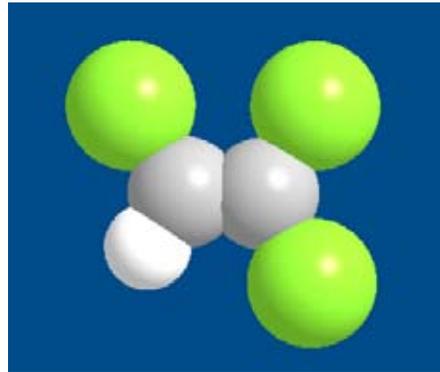


Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues

Trichloroethylene, a solvent widely used as a degreasing agent, is a common contaminant of air, soil, and water at manufacturing facilities, military installations, and hundreds of waste sites around the country. It is released into the air during degreasing operations and is found in soils and surface water as a result of direct discharges, and in groundwater from disposal operations. It can also be released in indoor air if tap water is contaminated, if vapors enter from contaminated groundwater nearby, or if certain consumer products (e.g., adhesives, typewriter correction fluid, paint removers) are used.



Responsibility for cleaning contaminated sites is shared among several government agencies.

To help protect people from potential health effects caused by exposure to trichloroethylene, risk assessments are conducted to guide policy and risk management decisions. Risk assessments require consideration of a great deal of scientific information on trichloroethylene. There has been much debate about the quality of some sources of information and how to assess the collective evidence.

At the request of an interagency group composed of the U.S. Department of Defense, Department of Energy, Environmental Protection Agency (EPA), and the National Aeronautics and Space Administration, this National Research Council report offers independent guidance on scientific issues related to assessing health risks of trichloroethylene. The report's authoring committee reviewed a large body of technical material on trichloroethylene, including relevant scientific literature, a draft risk assessment by EPA released in 2001, scientific and technical review comments on that draft assessment, and additional information provided by the sponsoring agencies and other interested parties.

Understanding of Health Effects and Mode of Action

Trichloroethylene is metabolized in the body by two major pathways (the oxidative pathway and the glutathione-conjugation pathway). There are many animal studies that show that trichloroethylene and its metabolites (products of metabolism) are associated with several health effects, including cancer. Studies of human populations (epidemiologic studies) suggest

that trichloroethylene may also affect human health, but less is known about the exposures needed to induce effects and physiologic responses. In all risk assessments, it is very difficult to assess the relevance of the findings of animal studies to humans. To do so requires an understanding of which metabolites are responsible for observed health effects and their “mode of action,” or how the metabolites cause health effects. The following are highlights of the committee’s findings:

Kidney Toxicity and Cancer

Trichloroethylene and some of its metabolites in the glutathione-conjugation pathway have been shown to be both toxic and carcinogenic to the kidneys. There is concordance between animal and human studies, which supports the conclusion that trichloroethylene is a potential kidney carcinogen. Studies with experimental animals and human tissues indicate a genotoxic mode of action. The metabolite S-dichlorovinyl-L-cysteine has been linked with the development of kidney cancer, but there are no studies of the carcinogenic potential of this metabolite. The magnitude of exposure needed to produce kidney damage is not clear. Thus, it is not possible to predict whether humans are more or less susceptible than other animals to trichloroethylene induced kidney cancer.

Liver Toxicity and Cancer

The epidemiologic evidence is mixed; some studies show an excess of liver cancer in trichloroethylene exposed populations while other studies do not. Animal data on trichloroethylene indicate that relatively high doses are needed to induce liver toxicity and cancer, even in susceptible strains of mice. Three major oxidative metabolites (trichloroacetic acid, dichloroacetic acid, and chloral hydrate) can contribute to liver toxicity and cancer in rodents. The mode of action of trichloroacetic acid as a rodent liver carcinogen is not a likely mode of action in the human liver. For the metabolite chloral hydrate, differing rates of oxidation and conjugation in rats and humans make it unlikely that the mode of action in mice is relevant to humans. The mode of action for the metabolite dichloroacetic acid in rodents is understood, but whether this metabolite is formed in humans has not been established and differences between mice and human suggest that humans would be much less susceptible to liver carcinogenesis. Thus, exposure to trichloroethylene at concentrations relevant to the general public is not likely to induce liver cancer in humans. However, it is possible that much higher exposure to trichloroethylene, such as in certain high-risk occupations or in heavily contaminated locales, could result in increased risks of liver toxicity and cancer.

Reproductive and Developmental Toxicity

Evidence from animal and epidemiologic studies suggest that exposure to trichloroethylene and one or more of its metabolites might be associated with congenital heart defects. Although there are inconsistencies in the animal data, plausibility for trichloroethylene-induced cardiac teratogenesis is increased by the fact that the most frequently observed cardiac defects in human studies are consistent with those found in animal studies. Research in animals and humans also indicates that trichloroethylene impairs intrauterine growth. However, the specific metabolites involved and the mode of action responsible for cardiac teratogenesis and poor intrauterine growth remain to be elucidated. Rodent studies also show that trichloroethylene can affect fertility in males (reduced spermatogenesis) and females (decreased fertility of oocytes), but the relevance of these findings to humans is not clear.

Neurotoxicity

Studies show that inhalation of trichloroethylene causes neurotoxic effects in laboratory animals and humans that are similar in nature (e.g., masseter reflex latency, motor incoordination, changes in heart rate) and occur at comparable concentrations of exposure. It has been suggested that exposure to trichloroethylene during early development could enhance its effects on the nervous system, but the available data are insufficient to draw firm conclusions. Some studies suggest a contribution of trichloroethylene to Parkinson’s disease. Multiple mechanisms appear to contribute to the neurotoxic action of trichloroethylene, and further study is needed to elucidate them more precisely.

Respiratory Toxicity and Cancer

Trichloroethylene has been shown to induce lung tumors in rodents. The mode of action for this effect is localization of trichloroethylene metabolites in the Clara cells of the lungs. The collective evidence indicates that rodents and humans are significantly different in their capacity to metabolize trichloroethylene in the lungs, with humans having less capacity. Results of most epidemiologic studies of occupational exposure to trichloroethylene do not show a strong association between trichloroethylene exposure and increased incidence of lung tumors. Thus, pulmonary cancer does not appear to be a critical end point in assessing human health risks to trichloroethylene.

Immunotoxicity

Studies in genetically susceptible rodents have shown that trichloroethylene exacerbates underlying autoimmune disease, and supporting information comes from multiple human studies of scleroderma and exposures to organic solvents. Some individuals might be genetically susceptible to developing autoimmune disease. The metabolites and the mode of action involved have not been elucidated, but a role for chloral has been implicated in mouse models.

New Analysis Needed to Synthesize Collective Evidence on Cancer Risk

A large body of epidemiologic studies is available on trichloroethylene and possible cancer risks. Synthesizing the data from multiple studies is difficult and requires a quantitative “meta-analysis” of the data. There are two available meta-analyses, one developed by Wartenberg et al., whose analysis EPA used in its draft health risk assessment, and another by Kelsh et al. The committee found several weaknesses in the techniques used in both analyses. Problems included the use of subjective, tiered systems to classify and weigh studies, separate analyses of case-control and cohort studies, and the fact that these analyses did not consider identifying amounts of exposure in the studies. The report recommends that a new meta-analysis be developed to support a human health risk assessment.

Pharmacokinetic Modeling is Useful in Guiding Research

Physiologically based pharmacokinetic (PBPK) models are used to describe the absorption, distribution, metabolism, and elimination of trichloroethylene in an organism. They can be used to estimate doses of metabolites in target tissues and organs (“dose metrics”), derive human equivalent doses from animal data, and make route-to-route extrapolations. Several PBPK models for trichloroethylene have been developed over the past few decades. The models EPA used in its draft risk assessment are the Fisher models, which were designed to focus on liver cancer in rats and humans, and the Clewell model, which is more complex and designed for covering liver toxicity and cancer, kidney toxicity and cancer, and lung cancer. A “harmonized” model has been developed as part of a joint effort between the U.S. Air Force and EPA. The committee found that the harmonized model is the best model available. However, the dose metrics most appropriate for different health end points has not been determined, so it is appropriate to consider multiple dose metrics generated from PBPK models as well as non-modeled metrics (e.g., no observed adverse effect level) when conducting a risk assessment.

PBPK models are useful tools for identify data gaps and research needs to reduce uncertainty in risk assessment. They do not resolve uncertainty about the mode of action, but can inform experimental designs for studying mode of action. Better understanding of mode of action will drive model elaboration in the future.

Improvements Needed to Estimate Health Risks at Low Doses

Because most of the population is exposed to trichloroethylene at doses lower than those in animal and occupational studies, it is important to estimate risk at these lower doses. This requires a few steps, including selection of a “point of departure,” which corresponds to a level of incremental health effects, such as a 5% increase in incidence of cancer, and selection of an appropriate model to extrapolate from the dose at the point of departure to zero dose. For risks of cancer, EPA’s guidelines call for selecting a point of departure

from among modeled doses near the lower end of the observed range (1%, 5%, and 10%). The report recommends that several points of departures be considered and compared for cancer and non-cancer end points. There are several approaches to extrapolating from the point of departure to zero, including linear and nonlinear methods. Because there is insufficient evidence on mode of action to establish the best dose-response model for trichloroethylene, it is appropriate under EPA's cancer guidelines to extrapolate the risk using a linear model where cancer risk is proportional to dose.

Evidence Strong Enough to Complete Risk Assessment

The committee found that the evidence on carcinogenic risk and other health hazards from exposure to trichloroethylene has strengthened since 2001. Hundreds of waste sites in the United States are contaminated with trichloroethylene, and it is well documented that individuals in many communities are exposed to the chemical, with associated health risks. Thus, the committee recommends that federal agencies finalize their risk assessment with currently available data so that risk management decisions can be made expeditiously.

Committee on Human Health Risks of Trichloroethylene: **Rogene F. Henderson** (*Chair*), Lovelace Respiratory Research Institute, Albuquerque, NM; **Scott Bartell**, Emory University, Atlanta, GA; **Scott W. Burchiel**, University of New Mexico, Albuquerque; **Deborah A. Cory-Slechta**, University of Medicine and Dentistry of New Jersey, Piscataway; **Mary E. Davis**, West Virginia University Medical Center, Morgantown; **Kelly J. Dix**, Lovelace Respiratory Research Institute, Albuquerque, NM; **Mark S. Goldberg**, McGill University, Montreal, Quebec, Canada; **Evan Kharasch**, Washington University in St. Louis, St. Louis, MO; **Serrine S. Lau**, University of Arizona, Tucson; **Jose Manautou**, University of Connecticut, Storrs; **D. Gail McCarver**, Medical College of Wisconsin, Milwaukee; **Harihara Mehendale**, University of Louisiana, Monroe; **Peter Mueller**, University of Texas, Houston; **John M. Peters**, University of Southern California, Los Angeles; **Thomas J. Smith**, Harvard School of Public Health, Boston, MA; **Leslie Stayner**, University of Illinois, Chicago; **Rochelle W. Tyl**, RTI International, Research Triangle Park, NC; **Jack P. Vanden Heuvel**, Penn State University, University Park, PA; **Janice W. Yager**, Electric Power Research Institute, Palo Alto, CA; **Susan N. J. Martel** (Study Director), National Research Council.

This report brief was prepared by the National Research Council based on the committee's report. For more information, contact the Board on Environmental Studies and Toxicology at (202) 334-3060 or visit <http://dels.nas.edu/best>. *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues* is available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; www.nap.edu.



This study was sponsored by the U.S. Department of Defense, U.S. Department of Energy, U.S. Environmental Protection Agency, and National Aeronautics and Space Administration.