United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Washington DC 20460

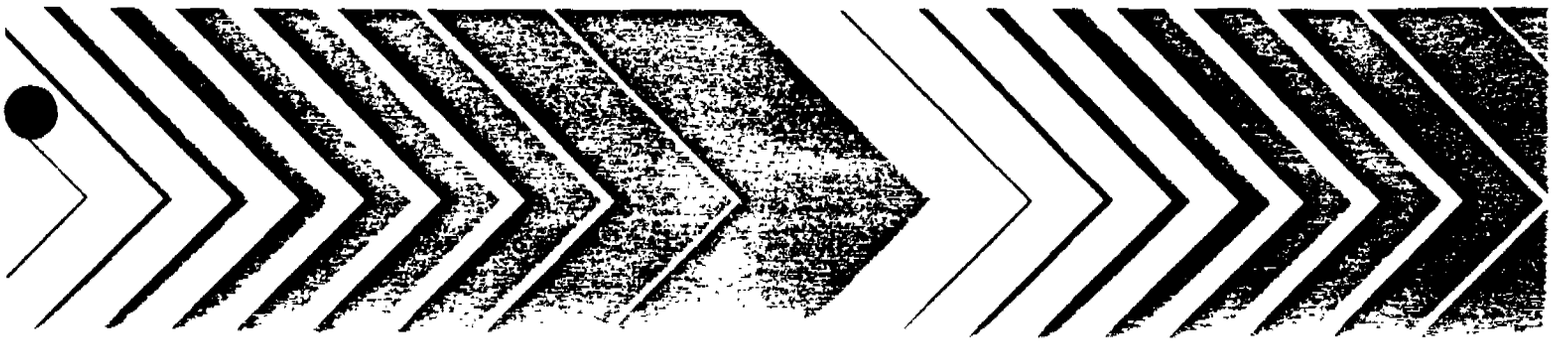
EPA 600 8 82 006F
Jun 1985
Final Report

Research and Development

EPA

Health Assessment Document for Trichloroethylene

Final Report



EPA/600/8-82/006F
July 1985
Final Report

Health Assessment Document for Trichloroethylene

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Research Triangle Park, NC 27711

1. EXECUTIVE SUMMARY

Trichloroethylene (1,1,2-trichloroethylene) (TCI) is a solvent widely used in the industrial degreasing of metals. It has no known natural sources. Current U.S. production is estimated at about 130,000 metric tons per year. Of the TCI used in the United States, 80 to 95 percent evaporates to the atmosphere. In addition to the workplace, TCI is found in a variety of urban and nonurban areas of the United States and other regions of the world. It has been measured in ambient air and water. An average ambient air concentration of about 1 part per billion (ppb) would be expected for some large urban centers. Concentrations as high as 32 ppb have been measured in urban centers in the United States, and 47 ppb has been measured in urban Tokyo. Ambient air concentrations of TCI are greatly influenced by the rate and geographic distribution of emissions and the rate of decomposition and transposition in the atmosphere. The average mixing ratio in the troposphere of the northern hemisphere is 11 to 17 parts per trillion (ppt). Reaction with hydroxyl radicals is the principal mechanism by which TCI is scavenged from the atmosphere.

TCI has been detected in both natural and municipal waters in the United States. Up to 403 ppb has been measured in some surface and subsurface waters. In finished drinking water, concentrations have ranged from 1 to as much as 32 ppb. There is no direct evidence of bioaccumulation of TCI in the food chain. Few studies have been made of the ecological consequences of TCI in the environment.

The pharmacokinetics and metabolism of TCI have been studied in man as well as in animals. Inhalation is the principal route of concern by which TCI enters the body. Ingestion of drinking water contaminated with TCI is another important concern. The extent of TCI absorption after oral ingestion is virtually complete; with air exposure, the amount of TCI absorbed increases in proportion to its concentration in inspired air, the respiratory rate, and duration of exposure. TCI distributes widely into body tissues. TCI is eliminated by two major processes, pulmonary excretion of unchanged TCI and liver metabolism to urinary metabolites. At air concentrations of 500 ppm (2690 mg/m^3) or less, humans are estimated to metabolize between 60 and 90 percent of absorbed TCI. The proportion of the TCI dose metabolized in rodents has been demonstrated to

decrease at higher doses; that is, metabolism becomes nonlinear and approaches saturation. However, metabolism is linearly proportional to the inhaled concentration dose in man, at least up to about 300 ppm (1614 mg/m^3). There is no evidence that TCI metabolism in man is saturation-dependent. Studies have not been made of TCI metabolism after oral exposure in man. At the levels found or expected in drinking water, virtually all TCI is expected to be absorbed and metabolized. There is persuasive experimental evidence that the metabolic pathways for TCI are qualitatively similar in mice, rats, and humans. In these species, the principal urinary metabolites of TCI that have been identified are trichloroethanol (TCE) and its glucuronide, and trichloroacetic acid (TCA). Minor metabolites have also been identified for each of these species. In the liver, TCI is first metabolized to chloral hydrate and to a reactive epoxide (TCI oxide) by a microsomal P_{450} system. Reactive intermediate metabolites such as TCI epoxide covalently bind to cellular macromolecules, principally protein, and to a much lesser extent, DNA. Hepatotoxicity of TCI has been shown to correlate with the amount of metabolism. Metabolism of TCI is enhanced by drugs (e.g., barbiturates, oral antidiabetic agents) and by other xenobiotics (e.g., PCBs) which induce the hepatic microsomal P_{450} metabolizing system. Heightened toxicity can result from drug interactions known to occur with ethanol, barbiturates, disulfiram, and Warfarin.

Excluding carcinogenicity as an end point, toxicity testing in experimental animals, coupled with limited human data derived principally from excessive exposure, suggests that long-term exposure of humans to environmental (ambient) levels of TCI is not likely to represent a health concern. Behavioral and psychological effects, particularly as they affect psychomotor performance, have been reported at levels of 200 ppm (1076 mg/m^3) in some, but not all, experimental and epidemiologic studies. There is no information that such impairment, representative of dysfunction of the central nervous system (CNS), would occur during chronic, low-level exposures. At levels found or expected in the ambient environment, such an effect would be unlikely. Similarly, dysfunction of the liver or kidneys would not be likely during or as a result of environmental exposures.

Teratogenicity is another health end point for which available data from experimental animals suggest that the conceptus is not uniquely susceptible to TCI. Exposure of rats, mice, and rabbits, during gestation, to levels (300 ppm

or 1614 mg/m^3) greatly in excess of those generally found in the environment, has not been observed to result in any teratogenic effects. The teratogenic potential of TCI for humans cannot be directly extrapolated from the observations in the animal studies. However, the animal studies suggest that at low ambient levels that do not cause maternal toxicity, TCI would not pose a significant hazard to the developing conceptus.

With respect to the mutagenic potential of TCI, available data provide suggestive evidence that commercial-grade TCI is a weakly-active, indirect mutagen, causing effects in a number of different test systems representing a wide evolutionary range of organisms. Thus, commercial TCI may have the potential to cause weak or borderline increases above the spontaneous level of mutagenic effects in exposed human tissue. Adverse effects in the testes of mice exposed to commercial TCI suggest that TCI could cause similar effects in humans. A conclusion about the mutagenic potential of pure TCI cannot be made. If TCI is mutagenic, the available data suggest that it would be a very weak, indirect mutagen.

The evidence reviewed in this document for the carcinogenicity of TCI in experimental animals includes: increases in the incidence of hepatocellular carcinomas in male and female B6C3F1 mice (three studies); malignant lymphomas in female Han:NMRI mice; and renal adenocarcinomas in male Fischer 344 rats. Statistically significant increases of malignant liver tumors were observed in both male and female B6C3F1 mice. A gavage study of purified TCI in both sexes of B6C3F1 mice was conducted with basically the same experimental design as a gavage study of technical grade TCI in male and female B6C3F1 mice to evaluate the role of epoxide stabilizers in TCI in the induction of hepatocellular carcinomas. Similar carcinogenic responses were observed for the purified epoxide-free and for stabilized TCI. The other studies provide some additional support to the overall body of evidence, particularly since two of them were carried out in a different species or strain. However, the third study in B6C3F1 mice, an inhalation study in which an increase in liver tumors was seen, was weakened by deficiencies in its conduct. In the inhalation study in Han:NMRI mice, a 30 percent incidence of spontaneous lymphoma in control mice, and the possibility of an indirect effect in treated mice, made these results difficult to interpret. A borderline response was observed in the gavage study of Fischer 344 rats.

A gavage study with male and female Osborne-Mendel rats was negative; however, this study may be considered inconclusive because of high mortality in the treatment groups. Exposure to airborne concentrations of TCI did not result in a carcinogenic effect in Han:Wist rats and Syrian hamsters, although higher dose levels of TCI probably could have been given to the test animals.

Other long-term animal studies did not suggest a carcinogenic potential for TCI. Most of these studies, however, were not specifically designed to evaluate carcinogenicity, involved only small treatment groups, lacked sufficient doses of TCI, or were of insufficient duration in view of the expected latency period for cancer induction.

TCI induced malignant tumors of the liver in both male and female B6C3F1 mice in multiple studies. This constitutes a signal that TCI might be carcinogenic in man. While kidney tumors observed in the NTP rat study are not strong indications of a response in a second species because of the small number of animals responding (3 of 49 animals) and because of the high mortality, the statistical significance after mortality corrections suggests that a carcinogenic effect may be taking place.

The U.S. Environmental Protection Agency's Proposed Guidelines for Carcinogen Assessment (U.S. EPA, 1984), take the position that the mouse-liver-tumor-only response, when other conditions for a classification of "sufficient" evidence in animal studies are met, should be considered as "sufficient" evidence of carcinogenicity. Thus, based on EPA's proposed cancer guidelines, the overall evidence for TCI would result in a classification of B2, i.e., a probable human carcinogen.

The TCI carcinogenicity results could be classified under the criteria of the International Agency for Research on Cancer (IARC) as either "sufficient" or "limited" depending on which of the differing current scientific views about chlorinated organic compound induction of liver tumors in mice is chosen. Since there are no adequate epidemiologic data in humans, the overall ranking of TCI under the criteria of the IARC depends primarily upon the position taken regarding the mouse liver tumor. Thus, the overall ranking could be either Group 2B or Group 3. The more conservative public health view would regard TCI as a probable human carcinogen (Group 2B), but there is also scientific sentiment for regarding TCI as an agent that cannot be classified as to its carcinogenicity for humans (Group 3).

Additional carcinogenicity studies on purified TCI (no detectable epoxides) are currently in progress. These studies and others published recently will be incorporated into any updates of this Health Assessment Document.

Four sets of gavage bioassay data on hepatocellular carcinomas in male and female mice provide a basis to calculate an upper-bound carcinogenic slope estimate for TCI using a linearized multistage model. The development of these risk estimates is for the purpose of evaluating the "what-if" question: If TCI is carcinogenic in humans, what is the possible magnitude of the public health impact? Since upper-bound potency estimates calculated on the basis of these data sets are comparable, ranging from 5.8×10^{-3} to 1.9×10^{-2} mg/kg/day, the geometric mean, 1.1×10^{-2} mg/kg/day is used to calculate the incremental lifetime cancer risk (i.e., unit risk) due to a unit exposure of TCI in drinking water and in air. The upper-bound estimate of the cancer risk due to 1 μg/L of TCI in drinking water is 3.2×10^{-7}. The upper-bound estimate of the cancer risk due to 1 $\mu g/m^3$ of TCI in air is 1.3×10^{-6}. The upper-bound nature of these estimates is such that the true risk is not likely to exceed this value and may be lower. The carcinogenic potential of TCI is generally considered to reside in cellular reactive intermediate metabolites, and therefore metabolic and pharmacokinetic factors have been used in the calculation of the drinking water and air unit risks.

None of the epidemiologic studies reviewed in this report provide positive evidence from which to estimate a unit risk for exposure to TCI. As an alternative, an upper-bound estimate has been calculated from one negative study. The calculation on the basis of human data results in a greater risk estimate than the estimate from animal data, and thus does not appear to contradict the risk estimate calculated from the animal data.

Expressed in terms of relative potency, TCI ranks in the lowest quartile among the 54 suspect or known human carcinogens evaluated by EPA's Carcinogen Assessment Group.

RECOMMENDATIONS FOR FURTHER STUDIES

Areas for which incomplete information is available, and which should be considered in formulating research needs, are presented below. The needs listed, however, are not necessarily in the order of relative priority.

1. Teratogenicity and Reproductive Effects. There are few animal studies via inhalation that adequately assess the teratogenic and reproductive effects potential of TCI. Uncertainty about these biological end points in humans should serve as a stimulus for future research.

2. Neurobehavioral Toxicity. There have been few animal studies of the effects of TCI on the nervous system and behavior. Most end points studied have been relatively insensitive. Further studies are warranted on more sensitive end points.