UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
THE ADMINISTRATOR

EPA-SAB-EHC-91-013

August 16, 1991

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of the Office of Research and Development draft document Response to Issues and Data Submissions on The Carcinogenicity of Tetrachloroethylene (Perchloroethylene," EPA/600/6-91/1002A, dated February 1991

Dear Mr. Reil

On February 22, 1991, EPA's Office of Health and Environmental Assessment (OHEA) (a component of the Office of Research and Development) asked the Science Advisory Board (SAB) to review the above-referenced draft document. OHEA wished to revisit issues and data concerning the identification of hazard, i.e., the weight of the animal evidence bearing on the potential for human carcinogenicity of perchloroethylene (hereafter referred to as "perc" or "PCE"), as well as other issues (noted below). Data have been submitted and issues raised in public comment connected with a variety of recent Agency rule-making actions, including action by the Agency's Office of Drinking Water.

Recently-generated laboratory data have led to the development of hypotheses about the mechanisms of perc tumorigenesis, but the data are still equivocal as to the relevancy of these hypotheses for human carcinogenesis. Consequently, the Agency decided to seek a new review by the SAB. In general terms, OHEA requested that the Board review the technical adequacy of discussions concerning the animal cancer data and related ancillary information, such as mutagenicity and metabolism, and the relationship of this information base to a hazard classification of PCE under the Agency's current cancer guidelines. The Environmental Health Committee met in Bethesda, Maryland, on March 26, 1991 to receive briefings from Agency officials and the public, and to discuss specific issues as the initial step in the preparation of a report.

The SAB last reviewed perc-related issues in late 1987. The Board's findings, summarized in a letter to the Administrator (March 9, 1988), were that the overall weight-of-evidence positions perc on the continuum between categories B2 and C.

It is the Committee's view that the major issues arising from the assessment of perc have not changed over the past four years, and that SAB's previous response remains appropriate. The available scientific evidence confirms that perchloroethylene should be considered as an animal carcinogen, based on three endpoints in two species: liver tumors in male and female mice, kidney tumors in male rats, and, possibly, mononuclear cell leukemia in male and female rats. Complications within each study and in their biological interpretations have made it difficult to categorize this compound. We do not consider the evidence strong enough to classify this compound as a probable human carcinogen (i.e., B2); on the other hand, the evidence for carcinogenicity is stronger than for most other compounds classified as possible human carcinogens (i.e., C). Therefore, in the spirit of the flexibility encouraged by the Guidelines, our best judgment places this compound on a continuum between these two categories.

The SAB Executive Committee (EC) examined this conclusion at their July 23 meeting. In particular, they discussed a concern of one Member that the EHC report arrived at a B2-to-C classification by "telescoping" the two-step qualitative and quantitative risk assessment process into one, contrary to typical EPA and International Agency for Research on Cancer (IARC) practice. However, both the EC and the EHC are aware that qualitative weight-of-evidence decisions made by the Agency have risk management impacts beyond EPA. Therefore, while risk management decisions are generally beyond the purview of the SAB, we feel that it is important to be as precise as possible about our views on the classification of this chemical, independent of quantitative considerations. In this case, that has meant moving beyond the current classification system, which albeit simplistic, is useful in dealing with the majority of chemicals.

Perchloroethylene, however, is an example of a chemical for which there is no compelling evidence of human cancer risk, but for which reductions in unnecessary human exposure might well be prudent. The available scientific information does not suggest to us the same regulatory responses that would be appropriate for a chemical whose bioassay responses were clearly relevant to human cancer.

The SAB is sensitive to the concerns of some that its recommended classification may appear to place perc beyond the reach of regulation, but does not see this classification as a retreat from public health concerns. As we noted to then-Administrator Thomas in a 1988 dialogue on perc, "... the distinction between the B2 and C categories can be an arbitrary distinction on a continuum of weight-of-evidence... From a scientific point of view, it seems inappropriate for EPA and other agencies to regulate substances that are classified B2 and not to consider regulations of compounds classified as C, regardless of the level of human exposure... A substance classified as C (limited evidence in animals) for which human exposure is high may represent a much greater threat to human health."

We recommend that the Agency continue its risk assessment effort on perchloroethylene, not only to improve the risk management for this widely-used solvent, but to serve as a model for addressing other chemicals that present similar ambiguities of interpretation. It would be especially helpful for future evaluations of such chemicals if the Agency focused on the implications of recent findings concerning perc for the assessment of dose-response. The quantitative assessment of the risk should include careful evaluation of the relevance of the animal endpoints to humans, including species differences, the pharmacokinetics of delivered dose to target organs and metabolite formation, and mechanistic information such as effects on cell proliferation. To the extent that such information suggests a departure from low-dose linearity, as assumed in the linearized multistage model used by EPA as the default procedure for dose-response assessment, appropriate alternative dose-response models should be used to explore the implications of available scientific information for human cancer risk.

The greatest gap in our knowledge arises from the absence of interpretable epidemiological data. The Agency should work with the relevant industries and other institutions to assure that further research on the human health risks of exposure to perchloroethylene is vigorously pursued.

The Science Advisory Board is pleased to have had the opportunity to review the draft document and to offer its advice. We would appreciate your response to the major points we have raised, particularly with regard to our position on flexibility in interpreting the current guidelines.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Bernard Weiss

Dr. Bernard Weiss, Acting Chairman
Environmental Health Committee

ENCLOSURE

United States
Environmental
Protection Agency

Science Advisory
Board (A-101)

EPA-SAB-EHC-91-013
August 1991

EPA

HEALTH EFFECTS ASSESSMENT OF PERCHLOROETHYLENE

REVIEW OF THE OFFICE OF RESEARCH AND DEVELOPMENT'S DRAFT DOCUMENT: "RESPONSE TO ISSUES AND DATA SUBMISSIONS ON THE CARCINOGENICITY OF PERCHLOROETHYLENE (EPA/600/6-91/002A) BY THE ENVIRONMENTAL HEALTH COMMITTEE

ABSTRACT

On March 26, 1991, EPA's Science Advisory Board (SAB) reviewed the draft Office of Health and Environmental Assessment (OHEA) document "Response to Issues and Data Submissions on The Carcinogenicity of Tetrachloroethylene (Perchloroethylene)," EPA/600/6-91/1002A, dated February 1991. The Board reviewed the technical adequacy of discussions concerning animal cancer data and related ancillary information, such as mutagenicity and metabolism, and the relationship of this information base to a hazard classification of PCE under the Agency's current cancer assessment guidelines.

It is the Committee's view that the major issues arising from the assessment of perchloroethylene (perc) have not changed over the past four years, and that SAB's previous response (SAB-EHC-87-018, January 1987) remains appropriate. The available scientific evidence confirms that perchloroethylene should be considered as an animal carcinogen, based on three endpoints in two species: liver tumors in male and female mice, kidney tumors in male rats, and, possibly, mononuclear cell leukemia in male and female rats. However, each of these endpoints is problematic with respect to its relevance for human cancer. The Committee found that the evidence does not warrant designation of perc as a probable human carcinogen, but noted that the evidence for carcinogenicity is stronger than for most other compounds classified as possible human carcinogens. Therefore, in the spirit of the flexibility encouraged by the Guidelines, the Committee places this compound on a continuum between these two categories.

Further research, particularly on the epidemiology of human occupational exposure, is recommended.

KEYWORDS:carcinogen; alpha-2u-globulin; peroxisome proliferation; carcinogen assessment guidelines; perchloroethylene; perc; PCE; liver tumors; mononuclear cell leukemia.

U. S. ENVIRONMENTAL PROTECTION AGENCY

NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
ENVIRONMENTAL HEALTH COMMITTEE

Perchloroethylene Review Panel

ACTING CHAIRMAN

Dr. Bernard Weiss, University of Rochester School of Medicine

MEMBERS & CONSULTANTS

Dr. Gary Carlson, School of Pharmacy, Purdue University

Dr. David Gaylor, National Center for Toxicological Research, Department of Health & Human Services

Dr. Michael A. Gallo, Department of Environmental and Community Medicine, UMDNJ-Robert Wood Johnson Medical School

Dr. Richard A. Griesemer, National Institute of Environmental Health Sciences

Dr. Joe H. Grisham, School of Medicine, University of North Carolina

Dr. Marshall Johnson, Jefferson Medical College

Dr. Nancy K. Kim, New York Department of Health

Dr. D. Warner North, Decision Focus Inc.

Dr. Martha J. Radike, Medical Center, University of Cincinnati

Dr. Stephen M. Rappaport, School of Public Health, University of North Carolina

Dr. Thomas S. Wallsten, University of North Carolina

Dr. Ronald Wyzga, Electric Power Research Institute

SCIENCE ADVISORY BOARD STAFF

Mr. Samuel Rondberg, Designated Federal Official, Environmental Health Committee Science Advisory Board, U.S. Environmental Protection Agency

Ms. Mary L. Winston, Staff Secretary, Environmental Health Committee, Science Advisory Board

Mr. A. Robert Flaak, Assistant Staff Director, Science Advisory Board

Dr. Donald G. Barnes, Staff Director, Science Advisory Board

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

It is the Committee's view that the major issues arising from the assessment of perchloroethylene (perc) have not changed over the past four years, and that SAB's previous response (SAB-EHC-87-018) remains appropriate. The available scientific evidence confirms that perchloroethylene should be considered as an animal carcinogen, based on three endpoints in two species: liver tumors in male and female mice, kidney tumors in male rats, and, possibly, mononuclear cell leukemia in male and female rats. However, each of these endpoints is problematic with respect to its relevance for human cancer. It is the Committee's judgment that the evidence does not warrant designation of perc as a probable human carcinogen; note however, that the evidence for carcinogenicity is stronger than for most other compounds classified as possible human carcinogens. Therefore, in the spirit of the flexibility encouraged by the Guidelines, our best judgment places this compound on a continuum between these two categories.

Perchloroethylene is typical of a widely used and economically important chemical for which there is no compelling evidence of human cancer risk. Reductions in unnecessary human exposure might well be prudent, but the available scientific information does not mandate the same regulatory actions that would be appropriate if the bioassay responses were clearly relevant to human cancer.

The Committee is sensitive to concerns that its recommended classification may seem, to some observers, to place perc beyond the reach of regulation, but does not see its classification as a retreat from public health concerns. We are convinced that it will stimulate further research (see below), and ultimately, lead to risk estimates that are sufficiently precise and dependable to offer a sound basis for risk management by EPA. In addition, as noted by the SAB in a 1988 letter on perc to then-Administrator Thomas, "From a scientific point of view, it seems inappropriate for EPA and other agencies to regulate substances that are classified B2 and not to consider regulations of compounds classified as C, regardless of the level of human exposure... A substance classified as C (limited evidence in animals) for which human exposure is high may represent a much greater threat to human health."

We recommend that the Agency continue its risk assessment effort on perchloroethylene in order to improve the risk management for this widely-used solvent. The Agency should produce a comprehensive health assessment update document summarizing recent findings and their implications for assessment of dose- response. The quantitative assessment of the risk should include careful evaluation of the relevance of the animal endpoints to humans, including species differences, the pharmacokinetics of delivered

dose to target organs and metabolite formation, and mechanistic information such as effects on cell proliferation. To the extent that such information suggests a departure from low-dose linearity as assumed in the linearized multistage model used by EPA as the default procedure for dose-response assessment, appropriate alternative dose-response models should be used to explore the implications of available scientific information for human cancer risk.

Continued research to resolve uncertainty in the health effects of perc is highly desirable, particularly in the area of epidemiological data. The Agency should work with the relevant industries and other institutions to assure that further research on the human health risks of perchloroethylene is vigorously pursued.

2. INTRODUCTION

2.1 Background

On February 22, 1991, EPA's Office of Health and Environmental Assessment (OHEA) (a component of the Office of Research and Development) asked the Science Advisory Board (SAB) to review the draft document *Response to Issues and Data Submissions on The Carcinogenicity of Tetrachloroethylene (Perchloroethylene)*, EPA/600/6-91/1002A, dated February 1991. OHEA wished to revisit issues and review data concerning the identification of hazard, i.e., the weight of the animal evidence bearing on the potential for human carcinogenicity of perchloroethylene (hereafter referred to as "perc" or "PCE"). Data have been submitted and issues raised in public comment connected with a variety of recent Agency rule-making actions, including action by the Agency's Office of Drinking Water. In general terms, OHEA requested that the Board review the technical adequacy of discussions concerning the animal cancer data and related ancillary information, such as mutagenicity and metabolism, and the relationship of this information base to a hazard classification of PCE under the Agency's current cancer guidelines.

The subject of a potential cancer hazard from PCE is not a new one in terms of past Science Advisory Board /EPA dialogue. The most recent exchange was a letter of advice, dated March 9, 1988, from the Board to the Administrator regarding the Board's perspectives on this topic; prior to that, in 1986, the Board reviewed a draft addendum to the Health Assessment for perc, and provided a report (SAB-EHC-87-018, January 1987) to (then) Administrator Thomas. Since the 1988 interchange, the Agency has continued to conduct research and to gather data on perc. Recently-generated laboratory data have led to the development of hypotheses about the mechanisms of perc tumorigenesis, but the data are still equivocal as to the relevancy of these hypotheses for human carcinogenesis. Consequently, the Agency decided to seek a new review by the SAB, the SAB accepted the request, and the Environmental Health Committee met in Bethesda, Maryland, on March 26, 1991 to receive briefings from Agency officials and the public, and to discuss the specific issues (see below) as the initial step in the preparation of a report.

2.2 Charge To The Committee

The "Response to Issues..." document provided to the Committee for review has a relatively narrow purpose (as noted in its Introduction), compared to the more typical comprehensive health assessment document that the Committee usually reviews for OHEA. OHEA's primary objective for the SAB review of the document was to revisit issues and review data concerning the weight of the animal evidence bearing on the

potential for human carcinogenicity. An earlier version of this response document is currently in the docket for the recently promulgated National Primary Drinking Water Standard for Tetrachloroethylene as published in the Federal Register on January 30, 1991.

In general terms, OHEA requested that the Committee review the technical adequacy of discussions in their document concerning the animal cancer data and related ancillary information, such as mutagenicity and metabolism, and the relationship of this information base to a hazard classification of PCE under the Agency's current cancer guidelines.[1] More specifically, the Committee was requested to focus on the topics and questions listed below.

a. Technical adequacy of discussions about the three animal bioassay tumor endpoints,particularly regarding the relevance of these tumor endpoints to the potential for human hazard at some dose.

b. Technical adequacy of discussions about ancillary information for mutagenicity and metabolism considerations and the appropriate use of this information in providing a better understanding of the animal bioassays or the relevance of these to the potential for human hazard.

c. Have all important issues been identified and appropriately considered, recognizing that many more fundamental scientific questions may exist but which may not be developed adequately to meaningfully discuss in a risk assessment context?

d. The soundness of the rationale used to weigh the evidence, from each endpoint and in the aggregate for human hazard potential. This topic relates to the logic of weighing animal evidence including the relevance of ancillary data to that process.

[1] It is important to note that the concept of "weight-of-evidence" under EPA's Cancer Risk Assessment Guideline identifies an agent's potential to be a human hazard. Questions about the quantitative relationship of dose to response and mechanisms of action that affect this relationship are dealt with as a separate quantitative dose-response assessment which typically follows the hazard identification part of a comprehensive assessment. The quantitative dose-response relationships for tetrachloroethylene need to be revisited, as noted in the response document, and OHEA will be doing so in the future.

3. SPECIFIC FINDINGS

3.1 Classification of Perc

3.1.1 Classification Issues

There are two issues associated with the classification of perc and other potentially carcinogenic compounds. First of all, any scheme used for such classification must be flexible and cannot escape the need for the introduction of scientific judgment into any specific determination. Secondly, risk management actions are often predicated upon a chemical's classification status. Other decision criteria, such as the extent of potential exposures, may be more important or equally important in determining risk management strategies, and these should be factored into risk management decisions.

One objective of the hazard identification step of risk assessment is to assess the likelihood that a compound is a potential human carcinogen. The hazard identification step was defined in the National Academy of Sciences 1983 report, *Risk Assessment in the Federal Government: Managing the Process*, as

> *... the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition (cancer, birth defect, etc.). It involves characterizing the nature and strength of the evidence of causation. Although the question of whether a substance causes cancer or other adverse health effects is theoretically a yes/no question, there are few chemicals on which the human data are definitive. Therefore, the question is often restated in terms of effects in laboratory animals or other test systems, e.g.,"Does the agent induce cancer in test animals?" Positive answers to such questions are typically taken as evidence that an agent may pose a cancer risk for any exposed humans. (p. 19)*

The current Agency *Guidelines for Carcinogen Risk Assessment* (EPA/600/8-87/045) state that:

> *The ... hazard identification part of risk assessment contains a review of the relevant biological and chemical information bearing on whether or not an agent may pose a carcinogenic hazard. (Federal Register, 51:33994 (1986))*

EPA's Guidelines stress that the following information should be reviewed as part of the hazard identification process:

a. physical-chemical properties and routes and patterns of exposure
b. structure-activity relationships
c. metabolic and pharmacokinetic properties
d. toxicologic effects
e. short-term tests
f. long-term animal studies.
g. human evidence

We agree fully with this position that hazard identification should include a broad review of relevant biological and chemical information. We are concerned that Agency practice tends to weight the results from long-term animal studies most heavily and at times appears to ignore the other available information.

The current Guidelines also indicate that for long-term animal studies, "Carcinogenic responses under conditions of the experiment should be reviewed carefully as they relate to the relevance of the evidence to human carcinogenic risks." They further state, "Judgments about the weight-of-evidence involve considerations of the quality and adequacy of the data and the kinds and consistency of responses induced by a suspect carcinogen."

These Guidelines recommend the evaluation of all available evidence and imply that considerable judgment is required within the hazard identification component of risk assessment. The portion of the Guidelines responding to public and Science Advisory Board comments devotes a whole section to mouse liver tumors and the need for judgment in interpreting this endpoint. Rat mononuclear cell leukemia and male rat kidney tumors involving the alpha-2-microglobulin mechanism are other endpoints for which judgment is required to assess the relevance for human cancer risk.

3.1.2 Data for Classification

In the case of perchloroethylene the Environmental Health Committee reviewed the available information and examined in detail the characteristics of the various long-term animal studies. Complications within each study and in their biological interpretations have made it difficult to categorize this compound. We do not consider the evidence strong enough to classify this compound as a probable human carcinogen (i.e., B2); on the other hand, the evidence for carcinogenicity is stronger than for most other compounds classified as possible human carcinogens (i.e., C). Therefore, in the spirit of the flexibility encouraged by the Guidelines, our best judgment places this compound on a continuum between these two categories.

3.1.3 Further Issues re Classification

This experience with perchloroethylene suggests that when the *Guidelines* are revised, their flexibility should be endorsed and strengthened, and that exceptions to a strict categorization are a practical necessity. It is particularly important to convey any uncertainty or deviation from a strict categorization scheme because many risk management practices are narrowly tied to the category in which a compound is placed. The SAB is uncomfortable with this practice and believes that deviations from a strict categorization scheme are appropriate and can help to convey a better sense of the scientific weight-of-evidence and associated uncertainties to risk managers.

In his letter of August 3, 1987 to the Science Advisory Board, requesting a reevaluation of the classification of perchloroethylene, Administrator Lee Thomas also expressed concern about the linkage between weight-of-evidence categorization and risk management practice by EPA and other regulatory agencies:

> *It is important to understand that a decision on the classification of any compound under the cancer guidelines is not an EPA decision to regulate that compound; however, it does weigh heavily on the type or extent of the possible regulation, especially under certain environmental statutes. A decision to regulate a compound represents a statement of potential hazard in the absence of other factors such as exposure. A regulatory decision by EPA on whether to control the sources of a specific compound, and the degree of control must necessarily weight hazard, potency, exposure and other factors. It is clear, however, that EPA's classification of a compound has major ramifications beyond its use in EPA's own decision making process. Rightly or wrongly, state environmental decisions and public perceptions of risk are often triggered by an EPA determination to classify a compound as a B2 carcinogen. This black-white interpretation of the classification system is troubling.*

As noted earlier, the Science Advisory Board carried out further review of perchloroethylene and responded to the Administrator with a letter report dated March 9, 1988. The Board provided its advice on hazard identification and weight-of-evidence classification of perchloroethylene in responding to the second of three specific questions. This question and SAB's response were as follows:

Question 2. What is the Board's view of the approach taken by EPA in using its guidelines to infer human carcinogenic potential from the total body of scientific evidence on perchloroethylene?

SAB Response. The issues regarding the application of the risk assessment guidelines appear not to represent disagreement among scientists about scientific evidence but, rather, the consequence of attempting to fit the weights of evidence into necessarily arbitrary categories of risk. Since the weights of evidence, and uncertainties associated with such evidence, for perchloroethylene and other compounds fall within a range of scientifically defensible choice, it may not be possible, in some instances, to fit them neatly into only one risk category. Moreover, the more incomplete the data, the less precision one can expect in classifying a compound within EPA's cancer guidelines. In addition, the type of evidence that places a compound in a particular category may vary considerably from substance to substance within that category. For perchloroethylene, as with trichloroethylene, the Science Advisory Board concludes that the overall weight of evidence lies on the continuum between the categories B2 and C of EPA's risk assessment guidelines for cancer.

As perchloroethylene illustrates, the distinction between the B2 and C categories can be an arbitrary distinction on a continuum of weight of evidence. The "black-white interpretation" that you referred to in your letter is indeed troubling. From a scientific point of view, it seems inappropriate for EPA and other agencies to regulate substances that are classified B2 and not to consider regulations of compounds classified as C, regardless of the level of human exposure. In the case of B2, B1, or even A category compounds where exposure levels are low, EPA may, with scientific justification, decline to regulate because the potential health effects appear to be trivial in magnitude. A substance classified as C (limited evidence in animals) for which human exposure is high may represent a much greater threat to human health.

EPA and other agencies (including those in state governments) may, therefore, wish to take steps to reduce high exposures to substances in the C category whenever there appears to be a potentially significant threat to human health (in the sense that the plausible upper bound estimate of potency times lifetime exposure is above the threshold where

regulation may be judged appropriate). Indoor exposure to perchloroethylene, such as might be found in dry cleaning establishments not using the equivalent of good industrial hygiene practices, could merit action under this criterion. So might high levels of exposure to other solvents, pesticides, or industrial chemicals that have been considered by the public as "safe" in the absence of sufficient evidence of carcinogenicity in animals. In many instances, this appearance of safety results from not yet having the results from well-designed bioassays such as those conducted by the National Toxicology Program.

3.2 Peroxisome Proliferation and Perchloroethylene

The EPA document on perc has an excellent section on the possible role of peroxisome proliferation in mouse liver tumorigenesis. The rationale that perc's major metabolite, trichloroacetic acid (TCA), may be involved is supported by the data being generated within EPA by DeAngelo and co-workers (1989). The rationalizations that the higher rate of metabolism in mice (compared to humans) and the ability of this pathway to become saturated lend support to the belief that it is unlikely that humans would metabolize perchloroethylene to trichloroacetic acid in sufficient quantities to cause liver tumors. While this concept of a threshold may be difficult for EPA to accept from a regulatory perspective, it has been used in its scientific publication for dichloroacetic acid (DeAngelo et al., 1991). The document also does a credible job in emphasizing that even under in vitro conditions, hepatocytes from mice are more sensitive to perchloroethylene than are those from rats or humans (albeit from limited data). The argument is made that, if peroxisome proliferation and carcinogenicity are causally linked, then there should be a better correlation between the activity of compounds as peroxisomal proliferators and their efficacy as hepatocarcinogens. While it would be gratifying to be able to make such a simple comparison, it tends to ignore other effects that these compounds may have such as cytotoxicity. The additional question of genotoxicity independent of peroxisomal proliferation is an important one. However, results presented at the Committee meeting suggest that the positive effects reported for single-strand breaks in DNA must be approached with caution since they may not be repeatable or may be re-lated to some protocol variation which needs verification. Although there is some discussion (pages 26 and 27 of the draft "response" document) of the relevance of peroxisome proliferation in humans to tumor formation in a generic sense, the Committee recommends that the EPA take a much closer and more thorough look at this generic issue since its resolution applies to many substances other than perc, and to more than issues of classification. In this regard, since the problem also applies to a number of drugs, it

may be advantageous to evaluate the approach taken by the FDA in dealing with peroxisome proliferators.

In addition, the Committee recommends that EPA should initiate or continue research efforts in two areas. One is the question of whether or not TCA has direct effects on DNA. The Agency should try to resolve discrepancies that now exist in the literature. The second is to continue to evaluate the role of peroxisomal proliferation in tumorigenesis. A great many studies are currently underway throughout the world which may provide information useful in evaluating this relationship.

3.3 Alpha-2-u Globulin

Exposure to perc is associated with an increased incidence of kidney tumors, but only in male rats. Similar results have been obtained with other agents, such as unleaded gasoline. The specificity of this outcome has stimulated considerable investigation. The mechanism most clearly identified begins with the binding of the chemical to alpha-2u-globulin, a protein synthesized by male rats, predominantly in the liver. Alpha-2-u-globulin accounts for about 30% of total urinary protein excreted by male rats, but its function remains undetermined.

Chronic exposure to perc, gasoline, and the other chemicals inducing male rat kidney tumors leads to a syndrome termed hyaline droplet nephropathy (hyaline droplet is a descriptive term for intercellular vacuoles containing amorphous material by light microscopy), prior to the development of tumors. Hyaline droplet nephropathy, which is virtually unique to the male rat, histologically features an accumulation of protein droplets (now known to represent alpha-2u-globulin) in the lysosomes of proximal tubule epithelial cells. Chemically modified alpha-2u-globulin accumulates apparently because the chemical-alpha-2u-globulin complex is less easily hydrolyzed (and more slowly excreted) than is the unbound protein. Accumulation of the protein droplets is correlated with increased cell turnover and the production of tumors, which appear to be triggered by increased cell proliferation, and not by direct genotoxicity from perc exposure.

Although proteins belonging to the alpha-2u-globulin protein superfamily are found in other species, including humans, the narrow specificity of the renal tumor-protein accumulation in male rats indicates a questionable relevance to human susceptibility, which should be carefully evaluated in risk classification. The "Response to Issues..." document notes the data implicating such accumulation and its consequences, but

also argues that events independent of this process play a role, perhaps the predominant role, in the perc carcinogenetic response.

The Committee urges EPA to explore further its argument that perc carcinogenicity is independent of the process described above, consulting with investigators actively engaged in alpha-2u-globulin research to determine how the discrepant views might be reconciled.

3.4 Epidemiological Data and Issues

There are few epidemiological data addressing perc. Brown and Kaplan (1987) conducted a retrospective cohort mortality study of 1690 workers employed in the dry cleaning industry. In their study, there appears to be an increase in mortality from cancer of the intestine and cancer of the urinary bladder with increasing time since first employment in dry cleaning shops using perc. Also, mortality from cancer of the intestine and cancer of the bladder appear to increase with length of employment. Since dry cleaning workers may be exposed to other petroleum solvents, these effects cannot be attributed solely to perc, and there does not appear to be adequate evidence to establish perc as a human carcinogen.

3.5 Tumor Responses to Perchloroethylene

Three putative tumor responses to perc were reviewed--mononuclear cell leukemia in F344/N rats, renal tumors in male rats, and hepatocellular tumors in both sexes of mice.

The evidence for mononuclear cell leukemias in F344/N rats, one of three putative tumor responses to perc exposure (along with renal tumors in male rats and hepatocellular tumors in male and female mice) now seems to be somewhat weaker than in the 1987 SAB review, because the incidence of leukemia in control rats was considerably higher in the cited National Toxicology Program (NTP) study (TR 311, 1986) than expected on the basis of NTP historic data (See Table 1, following). The consistently higher control rates of this tumor type in the study laboratory, coupled with widely variable incidence (in comparison with other NTP laboratories) weakens the significance of the findings. The findings cannot be disregarded, however.

Renal tumors in male rats have been consistently associated with exposure to chlorinated hydrocarbons. The incidence from exposure to perc was not greatly elevated (P value of 0.07) but such tumors are uncommon in control rats and included

	CONTROL MALES	CONTROL FEMALES
OBSERVED	56%	36%
EXPECTED IN THE LABORATORY	47% ±15%	29% ±6%
EXPECTED IN NTP STUDIES	29% ±12%	12% ±7%

Table I INCIDENCE OF LEUKEMIA IN F344/N RATS (NTP STUDY TR 311, 1986)

two carcinomas (4%) in the high dose group which were not found in untreated control rats. A possible association with alpha-2u-globulin hyaline droplet nephropathy was discounted. Although hyaline droplets were reported to be found after exposure to 1,000 ppm for 28 days by inhalation, no hyaline droplets were found at the carcinogenic doses of 200 and 400 ppm. For these reasons the evidence for renal tumors was judged to be stronger than in the previous review; it must be noted, however, that the failure to observe hyaline droplets may be due to the lack of sensitivity of the crude method used to detect droplets. At the same time, more evidence has accumulated to strengthen the alpha-2u-globulin argument.

Hepatocellular tumors with greatly exaggerated responses were found in male and female mice in two studies by inhalation and oral routes of exposure (NCI, 1977 and NTP, 1986). The possibility of association with peroxisome proliferation, (which was the best hypothesis in 1986) is now less certain. Peroxisome proliferation is not dose-related, and other mechanisms, including mediation through recently identified peroxisome receptors, are possible. It was concluded that the evidence for hepatocellular tumors in mice is still strong.

In summary, the available evidence indicates that exposure to tetrachloroethylene results in hepatic tumors in male and female mice, renal tumors in male rats, and, equivocally, in mononuclear cell leukemia in male and female rats.

3.6 Developmental Effects of Perchloroethylene

The relevant issues regarding perchloroethylene do not involve reproductive or developmental concerns. Moreover, unlike the assumptions that govern carcinogenicity, developmental and reproductive toxicity evaluation assumes that there are

exposures below which no detectable adverse effects are anticipated. Perc has not been adequately tested, but, thus far, has not demonstrated the reproductive system or its support organs to be a primary target. It is among that group of chemicals that apparently have little if any propensity to produce terata.

Schwetz et al. (1975) exposed pregnant rats and mice to 300 ppm of perc for 7 hours a day from days 7-15 of pregnancy, and made standard evaluations of the term fetuses. No frank congenital malformations were produced by this protocol, although, some mouse fetuses were small for gestational age.

Nelson et al. (1980) exposed pregnant rats to 900 ppm perc for 7 hours a day from days 7-13, as well as to 100 ppm on days 14-20 of pregnancy. Clear maternal toxicity was evident at 900 ppm. Postnatal sensory, motor, and behavioral measurements of the offspring were made. No consistent postnatal effects were evident, although brain acetylcholine levels were reduced in the young of 900 ppm treated mothers at weaning. No effects were reported in mothers or offspring at the 100 ppm exposure level.

No useful human epidemiological studies of the effects of perc exposure during gestation were located. Also, apparently absent from the published literature, are studies examining effects of perc specifically on either male or female reproductive performance. The topics of reproductive and developmental toxicity quite properly were not a focus of the EPA's issues for review, and were not addressed in the draft response document, in that adult systemic target organ toxicity is the real issue. Addressing reproduction and development in the document, at least in passing, would be useful to complete the picture, and, particularly, in view of the large data gaps, the undetermined No Observed Adverse Effects Level (NOAEL) for some aspects of development, and significant human exposure potential. Perc should not be listed as a teratogen at any level of exposure yet studied.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions

Based on our review of EPA's draft issue paper, *Response to Issues and Data Submissions on the Carcinogenicity of Tetrachloroethylene (Perchloroethylene)* EPA/600/6-91/002A, and the discussion at the public meeting March 26, 1991, we believe that the major issue has not changed over the past four years, and that SAB's previous response remains appropriate. The scientific evidence that has emerged over the past four years has confirmed that perchloroethylene should be considered as an animal carcinogen based on three endpoints in two species: liver tumors in male and female mice, rat kidney tumors in male rats, and, possibly, mononuclear cell leukemia in rats. Each of these endpoints is problematic with respect to its relevance for human cancer. It is the Committee's judgment that the evidence does not warrant designation of perchloroethylene as a probable human carcinogen, with the implication that such a designation carries for federal and state regulation.

Perchloroethylene is a prototype of a widely used and economically important chemical for which there is no compelling evidence of human cancer risk, accompanied by animal data of carcinogenicity whose extrapolation to humans is ambiguous. Such situations may occur with some frequency, and they should not cause paralysis in regulatory action. For such chemicals, pollution prevention and reductions in unnecessary human exposure could be prudent measures to take now to safeguard public health. However, at this time the available scientific information does not mandate the same regulatory actions as would be appropriate if the bioassay responses were clearly relevant to human cancer.

We wish to note here that the Committee is sensitive to concerns that its recommended classification may seem, to some observers, to place perc beyond the reach of regulation. As we noted to then-Administrator Thomas in a 1988 dialogue on perc, "... the distinction between the B2 and C categories can be an arbitrary distinction on a continuum of weight of evidence.... From a scientific point of view, it seems inappropriate for EPA and other agencies to regulate substances that are classified B2 and not to consider regulations of compounds classified as C, regardless of the level of human exposure... A substance classified as C (limited evidence in animals) for which human exposure is high may represent a much greater threat to human health."

The Committee's mandate, however, is to provide objective scientific advice; risk management is the Agency's function and domain. In light of the above comments,

the Committee does not believe that its classification is a retreat from public health concerns. On the contrary, it is convinced that it will stimulate further research (see below), and ultimately, lead to risk estimates that are sufficiently precise and dependable to offer a sound basis for risk management

4.2 Recommendations

We recommend that the Agency continue its risk assessment effort on perchloroethylene in support of risk management for this widely-used solvent. The Agency should produce a comprehensive health assessment update document that summarizes recent additions to scientific knowledge and their implications for evaluation of dose-response. The quantitative assessment of the risk should include careful assessment of the relevance of the animal endpoints to humans, including species differences, the pharmacokinetics of delivered dose to target organs and metabolite formation, and mechanistic information such as the effects of cell proliferation. To the extent that such information suggests a departure from low-dose linearity as assumed in the linearized multistage model used by EPA as the default procedure for dose-response assessment, appropriate alternative dose-response models should be used to explore the implications of available scientific information for human cancer risk.

The extensive information on the mechanisms by which perchloroethylene leads to tumors in mice and rats comes in large part from research sponsored by the chemical industry. Continued research to resolve uncertainty concerning the health effects of perchloroethylene appears highly desirable, particularly with regard to obtaining better epidemiological data. The Agency should take steps to work with the relevant industries and other institutions to assure that further research to illuminate the human health risks of perchloroethylene is vigorously pursued.

Three specific areas warrant emphasis: (a) We need to address the question of whether or not TCA, the principle metabolite of perc, has direct effects on DNA structure and attempt to resolve discrepancies that now exist in the literature; (b) The evaluation of the role of peroxisomal proliferation in tumorigenesis should be continued; and (c) Addition research should address the involvement of perchloroethylene in the etiology of kidney disease in humans. Perc, in conjunction with other solvents has been reported to cause membranous nephropathy in humans, but this lesion is quite distinct in mechanism of development, morphology, and function from the tubular lesions produced in male rats (Ehrenreich, Yunis and Churg, 1977).

5. REFERENCES

Brown, _; and Kaplan, _,; (1987) Retrospective cohort mortality study of dry cleaner workers using perchloroethylene. J. Occupational Med. 29, 535-541.

DeAngelo, A.B.; Daniel, F.B.; McMillan, L.; Wernsing, P.; Savage, R.E. Jr.; (1989) Species and strain sensitivity to the induction of peroxisome proliferation by chloroacetic acids. Toxicol. Appl. Pharmacol. 101, 285-298.

DeAngelo et al.; (1991) Carcinogenicity of dichloroacetic acid in the male B6C3F1 rat. Fundam. Appl. Toxicol. 16, 337-347.

Ehrenreich, T.; Yunis, S.L.; and Churg, J.; (1977) Membranous nephropathy following exposure to volatile hydrocarbons. Environ. Res. 14:35-45

NCI. (1977) Bioassay of tetrachloroethylene for possible carcinogenicity. Technical Report Series #13, U.S. HEW, NIH 77-813.

Nelson, B. K.; Taylor, B. I.; Setzer, I. V. and Homung, R. W. (1980). Behavioral teratology of perchloroethylene in rats. Journal of Environmental Pathology and Toxicology 3, 233-250.

NTP. (1986) Toxicology and carcinogenesis of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344/N rats and B6C3F1 mice (inhalation studies) NIH publication No. 86-2567. NTP TR311.

Schwetz, B. A.; Leong, B. M. I.; and Gehring, B. I. (1975). The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform and methylene chloride on em-bryonal and fetal development in mice and rats. Toxicology and Applied Pharmacology 32, 84-96.

Science Advisory Board, U.S. EPA (1987) Review of the Draft Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene), EPA-SAB-EHC-018, January, 1987.

U.S. EPA. (February, 1991 Draft) *Response to Issues and Data Submissions on the Carcinogenicity of Tetrachloroethylene (Perchloroethylene)(EPA/600/6-91/002A).*