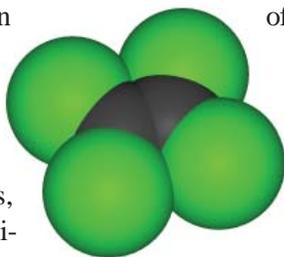


Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene

Tetrachloroethylene (also known as perchloroethylene, PCE, or PERC)—a chemical used for dry cleaning, metal degreasing, and other applications—is an environmental contaminant linked to a range of health effects in humans, including cancer. This report provides an independent scientific review of a U.S. Environmental Protection Agency (EPA) draft assessment of the health effects of tetrachloroethylene. EPA's assessments will be used to guide air- and water-quality standards and cleanup procedures to protect public health. The report finds that EPA's classification of tetrachloroethylene as "likely to be a human carcinogen" and toxic to the nervous system is supported in the draft assessment. However, the report suggests using better designed studies than those EPA chose in calculating the risks of tetrachloroethylene. It also proposed ways to strengthen the scientific basis for estimating safe inhalation and oral exposures to tetrachloroethylene and cancer risk estimates.

Tetrachloroethylene, also known as perchloroethylene, PCE, or PERC, is widely used as a solvent for dry cleaning, textile processing, degreasing metal parts, and as a precursor for other chemicals, but it is also an environmental contaminant that has been detected in the air, groundwater, surface waters, and soil. Dry-cleaning facilities are a large source of atmospheric emissions of the chemical, and leaks and improper disposal practices can lead to groundwater contamination.

In June 2008 EPA released a draft assessment, *Toxicological Review of Tetrachloroethylene in Support of Summary Information on the Integrated Risk Information System*, to provide quantitative estimates of the health risks of tetrachloroethylene exposure. The estimates will be used in EPA's Integrated Risk Information System, a database that assesses human health effects from exposure to a variety



of toxic chemical contaminants in the environment. EPA's reference values and cancer risk estimates will be used to establish air- and water-quality standards, and to inform procedures for cleanup of hazardous waste sites to protect public health.

At the request of EPA, the National Research Council (NRC) convened a committee to conduct an independent scientific review of the draft assessment of tetrachloroethylene, from toxicological, epidemiological, and human clinical perspectives. The committee was asked to evaluate the data and methods used to estimate risks posed by exposure to the chemical, to assess the value of the key studies used to make those estimates, and to determine if uncertainties affecting the risk estimates were adequately described. The committee was also charged with identifying research that could reduce uncertainty in the understanding of human health effects.

Types of Cancer Potentially Caused by Tetrachloroethylene

Mononuclear Cell Leukemia

Two studies have shown an increased incidence of mononuclear cell leukemia in rats. However, the significance of these data for humans is the subject of much debate. First, increased mononuclear cell leukemia was observed in a type of rat known to have a high background incidence of the disease. Second, there are differences of opinion on the relevance of this rodent leukemia for predicting human cancer.

Liver Cancer

Statistically significant increases in liver tumors were observed in male and female mice after exposure to tetrachloroethylene. The significance of these increases is debated because the strain of mouse used in the studies has a high background incidence of this type of cancer. However, the findings have been reproduced by several laboratories and show a dose-dependent relationship, meaning that the number of mice with tumors increased with dose.

Kidney Cancer

There is evidence of kidney tumors in rodents exposed to tetrachloroethylene. The increase in tumors was not statistically significant, but the background incidence of kidney cancer in rats is low, meaning that it is unlikely that the increased tumors formed due to chance. In addition, the tumors in the exposed rats were malignant whereas those in the control group were not.

Assessment of Health Effects from Exposure to Tetrachloroethylene

People can be exposed to tetrachloroethylene by breathing it in the air, absorbing it through the skin, or consuming it. In its draft assessment, EPA reviews a vast amount of scientific literature on the chemical. Information on the effects of tetrachloroethylene on human health come from studies of human populations exposed to the chemical (epidemiological studies), from laboratory research on rodents, and from cell culture studies that help illuminate how tetrachloroethylene acts in the body.

Assessment of Cancer Effects

In EPA's draft assessment, tetrachloroethylene is classified as "likely to be a human carcinogen." In the judgment of the NRC's expert committee, this classification is supported by data that meet the relevant criteria in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*. Tetrachloroethylene

is a carcinogen in laboratory animals, but studies of human populations have revealed only weak associations between exposure to the chemical and cancer. There is a long-standing debate about how to interpret and use the laboratory findings to predict human cancer risks. This debate is reflected in the committee's evaluation of which type of tetrachloroethylene-related cancer—leukemia, liver cancer, or kidney cancer—provides the strongest

data for EPA to estimate cancer risk. The majority of committee members judged that the leukemia data EPA chose to calculate cancer risks contained uncertainties that were too great to use. Those members concluded that a more scientifically defensible approach would be to use the dataset that has the least uncertainty rather than the cancer dataset that yields the highest estimates of risk. Following this approach, they suggested that EPA use the liver cancer data, followed by data on kidney cancer and leukemia.



Many metal products, such as this rolled steel coil, require degreasing in their manufacture.

However, other committee members judged that the leukemia data should be used for cancer risk estimation. Their opinions were based on the observation that the increases in mononuclear cell leukemia incidence in rats were statistically significant, were reproducible, and showed the highest sensitivity to tetrachloroethylene exposure. They concluded that additional statistical analyses and a better characterization of the way that tetrachloroethylene acts in the body to cause health effects would strengthen the use of leukemia data in the draft assessment.

Assessment of Potential Noncancer Health Effects

People exposed to tetrachloroethylene can suffer damage to the nervous and reproductive systems, kidneys, and liver. EPA's draft assessment sets reference values for amounts of daily exposure to the chemical that are not likely to present adverse health effects during a lifetime. Because impairments to the nervous system, called neurotoxic effects, are among the most sensitive to tetrachloroethylene exposure, EPA's reference values were based on these health impacts.

EPA estimated reference values using a human population study that measured adverse neurotoxic effects in people who lived near dry-cleaning facilities. This analysis resulted in an inhalation reference concentration of 2 parts per billion of tetrachloroethylene per day. However, the National Research Council committee identified methodological deficiencies in the study and recommended that EPA use five alternative studies that provide stronger methods and more reliable findings. When the committee used these studies to derive reference values using the same methods as EPA, it produced a range for the reference inhalation concentration of 6 to 50 parts per billion.

Concerns with the EPA Draft Assessment

Overall, concerns were raised about the approaches that EPA used to evaluate the data on tetrachloroethylene, and that inadequate information or rationales were used to support parts of its assessment—weaknesses that should be addressed to improve the soundness and reliability of EPA's proposed reference values and cancer risk estimates. It was recommended that EPA should use better designed studies than those used in the draft



Tetrachloroethylene is commonly used as a solvent in dry-cleaning.

assessment to calculate the quantitative risks of tetrachloroethylene. Improvements for characterizing and analyzing the evidence were suggested in order to strengthen the scientific basis for estimating safe exposures to tetrachloroethylene and cancer risks.

Major Findings and Recommendations for Improvements to the Draft Assessment

Here, the committee suggests improvements to the draft assessment that should be incorporated into the final assessment. The evidence supports EPA's conclusion that tetrachloroethylene is likely to be a human carcinogen, but the committee debated which type of tetrachloroethylene-related cancer—leukemia, liver tumors, or kidney cancer—provides the strongest data for EPA to calculate its cancer risk estimation. The modes of action by which tetrachloroethylene can cause increases in such cancers were an important consideration in EPA's draft assessment, but the draft assessment synthesized evidence for some types of cancer better than for others.

EPA's draft would be improved with greater consideration of the modes of action for cancer to support the conclusions drawn, with particular attention to outlining the proposed sequence of hypothesized tetrachloroethylene-associated key events leading to cancer.

EPA used three computer models, called physiologically based pharmacokinetic models, to

describe the way tetrachloroethylene works in an organism. The models are used to estimate the human equivalent exposure from animal data, and to estimate exposure from one route to another (such as from inhalation to the oral route). In some cases a single model was used, and in other cases all three, yet the different models could yield different results.

For consistency the committee recommends that EPA consider developing a single model that integrates elements of all three models. The agency should also explore incorporating all of the major metabolic pathways into the model.

EPA's quantitative assessment of uncertainty with regard to choice of dose-response models, physiologically based pharmacokinetic models, and variation between studies were supported. In particular, EPA's consideration of uncertainty due to different forms of dose-response models were particularly valuable.

The committee recommends that such quantitative evaluations be extended to additional datasets so that a greater array of uncertainties can be addressed.

For its noncancer assessment, EPA appropriately characterized neurotoxicity as the most sensitive noncancer health effect, but the study that EPA used to calculate its reference values had methodological deficiencies that seriously compromised its results. In calculating candidate values from several supporting neurotoxicity studies, EPA made adjustments inconsistently to address some uncertainties.

EPA should reconsider its choice of study as the basis for calculating its inhalation and oral reference values and is advised to use studies with stronger methodological designs. EPA should also review its calculations to ensure that uncertainty adjustments are justified better and applied consistently.

The Committee to Review EPA's Toxicological Assessment of Tetrachloroethylene: Sam Kacew (Chair), University of Ottawa, Ontario; **Bruce H. Alexander**, University of Minnesota School of Public Health, Minneapolis; **Margit L. Bleecker**, Center for Occupational and Environmental Neurology, Baltimore; **Gary P. Carlson**, Purdue University, West Lafayette; **Linda D. Cowan**, University of Oklahoma Health Sciences Center, Oklahoma City; **Mary E. Davis**, West Virginia University, Morgantown; **H. Christopher Frey**, North Carolina State University, Raleigh; **Joseph R. Landolph**, University of Southern California, Los Angeles; **M. E. (Bette) Meek**, University of Ottawa, Ontario; **David C. McMillan**, University of Nebraska Medical Center, Omaha; **M. Christopher Newland**, Auburn University, Auburn; **Julia Quint**, California Department of Public Health (retired), Berkeley; **Gary L. Rosner**, University of Texas M.D. Anderson Cancer Center, Houston; **Ivan Rusyn**, University of North Carolina, Chapel Hill; **Rolf Schulte-Hermann**, Medical University of Vienna, Austria; **Irvin R. Schultz**, Battelle Pacific Northwest Division, Sequim; **Robert Snyder**, Rutgers, The State University of New Jersey, Piscataway; **Robert F. White**, Boston University School of Public Health, Boston; **Luoping Zhang**, University of California, Berkeley; **Yiliang Zhu**, University of South Florida, Tampa; **Susan N. J. Martel** (Project Director), National Research Council.

The National Academies appointed the above committee of experts to address the specific task requested by the National Science Foundation. The members volunteered their time for this activity; their report is peer-reviewed and signed off by both the committee members and the National Academies. 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://nationalacademies.org/best>. Copies of *Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene* are available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; www.nap.edu.

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