Free Executive Summary

Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues

Committee on Human Health Risks of Trichloroethylene, National Research Council

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Summary

Trichloroethylene is a solvent used widely as a degreasing agent. It is a common environmental contaminant at Superfund sites and at many industry and government facilities, including certain manufacturing operations (e.g., aircraft, spacecraft). Releases to air occur primarily from degreasing operations. Trichloroethylene is also found in soils and surface water as a result of direct discharges and in groundwater due to leaching from disposal operations. Indoor air can become contaminated because of volatilization from contaminated water supplies and use of certain consumer products. Vapor intrusion through walls and floors can be a source of indoor exposure in buildings near contaminated groundwater.

To help protect the public from potential health effects caused by exposure to trichloroethylene, government agencies conduct risk assessments to develop exposure guidelines intended to restrict human contact with the chemical. This requires 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. Because several government agencies share responsibility for cleaning contaminated sites, 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 requested that the National Research Council (NRC) provide independent guidance on scientific issues related to trichloroethylene. In response to this request, the NRC convened the Committee on Human Health Risks of Trichloroethylene, which prepared this report.

THE COMMITTEE'S TASK AND APPROACH

The committee was asked to examine issues critical to developing an objective, realistic, scientifically based health risk assessment for trichloroethylene. It was asked to focus on hazard characterization and mode of action for trichloroethylene toxicity; possible approaches to synthesize epidemiologic data for characterization of hazard; human susceptibility in different subpopulations or life stages; evidence for effects from exposure to trichloroethylene alone compared with that for effects from mixtures of chemicals that include trichloroethylene; physiologically based pharmacokinetic (PBPK) modeling; dose-response assessment; and issues related to quantitative assessment of cancer and non-cancer risks. Special attention was given to the availability of appropriate data and methods to implement the committee's recommendations as well as the distinction between data analysis and data generation. The committee was asked

to distinguish between issues that can be addressed through short-term analyses and issues that are more appropriately addressed through medium- or long-term research projects. The committee was not asked to perform a risk assessment or to address risk management issues.

To accomplish its task, the committee held public data-gathering sessions to hear from the sponsoring agencies, other invited speakers, representatives from citizens' groups, and the public. The 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. Because of the extent of the scientific literature on trichloroethylene, the committee took advantage of recent compilations of information as starting points and evaluated new literature to assess how the state of knowledge has advanced.

In this report, the committee provides guidance in three major categories: hazard characterization, PBPK modeling, and dose-response assessment. The section on hazard characterization provides guidance for identifying and characterizing risks to human health. Intrinsic and extrinsic factors that could modify those risks are discussed, and attention is given to issues related to susceptibility and to mixtures containing trichloroethylene. PBPK models are reviewed, and dose-response issues related to the database on trichloroethylene are considered.

THE COMMITTEE'S EVALUATION

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.

Hazard Characterization

Synthesizing Epidemiologic Data

A large body of epidemiologic data is available on trichloroethylene and possible cancer outcomes, and quantitative analysis of the collective evidence will be the most informative for characterizing cancer hazards. Two approaches that used meta-analytic techniques were developed by Wartenberg et al. (2000),[1] whose analysis EPA used in its draft health risk assessment, and Kelsh et al. (2005),[2] who developed their analysis after EPA's assessment. The committee found several weaknesses in the techniques used in both analyses. Problems included the use of a tiered system to classify and weigh studies, separate analyses of case-control and

[1] Wartenberg, D., D. Reyner, and C.S. Scott. 2000. Trichloroethylene and cancer: Epidemiologic evidence. Environ. Health Perspect. 108(Suppl. 2):161-176.

[2] Kelsh, M.A., M. Weingart, J. Mandel, P. Mink, D. Alexander, R. Basu, R. Kalmes, and M. Goodman. 2005. A Meta-Analysis of Epidemiology Studies of Occupational TCE Exposure and Selected Cancers. Presentation by M.A. Kelsh at the Third Meeting on Assessing Human Health Risks of Trichloroethylene, June 9, 2005, Irvine, CA.

cohort studies, and the fact that these analyses did not consider identifying amounts of exposure in the studies. Another problem was the subjective assessment of quality to exclude or categorize studies. For example, Wartenberg et al. classified one study that showed a strong positive association between trichloroethylene and kidney cancer as being of the highest quality, whereas Kelsh et al. classified the same study as being of lower quality. The Kelsh et al. meta-analysis included several new studies that appear to strengthen the finding of an increased risk of kidney cancer. Because of the limitations with both analyses, the committee concludes that neither should be used for hazard characterization in the risk assessment of trichloroethylene.

Recommendations: A new meta-analysis of the epidemiologic data on trichloroethylene and cancer should be performed to support a human health risk assessment. Techniques that would improve on past analyses include the following:

- Documenting the essential design features, exposure (either qualitative or quantitative), and results of the epidemiologic studies.
- Excluding studies based on objective criteria (e.g., studies in which it was unclear that the study population was exposed [e.g., studies of dry-cleaning workers]).
- Classifying studies in terms of objective characteristics, such as on the basis of the study's design characteristics or documentation of exposure.
- Combining case-control and cohort studies in the analysis, unless it introduces substantial heterogeneity.
- Testing of heterogeneity (e.g., fixed or random effects models).
- Performing a sensitivity analysis in which each study is excluded from the analysis to determine whether any study significantly influences the findings.

Toxicity and Cancer

Trichloroethylene is metabolized in the body by two major pathways: the oxidative pathway and the glutathione-conjugation pathway. The metabolites these pathways generate are thought to be responsible for the toxicity and carcinogenicity observed in different organ systems. Key scientific issues for characterizing these hazards include identifying the metabolites responsible for the effects, elucidating the mode of action, and understanding the relevance of animal data for humans.

Kidney Toxicity and Cancer

Trichloroethylene and some of its metabolites in the glutathione-conjugation pathway have been shown to be nephrotoxic and nephrocarcinogenic. There is concordance between animal and human studies. In bioassays, rats developed tubular toxicity before they developed tumors. Investigations of nephrotoxicity in human populations show that highly exposed workers exhibit evidence of damage to the proximal tubule. The magnitude of exposure needed to produce kidney damage is not clear.

Trichloroethylene nephrotoxicity is associated with a multistep metabolic pathway. It is generally accepted that the metabolite *S*-(1,2-dichlorovinyl)-L-cysteine is the penultimate nephrotoxicant. The metabolite can undergo bioactivation by conjugation to reactive species that

are genotoxic and cytotoxic and by sulfoxidation. Sulfoxides are more potent nephrotoxicants than their parent *S*-conjugates. Both *S*-(1,2-dichlorovinyl)-L-cysteine and *S*-(1,2-dichlorovinyl)-L-cysteine sulfoxide appear to play a role in renal tubular cell toxicity.

Evidence from experimental, mechanistic, and epidemiologic studies supports the conclusion that trichloroethylene is a potential kidney carcinogen. In animal studies, the nephrocarcinogenic effects of trichloroethylene were more pronounced in male rats than in female rats and were absent in male and female mice. Studies on trichloroethylene metabolism in rodents and in humans indicate a bioactivation role in the development of nephrocarcinogenicity. This has been linked with the formation of *S*-(1,2-dichlorovinyl)-L-cysteine; however, there are no studies of the carcinogenic potential of this metabolite.

Animal studies show that trichloroethylene acts as a complete carcinogen (at the stages of both tumor initiation and promotion and progression) in a dose-dependent manner, with nephrotoxicity as the promoter for cells initiated by a trichloroethylene metabolite. It is not possible to predict whether humans are more or less susceptible to the carcinogenic effects than other animals, because species differences in the extent of formation of *S*-(1,2-dichlorovinyl)-L-cysteine have not been fully characterized. Furthermore, the cytochrome P-450 enzyme isoforms that metabolize trichloroethylene have polymorphisms within national populations, resulting in considerable interindividual differences in enzyme expression. The committee ruled out the accumulation of $\alpha_{2\mu}$-globulin, peroxisome-proliferator activated receptor α (PPARα) agonism, and formic acid production as modes of action for the production of renal tumors in rodents.

Renal clear cell carcinoma, the carcinoma most often induced by trichloroethylene, was shown to link with the homozygous inactivation of the von Hippel-Lindau (*VHL*) tumor suppressor gene. The evidence indicates a strong association between trichloroethylene and *VHL* mutation, especially in protein expression, and kidney cancer in humans. Some studies have reported increased occurrence of mutations in renal cancer cells of patients exposed to high concentrations of trichloroethylene. The genotoxic effect of trichloroethylene metabolites likely results from bioactivation pathways in the kidney leading to renal *VHL* gene damage and renal cell carcinomas. However, there remains a lack of direct evidence that alterations in the *VHL* gene initiate renal tumors, but the alterations, especially in protein expression, might contribute to tumor progression. In the absence of information on the temporal relationship between *VHL* mutations and renal tumor initiation, it is prudent to assume that trichloroethylene-induced *VHL* mutations are initiating events. Direct evidence of alterations in the *VHL* gene in association with tumor progression remains to be determined.

Liver Toxicity and Cancer

Animal data on trichloroethylene indicate that relatively high doses are needed to induce liver toxicity and cancer, even in susceptible strains of mice. The three major oxidative metabolites of trichloroethylene—trichloroacetic acid, dichloroacetic acid, and chloral hydrate—can contribute to liver toxicity and cancer in rodents. Trichloroethylene produces hepatotoxicity in experimental animals and humans that depends on generation of reactive intermediates by the enzyme cytochrome P-450 in the liver. Studies with laboratory animals indicate that trichloroethylene and its metabolites also produce liver effects independent of hepatotoxicity, including elevation in plasma bile acid concentration and accumulation of liver glycogen. The relevance and significance of these effects to humans remain to be elucidated.

Trichloroethylene, chloral hydrate, and trichloroacetic acid induce liver cancer in mice when blood concentrations achieve millimolar concentrations. In contrast, dichloroacetic acid is active in rats as well and requires a much lower concentration to produce liver tumors. Trichloroethylene and its metabolites promote liver cancer. The mode of action for trichloroacetic acid in liver is principally as a liver peroxisome proliferator and agonist of PPARα rather than as a genotoxicant. A significant lack of concordance in the sensitivity of human and rodent hepatocytes to peroxisome proliferators and early events associated with liver tumor promotion has been noted, with humans being much less sensitive. In addition, there is no supporting epidemiologic evidence of enhanced occurrence of liver tumors in humans administered potent rodent peroxisome proliferators. The weak carcinogenic activity in the liver of chloral hydrate in male $B6C3F_1$ mice combined with lower rates of oxidation and higher rates of conjugation in humans compared with mice indicate that the mode of action for mice is not relevant to humans.

Species differences in susceptibility and phenotypic differences in tumors derived from trichloroethylene and its metabolites suggest that there are mechanistic differences in the way these chemicals cause tumors that cannot be fully explained by peroxisome proliferation. In rodents, the promotional activity of dichloroacetic acid includes a significant effect on cellular metabolism and cellular proliferation that encompasses a mitogenic mode of action. Assuming a mitogenic mode of action for dichloroacetic acid as a rodent liver carcinogen, genotypic species differences between mice and humans suggest that humans would be much less susceptible to liver carcinogenesis.

Reproductive and Developmental Toxicity

Evidence from animal and epidemiologic studies suggests that several reproductive and developmental toxicity end points may be associated with trichloroethylene exposure, including infertility in males and females, impaired fetal growth, and cardiac teratogenesis. Multiple rodent studies indicate that trichloroethylene affects spermatogenesis and the fertilizing capability of sperm in males and decreased fertilizability of oocytes in females. The effects appear to depend on metabolic activation of trichloroethylene by CYP2E1, but which oxidative metabolite is the proximate toxicant remains unknown. The relevance of these effects on rodent reproduction for predicting human outcomes also is not clear.

Multiple animal studies have found decreased fetal growth after maternal exposure to trichloroethylene. Impaired fetal growth was also a consistent finding in different community studies of mothers exposed to drinking water contaminated with trichloroethylene or tetrachloroethylene, a compound that has some of the same metabolites as trichloroethylene. However, a mechanistic basis for this effect remains to be elucidated.

Multiple studies in mammalian and avian models suggest that trichloroethylene or one or more of its metabolites (trichloroacetic acid and dichloroacetic acid) can cause cardiac teratogenesis. The avian studies are the most convincing. Rodent studies have had mixed results, suggesting either methodological or strain differences. The committee noted that the low-dose studies showing a positive correlation in trichloroethylene-induced cardiac teratogenesis showed unusually flat dose-response curves and came from a single laboratory. The results need to be replicated in another laboratory to clarify the dose-response relationship.

Epidemiologic investigations of communities exposed to trichloroethylene have also reported mixed results. A 2- to 3-fold increase in risk of congenital heart defects was found in multiple studies, and the most frequently found defects were the same in animal and human studies (defects of the interventricular septae and the valves). In addition, mechanistic support is provided by studies in animals demonstrating altered proliferation in the endocardial cushions at low dose or alterations in endothelial cell activation and decreased expression of two markers of epithelial mesenchymal cell transformation, a key process in valve and septum formation. Evidence that trichloroacetic acid and dichloroacetic acid are as potent as trichloroethylene suggests that CYP2E1 metabolic activation, as well as the fractional formation of trichloroacetic acid from chloral, is important in trichloroethylene cardiac teratogenesis.

Neurotoxicity

Past evidence showed that inhalation of trichloroethylene causes neurotoxic effects in laboratory animals and humans that are similar in nature (e.g., massiter reflex latency, motor incoordination, changes in heart rate) and occur at comparable concentrations of exposure (7-16 parts per million [ppm]). New information has not added substantially to the understanding of these effects. In particular, there continue to be a lack of data for understanding the effects of chronic exposure to trichloroethylene. It is not yet possible to ascertain the extent of trichloroethylene-induced impairment of complex neurological functions such as learning, memory, and attention. Whether there is preferential vulnerability to trichloroethylene across these domains, what exposure parameters might be associated with the effects, the extent of their reversibility, and the impact of the developmental period of exposure on such effects remain to be elucidated. 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. Aging appears to enhance susceptibility of the nervous system after exposure to trichloroethylene. 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. It is well documented that the mode of action for this effect is localization of cytochrome P-450 metabolites of trichloroethylene in the Clara cells of the lungs and that pulmonary metabolism of trichloroethylene is species dependent. The proximate toxicant for the Clara cell, whether chloral, dichloracetyl chloride, or another metabolite, is still under study. 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

Among the immunotoxicity end points the committee evaluated, evidence for an effect of trichloroethylene was strongest for autoimmune disease. 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. The metabolites and the mode of action involved have not been elucidated, but a role for chloral has been implicated in mouse models. Some individuals might be genetically susceptible to developing autoimmune disease; alterations in the CYP2E1 gene are suspected to play a role.

Susceptibility Issues

Several factors can contribute to an individual's susceptibility to the toxic effects of trichloroethylene, including disease states and differences in the expression of enzymes involved in metabolizing and disposing of trichloroethylene. For example, conditions such as alcoholism, obesity, and diabetes are known to induce the expression of CYP2E1, which is the rate-limiting enzyme of trichloroethylene metabolism. However, it is not known which human enzymatic isoforms are most efficient at disposing of trichloroethylene and its metabolites. This information is critical for understanding the relevance of various common functional genetic polymorphisms already known among enzyme families involved in trichloroethylene disposition, as well as those that might be identified in the future.

How to include human variability in risk assessments is an ongoing challenge. Traditionally, an array of uncertainty factors has been used to account for human variability, particularly for vulnerable populations. More precise estimates of the risk to susceptible subpopulations can be developed with the use of PBPK modeling developed for specific types of individuals. It appears that such modeling could be developed for the fetus and child. Not enough is known about other susceptibility factors to provide quantitative estimates of how these factors affect risk.

A formalized assessment of the quantitation of the dispositional differences associated with obesity, alcoholism, and coexposures also might allow similar models to be developed to better evaluate nondevelopmental differences in susceptiblity.

Mixtures

The available data indicate that toxic effects of trichloroethylene are likely to change in the presence of exposure to other chemicals, including its metabolites and similar metabolites of other toxicants. Clear understanding of whether and which of the toxic effects might be increased, decreased, or unchanged is lacking, but it appears that the major potential mechanisms of such interactions at the biophase include altered xenobiotic metabolizing enzymes, toxicokinetic factors (absorption, distribution, and elimination), toxic metabolite accumulation in target or nontarget tissues, and toxicodynamic factors, such as cell death, cell proliferation,

expression of survival factors, and epigenetic and genotoxic mechanisms. However, to what extent and how such factors influence toxicity outcomes cannot be predicted.

There is a large database on the interaction between ethanol and trichloroethylene, where both the metabolism and the pattern of toxicity by trichloroethylene are changed. The bulk of this information is from studies of laboratory animals, but some human data suggest that this interaction can occur with consumption of alcohol. The significance of these alterations in patterns of toxicity and cancer is currently unknown.

PBPK Modeling

Several PBPK models for trichloroethylene have been developed over the past few decades. Each successive model has attempted to incorporate new information on the scientific understanding of trichloroethylene metabolism and the mode of action of toxicity. Models that have received the most recent attention are the Fisher models, the Clewell model, and a "harmonized" model. Each model has strengths and limitations, as the designers have tried to balance model complexity and uncertainty.

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.

This joint group also developed a description of the relevant uncertainties, variabilities, and errors for this modeling. Variability was described using an extension of the PBPK model to a population PBPK model. Random effects distributions in the population model formally described variability as a probability distribution. Uncertainty was characterized by taking a Bayesian perspective, where uncertainty about any unknown quantity is described as a probability distribution. The probability distribution conditional on the observed data is known as the posterior distribution. Markov chain Monte Carlo simulation was used to summarize the posterior distributions on parameters of interest. Errors in the reported numerical summaries were characterized with a standard diagnostic method. Overall, the committee found that the uncertainties, variability, and errors of the harmonized model were characterized appropriately.

None of the currently available PBPK models considers all possible routes of exposure to trichloroethylene (e.g., dermal) or dose metrics for all potential health end points (e.g., neurotoxicity, teratogenicity). The harmonized model is a reasonable extension of the Fisher and Clewell models and is the best model available, but the mode of action and appropriate dose metric for each health end point have not been established. Thus, it is appropriate to consider dose metrics generated from PBPK modeling along with other dose metrics that have been used in the past.

PBPK models do not resolve the uncertainty about the mode of action of trichloroethylene, but they can inform experimental designs for studying it. Better understanding of the mode of action of trichloroethylene will drive model elaboration.

Dose-Response Assessment

The key scientific issues related to the dose-response assessment for trichloroethylene include selecting the point of departure for low-dose extrapolation, methods for modeling from the point of departure to zero dose, and characterizing uncertainty and variability in estimates of cancer and non-cancer risk. To select the point of departure, estimates from continuous dose-response models are preferred to use of the lowest-observed-adverse-effect level (LOAEL) or the no-observed-adverse-effect level (NOAEL). It is important that criteria be established to determine whether certain toxicologic or epidemiologic data sets are suitable for modeling and that the modeling approach used be explained and justified. In the absence of modeled estimates, a LOAEL or NOAEL may be used.

For dose-response assessment 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. Several response levels (e.g., 1%, 5%, and 10%) and dose metrics are available for performing such assessments, and it is important to consider all relevant ones and to provide a clear rationale for selecting the point of departure.

There are several approaches to extrapolating from the point of departure to zero, including linear and nonlinear methods. Much emphasis has been given to incorporating mode-of-action information on the carcinogenicity of trichloroethylene in such extrapolations. However, the committee notes that information on response variability among humans is required in addition to mode of action information to clarify the shape of the low dose-response curve in humans. The mode of action for trichloroethylene as a kidney carcinogen remains unclear and likely involves multiple pathways. None of the existing epidemiologic data is suitable as a primary means of quantifying cancer risks.

Recommendations:

- Several points of departure should be considered and compared when performing point-of-departure-based dose-response assessments for cancer and non-cancer end points.
- When modeled estimates are used as points of departure in cancer and non-cancer risk assessments, it is important that (1) criteria are established for determining which data sets are suitable for modeling, (2) the selected response level is justified or multiple response levels are modeled and compared, (3) dose-response models are clearly described, (4) different dose metrics are considered and compared to assess whether the choice of metric substantially affects the dose-response assessment, and (5) when animal data are modeled, the methods for estimating human-equivalent doses are specified.
- Toxicologic data should be used to fit the primary dose-response model(s), and the available epidemiologic data should be used only for validation. Because the available information is insufficient to determine the best dose-response model for trichloroethylene, the default linear extrapolation procedure suggested in EPA's cancer guidelines can be applied but should first be explicitly defined.

RESEARCH RECOMMENDATIONS

Following are recommendations for areas of medium- to long-term study to aid the agencies in setting a research agenda to advance understanding of the human health risks from

trichloroethylene. This information will allow for more precise estimates of risk but is not necessary at this time for performing a credible risk assessment.

Kidney Toxicity and Cancer:

- Studies of the formation of *S*-(1,2-dichlorovinyl)-L-cysteine and *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine sulfoxides by human tissues (liver and kidney), the extent to which these reactions occur in vivo, the enzymes involved, and interindividual variability of these enzymes.
- Clarification of the toxicologic significance of trichloroethylene or *S*-(1,2-dichlorovinyl)-L-cysteine *S*-conjugate sulfoxidation products.
- Evaluation of the potential of missense specific mutations in the *VHL* gene contributing to tumor initiation and progression.
- Studies of nephrotoxicity in workers exposed occupationally to trichloroethylene using valid measures of exposure.
- Assessment of *VHL* gene mutations in relation to trichloroethylene exposure in populations from different geographic regions to validate the findings from existing assessments.

Liver Toxicity and Cancer:

- Elucidation of the significance of increased bile acids in relation to the hepatotoxic potential of trichloroethylene, as well as in relation to other systemic effects, and the significance of such changes in humans.
- Studies of trichloroethylene on glycogen accumulation to assess the significance of this effect and its relevance to humans.
- Determination of whether an autoimmune response might play a role in trichloroethylene-mediated liver disease.
- Determination of the metabolic pathway and yield for forming dichloroacetic acid from trichloroethylene either via trichloroacetic acid or other pathway(s).

Reproductive and Developmental Toxicity:

- Studies of trichloroethylene on sperm and oocytes and possible consequences on reproduction. Elucidation of the metabolites responsible for such effects.
- Determination of subpopulations at greatest risk as well as mechanisms for the putative gender and maternal age-based susceptibility for poor intrauterine growth.
- Evaluation of the relevant dose ranges and mode of action for trichloroethylene-induced developmental effects to determine the most appropriate species for human modeling. More information on metabolic activation in the avian model to evaluate interspecies differences, tissue-specific concentrations of trichloroethylene and its metabolites, and human data with better ascertainment of congenital heart disease and improved quantitative assessment of trichloroethylene exposures.

Neurotoxicity:

- Chronic exposure studies of the effects of trichloroethylene on the central nervous system to reduce reliance on short-term exposure data in risk assessments. Important research to pursue includes effects on functional end points, including cognitive deficits and motor and sensory function.
- Elucidation of the underlying mechanisms of trichloroethylene-induced neurotoxicity.

Immunotoxicity: Elucidation of the metabolites and modes of action by which trichloroethylene affects immunity and whether some individuals are genetically predisposed to developing autoimmune disease related to trichloroethylene exposure.

Susceptibility:

- Development of PBPK models for different physiologic stages of childhood development. Some research on children's exposure to trichloroethylene at different ages will be required to support model development (e.g., measurements of trichloroethylene metabolites in cord blood, breast milk, and meconium).
- Clarification of which human enzymatic isoforms are the most important in disposing of trichloroethylene and its metabolites.
- Better characterization of the impact of physiologic conditions and disease states on trichloroethylene toxicity.
- Evaluation of intersubject variation in pharmacodynamics across life stages and in various subpopulations is needed before pharmacodynamic factors can be quantitated in risk assessment. Before such pharmacodynamic data can be generated, the critical targets and modes of action must be clarified from animal or in vitro studies.

Mixtures:

- Toxicokinetic and toxicodynamic studies with mixtures to evaluate the effect of coexposures to other chemicals on toxic outcomes of trichloroethylene and its metabolites. Studies designed to evaluate modes of action in the presence of most commonly occurring toxicants are likely to yield more meaningful results than testing various combinations of compounds and doses.
- Testing the impact of lifestyle factors (e.g., alcohol consumption, chronic drug intake, caloric restriction), disease (e.g., diabetes), and special physiologic states (e.g., pregnancy, aging) on the toxicity of trichloroethylene.

PBPK Modeling:

- Future PBPK models for trichloroethylene risk assessment should include a description of dermal absorption.
- Studies to evaluate how well alternative dose metrics predict toxic response. PBPK models should be used to investigate alternative study designs.
- PBPK models should be developed for other toxicity end points, such as neurotoxicity and developmental outcomes. There may be little or no data available to confirm model predictions for certain tissue concentrations (e.g., brain) of trichloroethylene and metabolites in humans. However, inclusion of all relevant uncertainties can be formalized under Bayesian inference and implemented with Markov chain Monte Carlo approaches. Description of uncertainties in prior simulation might indicate that the approach is not practical without collecting additional data.
- Development of a combined PBPK model for trichloroethylene and ethanol.

Assessing the Human Health Risks of Trichloroethylene
Key Scientific Issues

Committee on Human Health Risks of Trichloroethylene

Board on Environmental Studies and Toxicology

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Preface

Trichloroethylene, an environmental contaminant, is widespread because of its extensive use as a degreasing agent, because of its use as a chemical intermediate in a variety of industries, and because of disposal practices. To help protect the public from potential health effects caused by exposure to trichloroethylene, government and state agencies perform risk assessments to develop guidelines intended to restrict the public's contact with the chemical. Such risk assessments require consideration of a wealth of scientific information on trichloroethylene. Government agencies and the scientific community have engaged in much debate over the quality of some data and how to assess the information. Because several government agencies share responsibility for cleaning up contaminated sites, an interagency group composed of the U.S. Department of Defense, the Department of Energy, the Environmental Protection Agency, and the National Aeronautics and Space Administration requested a study by the National Research Council (NRC) to provide independent guidance on scientific issues to support an objective and scientifically balanced health risk assessment for trichloroethylene.

In response to the agencies' request, the NRC convened the Committee on Human Health Risks of Trichloroethylene, which prepared this report. The members of the committee were selected for their expertise in pharmacokinetics, kidney toxicology, liver toxicology, reproductive and developmental toxicology, neurotoxicology, inhalation toxicology, immunotoxicology, carcinogenesis, epidemiology, physiologically based pharmacokinetic modeling, biostatistics, and risk assessment. Biographical information on the committee members is provided in Appendix A.

This report presents the committee's assessment of the critical scientific issues that should be addressed in any health risk assessment of trichloroethylene. The guidance is intended to help agencies characterize the hazards from trichloroethylene. The committee also provides guidance on the development of physiologically based pharmacokinetic modeling, dose-response assessments, and other factors to consider in performing quantitative risk assessments of cancer and non-cancer risks from trichloroethylene.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following

individuals for their review of this report: Adnan Elfarra, University of Wisconsin at Madison; Jeffrey Fisher, University of Georgia; Poh-Gek Forkert, Queen's University; James Gnarra, Louisiana State University School of Medicine; David Hoel, Medical University of South Carolina; James Klaunig, Indiana University School of Medicine; Jeffrey Larson, Tanox, Inc.; Richard Miller, University of Rochester; K. Michael Pollard, The Scripps Research Institute; Martha Sandy, California Environmental Protection Agency; and William Valentine, Vanderbilt University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Sam Kacew, University of Ottawa, and John C. Bailar, University of Chicago. Appointed by the NRC, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the individuals who made presentations to the committee at its public meetings. A list of those individuals is provided in Appendix B. The committee also thanks Richard Canady, who was with the U.S. Office of Science and Technology Policy during the first half of the study, for coordinating the committee's interactions with the interagency sponsors, facilitating responses to data requests, and providing background information.

The committee is grateful for the assistance of NRC staff in preparing the report. It particularly wishes to acknowledge the outstanding support from project director Susan Martel, who coordinated the project and contributed to the committee's report. Other staff members who contributed to this effort are James Reisa, director of the Board on Environmental Studies and Toxicology; Mirsada Karalic-Loncarevic, research associate; and Tamara Dawson, senior program assistant.

Finally, I would like to thank all the members of the committee for their efforts throughout the development of this report.

Rogene Henderson, Ph.D.
Chair, Committee on Human Health Risks of Trichloroethylene

Contents

Assessing the Human Health Risks of Trichloroethylene
Key Scientific Issues