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

March 9, 1988

SAB-EHC-88-011

Hon. Lee M. Thomas
Administrator
U.S. Environmental Protection
Agency
401 M Street, SW
Washington, D.C. 20460

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

Thank you for your thoughtful response of August 3 to the Science Advisory Board's review of scientific evidence associated with exposure to perchloroethylene. In your letter you asked the Board to provide further scientific advice on three issues that will subsequently bear on your risk management decision for this compound. The Board appreciates this opportunity for further scientific dialogue on these issues and hopes that its views in this letter can better promote consensus on the scientific issues under review.

As noted in your letter, the assessment of the scientific evidence from experimental animal studies centers on the relative significance for humans of the production of rat kidney and mouse liver tumors. This question is applicable to a broad range of chlorinated hydrocarbon compounds--including dichloromethane, para-dichlorobenzene, trichloromethane, and trichloroethylene--which produce tumors of the rat kidney and mouse liver under some experimental conditions. While recognizing the implications of such issues to these and other compounds, this letter is directed specifically to an assessment of perchloroethylene.

In responding to your letter, the Board's Environmental Health Committee and its Halogenated Organics Subcommittee organized a scientific workshop on August 12, 1987 to explore these and other issues with leading researchers in the field, EPA staff and members of the public. An agenda of the workshop is attached. The Board has utilized the information obtained in this workshop, and the discussions among Committee and Subcommittee members, to respond to your August 3 letter and also to advise the Agency on health effects evaluated in its Draft Health Assessment Document Addenda for Dichloromethane and Trichloroethylene. The Board's findings and recommendations on these latter two compounds will be transmitted to you in separate letters. Our response to your specific questions follows.

Question 1: Assuming that not all animal tumors are of equal significance to evaluating human hazard, what is the Science Advisory Board's current consensus position, based on scientific evidence or professional judgment, of the relative significance of male rat kidney or mouse hepatocellular tumors for human risk assessment?

SAB Response: In general, the Board's consensus conclusion on the significance of male rat kidney tumors stems from recent research (not yet published, but in

press) that indicates that for many halogenated organics, probably including perchloroethylene, the mechanism producing these type of tumors is probably not operative in humans and, therefore, may not be relevant for human risk assessment. This mechanism involves the metabolism of the compound in the liver and the binding of a protein (alpha-2u-globulin) with the metabolite as a conjugate molecule. This molecule is filtered and accumulates in the kidney. One hypothesis is that the conjugate is more difficult to metabolize than the alpha-2u-globulin alone. This protein then accumulates and is injurious to the cell. Repair is followed by a cancerous formation at the site in a low percentage of cases. From available scientific evidence, this mechanism appears to be unique to male rats.

Thus far, thirteen substances have been demonstrated to produce renal tumors in male rats through this mechanism including perchloroethylene, paradichlorobenzene and unleaded gasoline. Trichloroethylene, on the other hand, appears to produce renal tumors in male rats through a different (unknown) mechanism, thus creating important implications for human health risk assessment.

The Board's consensus on the significance of mouse liver tumors is that mechanistic explanations are not sufficiently well developed and validated at this time to change EPA's present approach expressed in its risk assessment guidelines for carcinogenicity. It concludes that the generation of mouse liver tumors by chemicals is an important predictor of potential risks to humans. Of the several mechanistic models under consideration (including regenerative hyperplasia, oncogene activation and tri-halomethyl radical formation), the one most promising for immediate application to risk assessment is characterized by proliferation of peroxisomes, an intracellular organelle, in the liver.

Peroxisome proliferation may be important for compounds such as perchloroethylene, but liver tumors observed after exposure to chlorinated solvents may involve different mechanisms. The importance of understanding the biological mechanisms is that they may provide a basis other than the bioassay statistical analysis for low-dose risk estimation. A plausible mechanism (peroxisome proliferation or something else) may imply low-dose nonlinearity for some substances that induce mouse liver tumors. However, different (presumably linear) mechanisms may operate for other substances, and these mechanisms may be consistent with linearity at low doses or a linear relationship to dose. These distinctions in low dose risk estimation should be explicitly included in the quantitative estimate of human risk.

Several substances that induce peroxisome proliferation in rodent livers, such as hypolipidemic drugs and the plasticizer di-ethylhexylphtalate (DEHP), also produce liver tumors in rodents. In summary, however, a causal relationship for this mechanism is plausible but unproven.

Some scientists have reported the detection of oncogenes after administration of presumably non-genotoxic agents.[1]

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[1] Steven H. Reynolds, Shari J. Stowers, Rachel M. Patterson, Robert R. Maronpot, Stuart A. Aaronson, Marshall W. Anderson, "Activated Oncogenes in B6C3F1 Mouse Liver Tumors: Implications for Risk Assessment," Science Vol. 237 (September 11, 1987), pp. 1309-1316.

Also, as you are aware, our increasing knowledge of the role of mechanisms of promotion (later events in the carcinogenic process) may well clarify our understanding of cancer induction: certainly this is the case with dioxin and may relate to the halogenated hydrocarbons.

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 choices, 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 B_2 and C of EPA's risk assessment guidelines for cancer.

As perchloroethylene illustrates, the distinction between the B_2 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 B_2 and not to consider regulation of compounds classified as C, regardless of the level of human exposure. In the case of B_2, B_1 or even A categorized 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 potential 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.

Finally, you noted the evaluation of perchloroethylene by the International Agency for Research on Cancer (IARC) as an example of evolving terminology for classifying potential carcinogens. In general, the Board believes that public understanding of complex scientific issues is enhanced when scientists and regulators can speak with a common voice. In view of its own experience of using the cancer risk assessment guidelines and, in particular, having to address the issue of the scientific uncertainty that exists among and within guideline categories, EPA should re-evaluate its labeling system and methods for characterizing uncertainty. It should also review whether to be more consistent with IARC's terminology.

Question 3: Is there research underway or anticipated that will clarify these rodent tumor responses and their relationship to human health risk assessment? What additional research should be undertaken?

SAB Response: Current research undertaken in various laboratories, including the National Institutes of Health, can reduce some of the uncertainties associated with rodent tumor responses. Research results and hypotheses presented at the Board's August 12 workshop has served to clarify our understanding of male rat kidney tumors and their significance for human risk assessment. In addition, the Reynolds et. al. paper supplements our knowledge of activated oncogenes in mouse livers tumors.

Several research efforts should be initiated to further narrow scientific uncertainty for perchloroethylene and structurally related compounds. These include:

- o Validation of mechanistic models for the rat kidney and mouse liver tumors through experimentation with selected known carcinogens and non-carcinogens.

- o Development of improved methods for assessing low-dose response to environmental pollutants that induce peroxisome proliferation.

Once again, we are pleased to have this opportunity to present the views of the Science Advisory Board on these important scientific issues. We hope that the consensus stated above assists you in making the difficult risk management decisions on perchloroethylene and other compounds.

Sincerely,

Norton Nelson, Chairman
Executive Committee

Richard A. Griesemer, Chairman
Environmental Health Committee

John Doull, Chairman
Halogenated Organics Subcommittee

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SCIENCE ADVISORY BOARD
ENVIRONMENTAL HEALTH COMMITTEE/HALOGENATED ORGANICS
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NOTE: This combined roster only include those individuals attending the meeting.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C 20460

AUG 3 1987

Dr. Norton Nelson
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THE ADMINISTRATOR

Dear Dr. Nelson:

Thank you for the letter that you and Dr. Richard Griesemer sent me on January 27, 1987 submitting the report of the Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee following its review of the Draft Health Assessment Document Addendum for Tetrachloroethylene (Perchloroethylene). Your letter has stimulated a wide and fruitful discussion on a number of scientific issues among EPA staff scientists and between the staff and senior policy officials, including myself. The thoroughness of these discussions accounts for the delay in responding to your letter.

The recommendation of the Halogenated Organics Subcommittee that perchloroethylene be classified in Category C of EPA's Risk Assessment Guidelines for Carcinogenicity disagrees with the position taken in the draft assessment document addendum that this compound meets the criteria established in the guidelines for a classification of B2. As you know from having participated in the review of the guidelines, they are not intended to be used in a rote like fashion but, rather, to represent the flexible use of the best scientific judgment based upon the weight of the evidence. Your letter has encouraged EPA scientists and managers to re-examine many of the assumptions and judgments applied both in the guidelines and in the assessment of perchloroethylene.

I personally welcome this continuation of the scientific dialogue. I would like to use this opportunity of responding to your letter not only to build consensus with the scientific community that the Science Advisory Board represents, but also with the Congress and the public. We all need to work together towards a better understanding of the issues involved in decision making under conditions of uncertainty.

At least two sets of issues are involved in the Agency's evaluation of your letter, both of which emphasize the need for additional consultations. The first concerns the assessment of the scientific evidence for perchloroethylene and, the second addresses the use of the results of the assessment to reach a decision on the hazard of perchloroethylene by applying the classifications expressed in the risk assessment guidelines for carcinogenicity. An additional set of issues pertains to how defensible, from a scientific point of view, a particular classification decision may be. This, in turn, raises the issue of how flexible the guidelines are in evaluating a compound such as perchloroethylene, and their utility in regulatory decision making in their current form.

More than one scientifically defensible position may exist on perchloroethylene (or other substances) because of the uncertainties in the available scientific data and because of the difficulties in extrapolating effects reported in test animals (such as mouse liver tumors and certain rat kidney tumors) to humans. The EPA cancer guidelines take the position that there is a continuum, or ladder, of hazard information depending on the available evidence. The Science Advisory Board supported the classification system developed in the guidelines, and the evidence needed to evaluate--both qualitatively and quantitatively--the risk posed by a compound. The Halogenated Organics Subcommittee report on perchloroethylene reminds us that more than one interpretation of the same scientific data is possible under the guidelines.

I have enclosed the response of EPA staff scientists to the Subcommittee's report. For reasons that are provided in the response, the staff believe that the scientific evidence seems to more closely support a B2 classification of perchloroethylene. After your review of the EPA staff response and before I reach a final decision in the coming weeks, however, I would like to have the benefit of further scientific advice from you and other members of the Science Advisory Board on some important issues that will bear on my decision. These include:

- Assuming that not all animal tumors are of equal significance to evaluating human hazard, what is the Science Advisory Board's current consensus position, based on scientific evidence or professional judgment, of the relative significance of male rat kidney or mouse hepatocellular tumors for human risk assessment?

- 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? I note, for example, the recent decision by the International Agency for Research on Cancer to classify perchloroethylene as a 2B carcinogen, based upon a determination of "sufficient" evidence of carcinogenicity in animals, under its new classification system but to label 2B as a category of "possible" human carcinogens.

- Is there research underway or anticipated that will clarify these rodent tumor responses and their relationship to human health risk assessment? What additional research should be undertaken?

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 weigh 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.

I note with interest the initiative taken by the Board in organizing a workshop on specific rodent tumors on August 12. I applaud your leadership in assembling scientific experts from a number of agencies and organizations to broaden the level of understanding on these issues. The workshop furthers my desire to continue a scientific dialogue on issues related to risk assessment and clearly addresses the issues I must decide relative to perchloroethylene.

Given the importance of these issues and their relationship to the regulatory decisions that I must make, I would appreciate your expeditious response to the issues I have identified, or others that you believe are also significant. Again, I thank you and other SAB members for your continuing efforts to improve the scientific basis for decision making in EPA.

Sincerely,

Lee M. Thomas

JUL 30 1987

EPA Staff Comments on Issues Regarding the Carcinogenicity of Perchloroethylene (Perc) Raised by the SAB

Introduction

Environmental Protection Agency staff scientists have reviewed the comments of the SAB and its Halogenated Organics Subcommittee and has prepared this detailed response to issues raised. These include points raised by the SAB about the NTP data and their interpretation by both the NTP and the Agency. As discussed in this document, some of these issues may be subject to alternative scientific interpretation. It would also appear that additional discussion regarding the Agency's interpretation of its Risk Assessment Guidelines would be valuable. Agency staff will be pleased to engage in such discussions with the SAB. Both quality of science and consistency of approach to data interpretation are important issues for the Agency in its dealings with the NTP, with its advisory groups, and with the public. The SAB's comments on the March, 1986 perchloroethylene addendum and the responses that follow suggest the need to focus closely on a number of these issues.

Quality Assurance of the Bioassay

The Agency staff agrees with the opinion of the subcommittee that the quality assurance information available on the NTP bioassay suggest that this was a scientifically acceptable, well-run study. The NTP is convinced that the study data, documents, and materials in the NTP archives support the data and interpretations presented in their technical report. The Agency will incorporate additional statements regarding the implications of the quality assurance information in the final version of the addendum.

based on a Life Table analysis. The Fisher Exact test values were inadvertantly replaced by these values in the preparation of the document. The appropriate values, as calculated by the NTP and confirmed by Agency statisticians are as follows:

	Control	200 PPM	400 PPM
Overall Rate	1/49 (2%)	3/49 (6%)	4/50 (8%)
Life Table	P = 0.054	P = 0.259	P = 0.070
Fisher Exact (one-tailed)		P = 0.309	P = 0.187

The correct values for the Fisher Exact test will appear in the final version of the addendum. In addition, a discussion of the results of the trend and Life Table analysis included in the NTP report will be presented.

3) The SAB raises questions about the rat kidney response seen in this study. The NTP indicates in the technical report that because these lesions appeared consistently in dosed animals but not in controls and are considered uncommon tumors, they are considered to be caused by perchloroethylene. As of August, 1985, the historical incidences for adenomas in Battelle PNL chamber controls and in NTP program untreated controls are 1/249 (0.4%) and 4/1,968 (0.2%) respectively. No malignant renal tubular cell tumors have ever been observed in control groups. The latest information available on these control rates will be included in the final addendum. Given that no malignant renal tumors have been seen in control animals, the probability of finding 2 malignancies in 50 animals by chance with a historical control incidence of 0/1,968 is highly unlikely ($p < .001$, Fisher Exact test, one-tailed).

4) The Agency staff can find little support for the subcommittee view that renal tubular cell neoplasia in control groups tends to be under-reported. In this specific case, while the subcommittee did receive public comment that review of control groups from Batelle showed undiagnosed renal tumors (1 in each of 3 groups examined), follow-up review by an NTP panel of pathologists failed to confirm this discrepancy. The Agency has contributed to the development of a well designed and thorough review process for NTP studies and staff has considerable confidence in them. Of course, NTP data, as with all other data considered by the EPA, should be subject to further review by both Agency and other scientists.

5) Although the kidney response is elevated but not significant at a $p = 0.5$ level compared to the concurrent control group, it does represent an increased incidence of a rare carcinogenic event apparently attributable to perchloroethylene. While not reason enough on its own to suggest a strong positive carcinogenic response in rats, this rare event does add to the weight of evidence. Although the relevence of such a response to humans, especially at low doses has been questioned, there is little doubt that the kidney is a target organ for perchloroethylene and other chlorinated ethanes and ethylenes in mammalian species and this also contributes to our concern.

o Mononuclear Cell Leukemia in Rats

1) The SAB disagreed with the Agency's (and the NTP's) position that a marginally statistically significant increase in mononuclear cell leukemia is seen in both sexes of rats exposed to perchloroethylene in the NTP study. Our analysis of these data does not support the supposition that "faulty pathological diagnoses or some unusual circumstances in the rat colony at the time" are the basis for this response.

2) The SAB has stated that "the pathology of these tumors is not well understood, and little background information is available in the literature." However, Agency staff concur with NTP scientists on the point that rat mononuclear cell leukemia is a well characterized disease. There appears to be a substantial data base characterizing the disease both biologically and pathologically. The literature speaks to origin, time of onset, progression, and clinical pathology of this disease. References to this work will be included in the discussion of mononuclear cell leukemia in the final version of the addendum.

3) The SAB suggests that "the results of the statistical analysis are not convincing" and takes issue with the use of "staging in the assessment of this response." The Agency's position with regard to the relationship between the statistical analysis of the leukemia response and the staging of that response will be clarified in the final document. The Fisher Exact test shows a marginally statistically significant response in both sexes. In contrast to the somewhat equivocal findings in male rats, the leukemias in the female rats seem to be clearly elevated by perchloroethylene. Discussions with the NTP confirm this fact and suggest that the staging was used as a supplemental analysis to determine whether the statistical difference might be due to differential diagnosis of the lesions. This situation might have been suspected had the difference been due primarily to early stage leukemia in the dosed groups. However, this was not the case. Considering only advanced (stage 3 as defined by NTP criteria) cases resulted in slightly less significance to the response in males and slightly more in females compared to the overall incidence. Staging did not, therefore, strongly influence the significance of this response. As a comparative

diagnostic test, staging seems quite appropriate and the similarities or differences with the staging of human leukemias as a measure of leukemic progression seems to be a moot point.

4) The SAB states that "18 versus 30 is not a striking observation" with regard to the leukemia incidence in control and female low dose groups respectively. Based on evidence accumulated by the NTP, however, 19/50 is the highest incidence ever seen in an untreated control group in some 2000 animals which have been examined in the Program. Dr. Joseph Haseman of the NTP has addressed the question of a chance finding of such results if two of six experimental groups are drawn at random. In an internal memorandum responding to the SAB comments, Dr. Haseman states "the answer is that it is extremely unlikely (exact p-value difficult to determine precisely, but at least $p < 0.001$) that by chance alone one would find a statistically significant increase in leukemia in all four of the rat groups dosed with tetrachloroethylene. It is this consistency of response across both doses of both sexes that makes the effect almost certainly due to the administration of tetrachloroethylene." (Haseman, 1987)

5) The SAB commented on the apparent contradictory positions on the use of a time-to-tumor analysis found in the draft Addendum and presented orally at the subcommittee meeting. The Agency will clarify the time-to-tumor analysis issue in the final version of the addendum. Agency staff scientists agree with the NTP report which indicates that Life Table analyses add support to the statistical significance of the response noted by comparing overall incidences using the Fisher Exact test. Supporting data and time-to-tumor analyses will be added to the final version of the Addendum.

6) Agency scientists believe that there is scientific support for the conclusion that perchloroethylene exposure is associated with increased frequency of mononuclear cell leukemia in rats, based on the NTP data. While scientists may disagree on the strength of the evidence, it is generally felt that these data show "some evidence" of Perchloroethylene-related carcinogenicity if not "clear evidence", to use NTP's terms. For an indication of the range of opinions among the NTP's Board of Scientific Counselors Review Panel, see p. 14-15 of the NTP Technical Report (NTP, 1986). It is reasonable to conclude that these results add to the weight of evidence for a carcinogenic response in rats. At present, there is no satisfactory explanation as to why these results were not seen in previous studies. Shortcomings of the earlier studies and the fact that a different route of exposure was used may have played a role in the inconsistency of reported response. Exposure via the oral route was more acutely toxic and caused significantly higher mortality in all three dose groups in both sexes in the NCI study (1977). In the only other rat bioassay of Perc, survial was significantly reduced in the high dose groups of both sexes (Rampy et al., 1978). Since mononuclear cell leukemia is a disease of old age, high non-tumor mortality in treated groups in both of these studies could have masked late appearing cancer effects. The results of the completed NTP Gavage Study of four rat strains may help to clarify this issue. A determination as to the utility of these studies for assessing the potential carcinogenicity of perchloroethylene in rats will be made once the resolution of audit problems is completed by the NTP. A decision in this regard is expected by September, 1987.

o Liver Tumors in Mice

1) The SAB suggests that adenomas and carcinomas be analyzed both separately and combined. Such an analysis has been presented on p. 3-14 of the

draft Addendum. The statement by the SAB that "It should be remembered that many mice with hepatic carcinomas also have adenomas that have not been included in the summary tallies" is also answered in the draft Addendum. Mice with both lesions are enumerated in the footnotes in Table 3-6 on p. 3-14. In no dose group was the incidence of mice with both lesions more than 10%.

2) Despite acknowledging that the results of this study confirm previous results and predictions based on route to route extrapolation, the SAB concludes that "no new, dispositive information has been gained". The fact that a strong carcinogenic response has been demonstrated in two separate experiments, in different laboratories, using different routes of exposure, producing similar dose-related responses, increases the weight of the evidence that the response is indicative of a carcinogenic response in animals. While this interpretation can be debated because the response is seen in mouse liver and is accompanied by some non-neoplastic pathology, the confirmatory finding as well as the nature of the response is viewed by many in the science community as "sufficient evidence" of an animal carcinogenic response, as is stated in the Agency's Carcinogen Risk Assessment Guidelines. Additional support for this view comes from the recent deliberations on the classification of perchloroethylene by IARC. The final statement of the IARC review group is expected to show an upgrade of the animal evidence of carcinogenicity of perchloroethylene from "limited" to "sufficient" based strongly on the new confirmatory data on mice from the NTP study. It is the position of the Agency, therefore, that the new inhalation liver tumor data from the NTP study should add to the weight-of-the-evidence determination for perchloroethylene.

Other Data from the NTP Bioassay

The SAB has requested that "Agency staff fully assess all of the information available from the National Toxicology Program study." The Agency agrees that additional discussion of other data from the NTP bioassay should be included in the final Addendum. Although not statistically significant, increases in pathology are noted in the kidneys, respiratory tract and brain in both sexes and in the testes in males. Adequate discussion of these responses and their potential implications for an analysis of neoplasia in these animals is presented in the NTP report and will be summarized in the Addendum. A discussion of mortality outcomes including a time-to-death analysis will be provided to assess the hypothesis that the kidney is also a target organ for chronic toxicity in the mice.

Statistical Analysis of the Bioassay Results

The Agency has used one-tailed statistical analyses in this Addendum and will state this as the SAB requests. Agency statisticians as well as those at the NTP feel that this is an appropriate approach when trying to detect a carcinogenic response. While recognizing that chemicals may influence tumor incidence in either a positive or negative way, in this case, no evidence of decreased tumor incidence is found, nor would a two-tailed test radically change the significance of the results. The fact that the rat leukemia data is shown to be significant even by a two-tailed analysis might be viewed as adding additional weight to the significance of the response. This point will be added to the discussion.

Metabolism and Pharmacokinetics

The Agency appreciates the SAB's insights on some of the assumptions made in the pharmacokinetic modeling of perchloroethylene. Much has transpired since the subcommittee meeting with regard to the physiologically-based pharmacokinetic

modeling of chlorinated solvents. The final addendum will present the results of an interagency effort to reach consensus on aspects of modeling these compounds. This effort will not substantially change the presentation as reviewed by the SAB, but will provide some alternative approaches and their respective strengths and weaknesses given the current state of our knowledge on this chemical and this field. Specific assumptions related to a hypothetical genotoxic metabolite will be revisited in the final addendum.

Mechanism

The SAB "hypothesizes that, operationally, perchloroethylene may be an indirect acting carcinogen or carcinogenic promoter of low potency." Of the six pieces of "evidence" laid out by the SAB to support this contention, none addresses the issue of promotion directly. The facts that perchloroethylene is not mutagenic in routine testing and binds to DNA only minimally does not indicate a promoting compound but suggests interpretation of the bioassay data as promotion by default. The fact that perchloroethylene induces liver carcinoma in B6C3F1 mice does not argue strongly for either an indirect or a promoting carcinogen since this does not appear to be the only species or organ site affected by perchloroethylene and direct-acting, genotoxic carcinogens also induce liver tumors in mice. The fact that perchloroethylene is a peroxisome proliferator still does not fully explain its carcinogenic mechanism nor confirm its promotional capability. While perchloroethylene produces trichloroacetic acid (TCA) which is a potent peroxisome proliferator, TCA also acts as a complete carcinogen, perhaps indirectly, in the mouse liver (Herren-Freund et al, 1987 in press), and specifically does not enhance the response in ethyl nitrosourea pretreated animals. Perchloroethylene's consistent carcinogenic behavior when compared with other halo-substituted ethylenes argues neither for nor against a

specific mechanism. In summary, data do not support the contention that perchloroethylene is solely a promoter, and the evidence for an indirect mechanism of carcinogenicity, while accumulating for certain tumor sites, is far from certain. The mechanism(s) by which chlorinated hydrocarbons, and specifically perchloroethylene produce a carcinogenic response remains unknown. While peroxisome proliferation may play a role in the mouse liver response, this finding is not sufficient to explain the rat kidney response (See Goldsworthy and Popp, 1987, for a discussion of this issue). These issues will only be resolved with additional research. At the present time, Agency staff have maintained a position of concern for a potential for carcinogenic response in humans exposed to chemicals producing such responses in animals. Qualitatively, no strong scientific argument can yet be made for the irrelevance of these tumors to man on a mechanistic basis, although differences of opinion on their relevance are recognized by the scientific community.

Epidemiology

The Agency will include a discussion of the latest information on epidemiologic studies related to perchloroethylene exposure. Given the projected potency of carcinogenic response based on animal data, it is unlikely that studies with sufficient power to determine a positive response will be forthcoming.

Weight of Evidence Category

While recognizing that the available data may be subject to alternative interpretations, the staff believes that perchloroethylene should fall more readily into the B2 category, probably carcinogenic to humans, based on sufficient animal but inadequate human evidence of carcinogenicity. The Agency's interpretation of the bioassay data described above leads to the conclusions that 1) a

statistically significant tumor response related to perchloroethylene exposure is seen in both mice and rats; 2) three tumor sites are identified (rat leukemia and kidney and mouse liver); 3) positive results are found in the mouse by two routes of administration (gavage and inhalation); 4) a shortening of time-to-tumor is noted in both species at two different sites (mouse liver and rat leukemia); 5) malignant mouse liver tumors are seen in both sexes and at both doses; 6) renal tumors in the rat show a dose-related trend; 7) metabolism of perchloroethylene appears to be similar in rodents and man; and 8) the mechanism of carcinogenic action of perchloroethylene is currently unknown although several mechanisms have been hypothesized. Both the rat data *in toto* when considered with the mouse data, or the mouse data alone, when viewed as described above, support this classification under the current EPA Guidelines. The Agency currently takes the position that these rodent responses are generally considered to be relevant to man in the context of hazard identification, that is, there is a potential for producing a carcinogenic response at some dose in humans. While the Agency has considered arguments against the use of each of these animal responses individually to assess the hazard to humans, the overall weight of the evidence is the more pertinent issue. The sum of the carcinogenic responses and the confirmatory nature of the mouse data would seem to override the position adopted by the SAB that the animal evidence is only limited. The decision of IARC, when published, is expected to further support the view that results of the NTP study raise the weight of the evidence of animal carcinogenicity of perchloroethylene from limited to sufficient.

Unless downgraded on the basis of data indicating a species-specific response, sufficient evidence in animals with inadequate evidence in humans is indicative of a probable human carcinogen under EPA's current Guidelines for

Carcinogen Risk Assessment. According to Agency representatives to an IARC committee drafting a new IARC Monographs preamble, the IARC will also use the terms "probable" and "possible" human carcinogen in its overall evaluation of carcinogens. Since the classification schemes are not exactly comparable sufficient animal evidence will place perchloroethylene in Category 2B which the IARC will term "possible" carcinogenic to man. The implications of use of the terms "possible" and "probably" in EPA's risk assessments in light of this development should be a point for discussion among Agency scientists and the SAB.

Quantitative Potency Estimate

The Agency agrees with the SAB that the basis for the range of upper bounds on the risk should be very clear in the final Addendum. The influence of various approaches and assumptions, including the use of physiologically based pharmacokinetic modeling, on the risk estimates will be described in greater detail or clarified in the final Addendum. The implications for Agency-decision making of both the qualitative and quantitative assessments for perchloroethylene are recognized and both points were explicitly included in the current addendum summary on pages 1-2 and 1-5, that is while being ranked as a B2 carcinogen (qualitatively), its relative potency is among the lowest evaluated by the Agency (quantitatively).

Miscellaneous Issues

1) A discussion of research needs will be added to the final addendum. Recent discussions in the Inter-Agency Health Risk Assessment Committee of the Integrated Solvents Project will provide the basis for much of this discussion. Issues relating to metabolism, pharmacokinetics and pharmacodynamics are of particular interest to this group.

2) In response to the SAB's request, the Agency will supply the SAB with a recent report from a jointly funded project entitled, "Investigation of Cancer Risk Assessment Methods" prepared by K.S. Crump and Company. This report is the result of a two year study to examine the assumptions, other than those involving low dose extrapolation, used in quantitative cancer risk assessment. The study was funded by the Department of Defense [through an interagency transfer of funds to the Environmental Protection Agency (EPA)], the EPA, the Electric Power Research Institute and, in its latter stages, by the Risk Science Institute. The objectives of the study were as follows:

1. To identify and express quantitatively uncertainties that are involved in the process of risk estimation, excluding the uncertainties in the low dose extrapolation model;
2. To examine the impact of the different assumptions that are made in risk estimation;
3. To compare results calculated from human and animal data, including the identification of the assumptions that produce the best correlation of risk estimates between humans and animals;
4. To develop guidelines for presenting a range of risk estimates based on different but scientifically acceptable assumptions or assumptions that have considerable backing in the scientific community.

These objectives are pursued using empirical methods in which carcinogenicity data for 44 chemicals are analyzed systematically in a variety of ways. Particular attention is placed on those 23 chemicals for which there exist data from both animal and epidemiological studies suitable for making quantitative comparisons.

Conclusion

The Agency's staff scientists have responded to the questions and issues raised by the SAB, focusing mainly on the evidence of carcinogenesis in animals provided by the NTP study. The Agency has presented evidence for the appropriateness of using the mononuclear cell leukemia response in the rats and liver tumors in mice in a weight-of-evidence approach and has presented additional interpretive considerations for the rat kidney tumor response. It concludes that, despite uncertainties with extrapolation from each of these endpoints taken individually, the body of evidence for carcinogenicity in both rats and mice is sufficient which leads to the conclusion that perchloroethylene would probably be carcinogenic to humans at some dose: a B2 carcinogen under EPA Guidelines. We hope that this response to comments will strengthen the articulation of the Agency's position on the potential carcinogenicity of perchloroethylene as will be found in the final Addendum.

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