



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

December 17, 1984

OFFICE OF  
THE ADMINISTRATOR

Hon. William D. Ruckelshaus  
Administrator  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

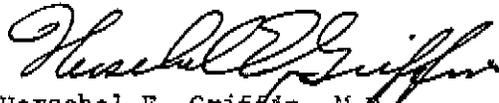
The Environmental Health Committee of the Science Advisory Board met on May 9-10, 1984 and reviewed a Draft Health Assessment Document for Trichloroethylene dated December 1983 and prepared by the Office of Health and Environmental Assessment (OHEA) in EPA's Office of Research and Development. The purpose of the document, an earlier draft of which was reviewed by the Committee, is to serve as a multimedia reference tool for general use in the Agency and to specifically serve as a scientific basis for making regulatory decisions by the Office of Air and Radiation. The attached Committee report presents its key findings and conclusions. Technical comments from individual Committee members have also been transmitted directly to OHEA.

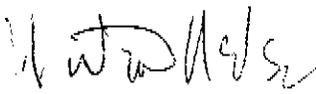
The critical scientific issue addressed by the Committee in its assessment of the trichloroethylene document was the evidence for carcinogenicity. The Committee reached no unanimous opinion concerning this issue nor the question of the classification of this compound using the criteria developed by the International Agency for Research on Cancer (IARC). The majority of members believe that the classification of trichloroethylene is consistent with IARC category 3, while one member concurs with the position expressed in the document.

The issue of the carcinogenicity of this compound is made exceedingly difficult due to the presence of liver tumors in the test animals. An interpretation of the significance of these tumors, as noted in the health assessment document, has not been resolved within the scientific community. Also, their relevance for projecting human health effects is not really known at this time. OHEA staff believe that detection of mouse liver tumors is a signal in the data that warrants increased concern over possible health effects. The Committee concurs that such a signal exists, but it believes that an interpretation of its overall significance is less certain. As a result, a definitive scientific opinion concerning the carcinogenicity of trichloroethylene cannot be reached by this Committee.

We appreciate the opportunity to review the trichloroethylene health assessment document and provide advice on this public health issue. The Board does not anticipate another review of this document unless specifically requested by the Agency in the future. We request a formal response to our advice.

Sincerely,

  
Herschel E. Griffin, M.D.  
Chair, Environmental Health Committee

  
Norton Nelson, Ph.D.  
Chair, Executive Committee

Attachments

cc: Alvin L. Alm (A-101)  
Joseph A. Cannon (ANR-443)  
Bernard D. Goldstein (RD-672)  
John A. Moore (TS-788)  
Jack E. Ravan (WH-556)  
Milton Russell (PM-219)  
Lee M. Thomas (WH-562A)  
Terry F. Yosie (A-101)

KEY FINDINGS AND CONCLUSIONS OF THE ENVIRONMENTAL HEALTH COMMITTEE  
ON THE DRAFT HEALTH ASSESSMENT DOCUMENT FOR TRICHLOROETHYLENE

The Environmental Health Committee of the Science Advisory Board met on May 9-10, 1984, to review a Draft Health Assessment Document for Trichloroethylene (1,1,2-trichloroethylene) dated December, 1983. The document, a previous draft of which was reviewed by the Committee, was prepared by the Office of Health and Environmental Assessment (OHEA) in the Office of Research and Development.

The Committee concurs with the assessment in the sense that existing OHEA policies have been applied in a workmanlike way that is consistent with its assessment of other chemicals. The Committee has concerns, moreover, with some of the assumptions used in the evaluation of the carcinogenicity of trichloroethylene. Contingent on the correction of these and other matters described below, the draft document is scientifically adequate as a comprehensive reference document for the purpose of regulatory decision making.

I. Qualitative Health Assessment of Trichloroethylene

A. Carcinogenicity

According to the health assessment document, there are six completed studies of trichloroethylene. Three more are in progress. Evaluation of the completed carcinogenicity studies reveals significant increases in liver tumor incidence among hybrid B6C3F1 mice of both sexes in two experiments, with one experiment weakened by deficiencies in the way the study was conducted. According to the health assessment document, three experiments are technically flawed to a point where the data cannot be used, and the remainder report no evidence of carcinogenicity (pp. 8-105-108).

The document points out that the scientific community disagrees about the relevance of this data to human carcinogenicity because some scientists believe that the mouse liver reacts anomalously to chlorinated organic compounds, perhaps due to unique differences in the metabolism of chlorinated organic compounds by the mouse (lipid peroxidation, for example). Other scientists believe that the organ site of increased tumor incidence in rodents is not predictive of the organ site in humans, only the increased incidence of tumors generally. Therefore, these other scientists would treat the increased incidence of mouse liver tumors identically to the increased incidence of tumors at any other rodent organ site. The Committee did not reach a definitive opinion on this issue in its review of trichloroethylene.

The document concludes that based on the available animal cancer bioassay data, the classification of the trichloroethylene results under the criteria of the International Agency for Research on Cancer (IARC) could be either "sufficient" or "limited", depending on the differing current scientific views about the induction of liver tumors in mice

by chlorinated organic compounds. The document further states that because there are no adequate epidemiological data in humans, the overall ranking of trichloroethylene under the IARC criteria could be either Group 2B or Group 3. The more conservative scientific sentiment would regard trichloroethylene as a probable human carcinogen, but there is considerable scientific sentiment for regarding this compound as an agent that cannot be classified as to its carcinogenicity in humans.

IARC category 3 is defined as "cannot be classified as to its carcinogenicity for humans" and category 2B is defined as "a probable carcinogen for humans." The majority of the Committee members believe that the classification of trichloroethylene is consistent with category 3, while one member concurred with the statement in the document. A definitive statement on the carcinogenicity of this compound cannot be made by this Committee at this time because the interpretation of male mouse hepatocellular carcinoma is uncertain and the animal evidence is limited at this time.

The data from epidemiologic studies for trichloroethylene are negative, the numbers of persons in the studied populations are small, and the studies have low statistical power. Although the epidemiological studies estimate zero risk, the confidence limits of this estimate are broad and thus would not necessarily contradict the positive estimate based on mouse liver tumor incidence.

The justification of the linear dose-effect model for low dose extrapolation is not satisfactory (p. 8-82 to 8-83). It is inappropriate and misleading to describe the linear model as having the "best scientific basis" among competing models for low-dose extrapolation of carcinogenic potency. The Agency's procedure to make risk estimates from animal data is to fit a nonlinear model (the multistage) and calculate the largest linear term (in the sense of a 95 percent confidence limit) that is consistent with the data. This linear term will dominate in the calculation of the dose-effect relationship for low-dose extrapolation. The EPA's procedure is therefore appropriate for calculating a plausible upper bound estimate of effect that is linear in dose, but it is potentially misleading to describe the underlying model as linear.

#### B. Metabolism

The document did not adequately analyse the available data on metabolism of trichloroethylene; neither were these data integrated into the quantitative risk estimate.

#### C. Neurotoxicology

The Committee advises OHEA to use the resources of the Neurotoxicology Division in ORD's Health Effects Research Laboratory to revise the sections on neurotoxicology.

#### D. Mutagenicity

The results obtained with trichloroethylene in conventional mutagenicity test systems are marginal. In addition, they may have been partly influenced by impurities or added epoxide stabilizers.

### II. Quantitative Assessment of Carcinogenic Potency for Trichloroethylene

The document presents a unit risk estimate for trichloroethylene to estimate the upper limit to the carcinogenic potency of the chemical, assuming that it is indeed a carcinogen. EPA's policy has been to assess the quantitative potency of a carcinogen independently of the quality of the evidence that the chemical is a carcinogen. As a general matter, this may be an acceptable procedure for known human carcinogens for which abundant data are available. The Committee advises, however, that the quality of evidence for a carcinogen is not independent of potency in all cases or in all ways. For example, a particularly good experimental dose-response curve will be important both to the evidence that the chemical is a carcinogen and to the evaluation of potency. On the other hand, testing of a low potency carcinogen is likely to lead to ambiguous bioassay evidence, with some assays positive and others negative.

The ambiguous bioassay evidence found for trichloroethylene may be a specific example of this phenomenon. The rationale to develop a unit risk estimate for trichloroethylene should relate to data quality. The Committee advises that the Agency always is in a position to engage in "what-if" analysis, as a matter of policy analysis, if the evidence for carcinogenicity is insufficient. However, a unit risk estimate for a potential carcinogen with insufficient evidence should not be justified by the Agency on scientific grounds.

The Agency's policy for the quantitative evaluation of carcinogenic potency has been to estimate a plausible upper bound from available dose-response data. The current procedure to locate the plausible upper bound has the advantage of consensus support from the risk assessment community, while no similar consensus exists for any procedure to give a best estimate of carcinogenic potency. In general, a plausible upper bound is not the same as the best estimate or maximum likelihood for expected value of carcinogenic potency because for some carcinogens the reasonable expectation of risk is not the same as the plausible upper bound. In the case of trichloroethylene, however, good reasons exist to believe that at low exposures the plausible upper bound is an overestimate. For example, the Agency's procedure does not account for metabolism, but the evidence points to a causal requirement for metabolism of trichloroethylene before carcinogenic effects can occur.

For the present, the Committee understands OHEA's assumptions for the evaluation of carcinogenicity but disagrees with them in their application to the quantitative assessment of trichloroethylene, assuming that this chemical is indeed classified within IARC category 3.

### III. Exposure Assessment

The document does not contain an exposure assessment. In anticipation of the integration of the health assessment with exposure information, however, the Committee advises that the relationship of no-observed-effect-level to potential ambient exposure needs to be laid out in detail.

### IV. Research Needs

Trichloroethylene is used for metal cleaning in the U.S., and persons with this occupation are exposed to higher and more prolonged levels than the general population. Typically, EPA faces a quandary in assessing the effects of environmental exposures based on data from instances of high exposures to small groups with confounding occupational factors. Metal cleaning with trichloroethylene continues in this country, and more occupational studies will occur under the auspices of the National Institute for Occupational Safety and Health. These studies, however, will not resolve the problem of inferring the effects of environmental exposures from occupational epidemiology. The Committee advises that to the extent consistent with other research needs, EPA should conduct research on the effects of environmental trichloroethylene exposures to insure that better data are available in the future.

### V. Additional Issues & Recommendations

The document had a high level of typographical errors and editorial inconsistencies which need correction. Wording of the weight of the evidence categories needs improvement. In addition to oral comments at the May 9-10 meeting, for which a transcript is available, individual members of the Committee have provided detailed written technical comments on trichloroethylene which have been communicated directly to OHEA. The Committee advises the use of these comments in revising the document.

The Committee believes that the Agency should use the adjective "conservative" more carefully, when referring to scientific matters. A "conservative scientist" is one who avoids drawing conclusions not fully supported by the objective evidence. While it may be a prudent public health policy elsewhere to avoid possible risks, this practice incorporates factors into decision making besides those drawn explicitly from existing scientific evidence. The health assessment document should define "conservative science" so as not to confuse readers about this issue.