabolism that make the TCE relatively nontoxic.

Humans also metabolize TCE to trichloroethanol and trichloroacetic acid (Ertle et al., 1972; Ikeda and Imamura, 1973; Kimmerle and Eben, 1973; Monster et al., 1976; Mueller et al., 1974). However, Nomiyama and Nomiyama (1979) conducted a more detailed study of the metabolism of TCE in humans and other species. Rats metabolized TCE most rapidly, while the metabolic rate was slowest in humans. The ratio of trichloroethanol to trichloroacetic acid was largest in rabbits and smallest in humans. In humans, trichloroacetic acid was a major metabolite, while it was a minor metabolite in rabbits. This difference in metabolism needs to be considered in risk assessments.

MUTAGENESIS

A number of studies have established that TCE is not a very potent mutagen (Simmon and Baden, 1980). Comparatively speaking, in vitro mutagenicity studies with TCE have been quite numerous. In some systems they have been negative and in others weakly positive. Usually the better purified technical TCE showed less of an effect or was completely negative. The TCE used in some in vitro tests where a positive response was observed contained highly mutagenic impurities. A detailed review of the results of mutagenicity testing can be found (National Research Council, 1980, 1983).

Increased chromosomal aberrations were reported in exposed workers by Konietzko et al. (1978), and sister-chromatid exchange was increased as well (Gu et al., 1981a,b). Chromosome studies of lymphocyte cultures were performed on 28 TCE workers who were employed as degreasers and had an age range of 23-67 yr with an average age of 42.5 yr (Konietzko et al., 1978). These workers were exposed to technical-

grade TCE which most likely contained antioxidants as stabilizers. However, the type and amount was not determined. The lengths of exposure ranged from 1 to 21 yr. As controls, blood specimens were used from healthy young men who happened to be in the institute at the time these studies were conducted. Therefore, the controls were not well matched. The authors point out that the workers who had a higher incidence of chromosome abberrations than the controls had been exposed to technical TCE that could have been contaminated with epichlorhydrin and 1,2-epoxybutane. Both of these compounds are mutagenic and carcinogenic, and it is therefore not clear whether the chromosome abberrations observed in the exposed workers were actually caused by TCE; nor were other environmental factors ruled out.

TCE also induces transformation of rat embryo cells (Price et al., 1978), of Syrian hamster embryo cells (Amacher and Zelljadt, 1983), and of unscheduled DNA synthesis in human lymphocytes (Perocco and Prodi, 1981). It is not entirely clear, however, whether carcinogenicity is actually caused by the same characteristics that result in mutagenic effects (Stott et al., 1982).

CARCINOGENESIS

A number of studies have been conducted in rodents to evaluate the carcinogenicity of TCE. The National Cancer Institute (1976) conducted gavage studies in Osborne-Mendel rats and B6C3F1 mice. The animals were given industrial-grade TCE, which was later shown to be contaminated with other chemicals (Henschler et al., 1977). The proportion of all identified contaminants amounted to 0.65%. Two contaminants, the epichlorohydrin and the 1,2-expoxibutane, are strong monofunctional alkylating agents. In addition, carbon tetrachloride, chloroform, 1,1,1-trichloroethane, diisobutylene, ethyl acetate pentanol-2, and butanol-2 were also identified. The 50 male and 50 female rats and mice per dosage group and 20 matched controls were dosed 5 d/wk by stomach tube. The results in the experimental animals were also compared with historical controls. The animals were dosed for 78 wk. Rats were killed 110 wk after the study began and the mice 90 wk after the study began. The study was started when the animals were approximately 6 wk of age. The rats received initial doses of 1300 and 650 mg/kg body weight, respectively. Dosages were decreased because of high mortality. This resulted in a final time-weighted average dose of 549 mg/kg/d for the low-dose and 1097 mg/kg/d for the high-dose rats. In mice, the initial doses were 1000 and 2000 mg/kg for males and 700 and 1400 mg/kg for females. The doses in the mice were increased so that time-weighted average doses were 1169 and 2339 mg/kg for male mice and 869 and 1739 mg/kg for female mice. The doses in the mice were increased because there was little toxicity in contrast to the high toxicity in rats. No dose-related tumors were observed in the rats. In the mice and rats, however, at the

high and low dose, a chronic nephropathy was observed upon histopathological examination. In the mice, primary hepatocellular carcinomas were observed. In the males, 26 of the 50 mice had such tumors at the low dose, and 31 of 48 had them at the high dose. Only 1 of 20 in the matched controls had a hepatocellular carcinoma, and 5 of 77 historical controls had a hepatocellular carcinoma. The differences between the treated and the matched control males at both dosage levels were highly significant ($p < 0.01$); however, the difference at the low dose was less ($p = 0.09$). Most of the hepatocellular carcinomas metastasized to the lungs. At the high doses, hepatocellular carcinomas were seen relatively early. The first was seen 27 wk after the male mice were initially exposed.

Among the positive controls, in the National Cancer Institute (1976) study, hepatocellular carcinomas developed in virtually all male and female mice exposed to carbon tetrachloride. The response in the Osborne-Mendel rat was considerably less. Hepatocellular carcinomas developed in only about 5% of the animals. Thus, there appears to be a marked difference in sensitivity to induction of carcinomas by chlorinated aliphatic compounds between the B6C3F1 mouse and the Osborne-Mendel rat. However, in the rats, early mortality must be considered in evaluating the negative results in this species.

One problem with the National Cancer Institute (1976) study is that TCE-treated animals were housed in rooms where rats or mice treated with other chemicals were also housed. For the rats, these chemicals could be one of the following: dibromochloropropane, ethylene dichloride, 1,1-dichloroethane, and carbon disulfide. The mice treated with TCE were maintained in a room housing other mice being treated with one of the following compounds: 1,1,2,2-tetrachloroethane, chloroform, 3-chloropropane, chloropicrin, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, ethylene dichloride, 1,1-dichloroethane, 3-sulfolane, iodoform, methylchloroform, 1,1,2-trichloroethane, tetrachloroethylene, hexachloroethane, carbon disulfide, trichlorofluoromethane, and carbon tetrachloride (National Cancer Institute, 1976). Because of the large number of other groups of animals that were also subjects in experiments, these animals were either very close together or the rooms must have been extremely large. The bedding of the mice was changed twice weekly. It is not clear how much of the material might have evaporated from the bedding. No air-level measurements were conducted in these animal rooms. However, the room air was exchanged 10-15 times/h. At the high dose, for instance, each mouse received a total amount of 182.44 g/kg body weight of TCE over a 78-wk period; the total amount for the low-dose male mice was 91.2 g/kg body weight. The amount for the high-dose females was 135.6 g TCE/kg, and for the low-dose females it was 67.78 g/kg.

These high doses raise questions about the validity of these studies for humans who may be exposed to low environmental levels. The dis-

tribution, metabolism, and elimination of TCE at these high concentrations may be quite different. Furthermore, such high doses result in focal hepatocellular necrosis with possible subsequent cell proliferation. Such toxic effects on the liver would promote liver tumor formation (Farber, 1981). Similar hepatotoxic effects would not occur at lower dose levels.

Because of the concern about the results of the 1976 study of TCE in rats and mice due to the presence of contaminants, most notably epichlorohydrin, in the test material, a new study was undertaken to evaluate TCE that was as free of contamination as possible (National Toxicology Program, 1983). For this study, high-purity TCE was obtained and analyzed. Sampling of the TCE revealed impurities ranging from 0.01 to 0.04% in the two lots obtained. The material was checked for continued purity throughout the course of the study, and although there was 8 ppm of an amine stabilizer (diisopropylamine), there was no evidence of epichlorohydrin.

The contaminant-free TCE was administered in corn oil by gavage to groups of F344/N rats and B6C3F1 mice over 2 periods, 13 wk and 2 yr. From the results of the 13-wk phase, which all animals survived, the doses chosen for the 2-yr study were 500 and 1000 mg/kg for rats of both sexes. For mice of both sexes, the single dose-level chosen was 1000 mg/kg. The results of the 2-yr study showed that survival of rats at both dosages and of male mice was significantly less ($p = 0.005$) than that of the vehicle controls. The body weights of rats of both sexes were lower, as were those of the male mice. The weights of the female mice were comparable to those of controls.

Renal changes (toxic nephrosis) were present in nearly all (96/98 male, 97/97 female) rats. The same changes were seen in 45/50 male mice and 48/49 female mice.

Renal adenocarcinomas were found in three high-dose male rats killed at the end of the study. This finding was statistically significant ($p = 0.05$) compared to controls. Four other renal tumors were found in male rats (one transitional-cell tumor of the renal pelvis and two tubular-cell adenomas in animals receiving the low dose, and one carcinoma of the renal pelvis in a rat receiving the higher dose).

Although some other tumors were found (six peritoneal mesotheliomias that the investigators considered may have been related to the administration of TCE), the results in the F344/N rats were considered to be equivocal insofar as determining the carcinogenicity of TCE. This conclusion was based on the reduced survival of both groups receiving TCE compared with the vehicle controls, and because of a gavage error during the experiment that caused the death of 20% of the animals.

In the 2-yr study in mice, increased numbers of hepatocellular carcinomas were found in both males (30/50) and females (13/49) as compared with controls (8/48 and 2/48 respectively). The incidence of

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hepatocellular adenomas were also increased in both sexes, 8/50 and 8/49 as compared to 3/48 and 2/48. Thus, the results of this study essentially paralleled those of the 1976 study. However, these studies are still in draft form and have not undergone final peer review at the time of this writing (National Toxicology Program, 1983).

In an inhalation study with TCE that contained trace amount of contaminants of carbon tetrachloride, benzene, epichlorohydrin, and 1,1,2-trichlorqethane, Crj: CD-1 (ICR) mice at 150 and 450 ppm exposure for 107 wk developed an incidence of 16 and 15% adenocarcinomas of the lungs, while the incidence in the controls was 2%. The incidence of total lung tumors—that is, adenomas and adenocarcinomas—was not significantly increased if controls were compared to exposed mice. In addition, the incidence at the higher dose was about the same as that at the lower dose. It is not stated in the paper whether the microscopic slides were examined in a blind fashion or whether the treatment was known to the pathologist. Studies in rats did not show a higher incidence of carcinomas of any site (Fukuda et al. 1983).

Henschler et al. (1980) conducted an inhalation study with TCE in three animal species. These authors used pure TCE, which was stabilized by an amine base. Mice, rate, and Syrian hamsters of both sexes were used. The animals inhaled 100 and 500 ppm of TCE for 6 h/d, 5 d/wk, for 18 mo. No significant increase in tumor formation was observed in any species or dosing group. The exposed female mice, however, had an increased incidence of malignant lymphomas. The incidence rates for the female mice were as follows: 9/29 in the controls; 17/30 in the females receiving 100 ppm TCE; 18/28 in the females receiving 500 ppm TCE. The MRI mouse strain used normally has a relatively high spontaneous incidence of lymphomas. It was not clear to the authors whether the increased incidence of lymphomas had any relationship to TCE exposure. The occurrence of lymphomas is apparently associated with a virus infection that occurs in these mice. In connection with this, Sanders et al. (1982) studied the effects of TCE on the immune system on male and female CD-1 mice by exposing the mice to TCE in drinking water for either 4 or 6 mo. The doses given were 0.1, 1.0, 2.5, and 5 mg/m water. In the female mice, humoral immunity was inhibited only at the highest concentration of TCE (2.5 and 5 mg/1). Cell-mediated immunity and bone-marrow stem-cell colonization were inhibited at all four concentrations of TCE. The males were relatively unaffected after 4 and 6 mo of exposure.

Van Duuren et al. (1983) tested the carcinogenic effect of a number of structurally related chloroalkenes on the skin and in the subcutis. The materials were repeatedly applied to the skin three times weekly or injected subcutaneously once a week into female ICR/Ha Swiss mice. The length of treatment was not given in the paper; however, the median survival of the mice ranged from 418 to 576 d. A number of the

chloroalkenes produced squamous carcinomas of the skin in mice that were treated dermally, and fibrosarcomas of the subcutaneous tissue at the site of injetion of those mice that were injected subcutaneously. However, the tests were negative in both instances for the trichloroethylene oxide (TCEO). In an earlier study, Van Duuren et al. (1979) gave purified TCE to male and female mice as dermal applications, either alone or in combination with a promoter, by weekly subcutaneous injections, or by weekly oral doses. TCE was not carcinogenic under the conditions of these tests.

In addition to the differences between different animal species in susceptibility to TCE-induced toxicity and carcinogenicity, there are also differences between strains. Kjellstrand et al. (1983), found that following short-term exposure to 150 ppm TCE in air for 30 d, female mice seem to be less sensitive to the hepatoxic effects of the TCE than male mice, and strain NZB was more sensitive to the exposure than the other strains. Furthermore, the plasma butylcholinesterase ativity in TCE-exposed males increased in all strains, but this was not nearly as pronounced in the females of the same strains. The authors also observed that there was no correlation between increase in liver weight and plasma butylcholinesterase activity.

HUMAN STUDIES

The acute clinical toxicity of TCE in humans is well known and has been described in standard textbooks on toxicology and occupational health. This information will therefore not be extensively reviewed. A very high dose may of course result in toxicity. On the other hand, 5 human volunteers exposed to 200 ppm (1070 mg/m^3) in air for 7 h/d for 5 d only had mild untoward subjective responses such as dryness of the throat and feeling fatigued and no untoward objective responses, with normal performance and neurological tests as well as normal clinical and laboratory tests (Stewart et al., 1970). Similarly, serum enzyme levels were normal in 20 volunteers after exposure to 95 ppm TCE in air for 4 h (Konietzko and Reill, 1980).

Thiele et al. (1982) describe a case of a worker who had had repeated exposures to high concentrations of TCE and, at one point, also to 1,1,1-trichloroethane. His exposures started in 1972. He had several attacks of nausea, vomiting, anorexia, fatigue, and jaundice. His final exposure occurred in 1979; subsequently, the diagnosis of cirrhosis of the liver was made by liver needle biopsy. He showed no evidence of having had viral hepatitis in the past, nor was there a history of excessive alcohol consumption.

Tola et al. (1980) studied the mortality of 2117 workers exposed to TCE sometime between 1963 and 1976. In this group, there were 1148 men and 969 women. Ninety-eight of these workers had had episodes of acute poisoning. Thirty-three deaths occurred among the males, versus

36 expected, and 13 deaths occurred among the females, versus 29.8 expected. Among the males, 5 neoplasms were observed versus 6.3 expected. Among the females, there were 4 neoplasms, versus 6 expected. From the Registry of Congenital Malformations, no malformed babies were found to have been born to the exposed mothers. On the basis of the National Incidence figure, three malformed babies would have been expected. Tola et al. (1980), in discussing their findings, pointed out that the total mortality and the cancer mortality in their workers were lower than expected, and conclusions from this study must be made with caution. The age structure of the cohort was relatively young, and the follow-up period was brief. However, it does not appear given the short latency period of 6-13 yr that TCE is a strong human carcinogen. Similarly, Axelson et al. (1978) concluded from their study that TCE is probably not a serious cancer hazard, particularly at low exposure, although they also pointed out the limitations of their study. One additional difficulty with studying worker populations is that they are exposed to technical-grade TCE, which contains alkylating agents as stabilizers. In some industrial operations, the heating of TCE results in breakdown products to which the workers are also exposed. Thus, most workers are exposed to mixtures of chemicals, and even if a higher incidence of cancer were found it might not be possible to specifically associate it with exposure to TCE.

The National Institute of Occupational Safety and Health (NIOSH) has published two documents on TCE. The first, *Criteria for a Recommended Standard, Occupational Exposure to Trichloroethylene*, was published in 1973. From this document, in which the uses, exposures, and biological effects of TCE were reviewed, a recommended air standard of 100 ppm as a time-weighted average (TWA) for an 8-h workday or a peak level of 150 ppm measured over a sampling period of 10 min. The carcinogenic potential of the compound was not assessed.

The release of the National Cancer Institute (NCI) report on March 21, 1975, following the 1974 confirmation of the carcinogenicity of vinyl chloride and its similarity in chemical structure and metabolism to TCE, caused NIOSH to issue in June 1975 a brief announcement to the occupational community alerting them to TCEs potential carcinogenicity. The Occupational Safety and Health Administration (OSHA), while expressing concern, did not declare it to be carcinogenic, but did propose to modify its existing limits from a 200 ppm ceiling to 150 ppm, retaining its 8-hour TWA of 100 ppm.

In 1978, NIOSH published a Special Occupational Hazard Review (SOHR) on TCE that covered the carcinogenic hazard presented by TCE. This publication summarized the available exposure data and the literature on long-term effects. At the time the review was being written, NIOSH estimated that 100,000 workers were exposed full-time to TCE, with up to 3.5 million others exposed to continuous low levels r sub-

jected to brief exposures. The SOHR concluded that there was "strong presumptive evidence" that the TCE epoxide produced during the metabolism of TCE is responsible for its carcinogenic and mutagenic activity and noted that the metabolite's covalent binding with cellular marcromolecules, including DNA, had been demonstrated in vitro. However, the document emphasized that no evidence was known "which associates TCE with an increased risk of cancer in humans."

NIOSH further concluded that TCE did have a carcinogenic potential in the workplace but it was "not considered to be a potent carcinogen." Therefore, improving work practices, better maintenance, and other actions were recommended that would lessen exposure to workers. It also suggested that a TWA of 25 ppm for workers was achievable with technology then available.

In December 1983, a draft *Health Assessment Document* for TCE was released by the U.S. Environmental Protection Agency (EPA). In the document, EPA provides a detailed review of the available data on environmental exposure pharmacokinetics, and metabolism. Many of these studies have been discussed in the current paper and in the previously cited work. EPA also reviewed metabolic pathways leading to covalent binding to cellular macromolecules and noted that increased toxicities can occur when subjects have prior exposure to ethanol, barbiturate, disulfiram, and warfarin.

After analyzing the available experimental and epidemiologic information, EPA (1984) concluded that "...long-term exposure of humans to environmental (ambient) levels of TCE is not likely to represent a health concern."

CONCLUSIONS

In its publication *Drinking Water and Health*, the National Research Council (NRC) reviewed the available information on TCE. They concluded that TCE was of low acute and chronic toxicity in humans as well as in other mammals. The committee on drinking water and health made a risk assessment for TCE based on the gavage study done by the National Cancer Institute (1976) and concluded that at one $\mu g/l$ (1 ppb), the estimated risk for humans of a lifetime probability of additional cancer would be $0.36\text{-}1.1 \times 10^{-7}$ (National Research Council, 1977). Since then, using more recent animal data (National Research Council, 1980, 1983), the Safe Drinking Water Committee of the National Research Council has recalculated the cancer risk estimate. Based on the National Toxicology Program (1983) carcinogenesis study the averaged upper 95% confidence estimate of lifetime risk for 1 μg TCE/l water is 3.3×10^{-7}. The differences in metabolism of TCE in B6C3F1 mice and in other species including humans, and the fact that the TCE used in the National Cancer Institute study was contaminated with epichlorohydrin, makes this prediction extremely questionable. In addition, this extrapolation was made

from a rather high exposure, where the capacity of normal detoxification pathways and mechanisms was very likely to be exceeded. Such would not be the case at lower, environmentally encountered concentrations. In addition, TCE has not been shown to be a potent carcinogen in rats, nor does it seem to be a potent carcinogen in other strains of mice. In addition, several animal studies have not demonstrated that TCE is particularly fetotoxic or teratogenic (Schwetz et al., 1975; Dorfmueller et al., 1979; Land et al. 1981). Unfortunately, the epidemiology studies that have been conducted are rather limited. Essentially, the results have been negative; however, the number of persons examined so far for chronic toxic effects is small compared with the enormous size of the work force that is exposed to TCE over prolonged periods of time. Apparently, TCE is neither fetotoxic nor teratogenic. On an empirical basis, the occupational experience with TCE does not suggest that this compound is a potent carcinogen. Adequate epidemiology studies to prove or disprove this impression have not been conducted. On the other hand, the risk associated with exposure to trace amounts (ppb) of TCE concentrations in water appear to be minimal or perhaps negligible. Because of the interspecies differences in metabolism of TCE, it is important that the theoretical risks attributed to TCE in the past be reexamined. In this respect, it is particularly important to determine whether the minor pathways of TCE metabolism that generate the proximate carcinogens (1) occur only at high dosage levels, and (2) are operative in humans. At low doses at which TCE is excreted by first-order kinetics, metabolic pathways leading to the formation of the proximate carcinogen probably are not activated in humans or in other species.

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