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

January 27, 1987

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

SAB-EHC-87-018

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Science Advisory Board's Environmental Health Committee has completed its review of a draft Addendum to the Health Assessment Document for Perchloroethylene. The Committee previously reviewed the draft Health Assessment Document on May 9-10, 1984. An Addendum is desirable because of newly available data, primarily an inhalation bioassay of rodents by the National Toxicology Program. The Committee has conducted its review primarily through the Halogenated Organics Subcommittee, whose report is attached.

The Subcommittee believes it is reasonable to describe the weight of the epidemiological evidence in humans as conforming to the EPA guideline for carcinogen risk assessment definition of "inadequate." The Subcommittee concludes that the animal evidence of carcinogenicity is "limited" because of positive results in only one strain of mouse of a type of tumor that is common and difficult to interpret. Thus, the Subcommittee concludes that perchloroethylene belongs in the overall weight-of-the-evidence category C (possible human carcinogen).

Given the current evidence, the Subcommittee hypothesizes that, operationally, perchloroethylene may be an indirect acting carcinogen or carcinogenic promoter of low potency. By promoter, the Subcommittee means that perchloroethylene alone does not induce tumors. Instead, perchloroethylene appears to act in concert with other substances, endogenous processes, viruses, oncogenes, or radiation, which can initiate cancer in the absence of promoters.

We appreciate the opportunity to comment on this important public health issue and request that EPA formally respond to our report.

Sincerely,

Norton Nelson
Chair, Executive Committee

Richard Griesemer
Richard A. Griesemer
Chair, Environmental Health Committee

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

October 26, 1986

OFFICE OF
THE ADMINISTRATOR

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Dr. Griesemer:

The Halogenated Organics Subcommittee of the Environmental Health Committee has completed its review of a draft Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene; Updated Carcinogenicity Assessment; EPA-600/8-82/005FA; March, 1986). The Environmental Health Committee previously reviewed the draft Health Assessment Document for Perchloroethylene on May 9-10, 1984, and transmitted a report on this draft to the Agency on January 4, 1985.

The draft Addendum is based on a National Toxicology Program inhalation bioassay of perchloroethylene in rodents. The Subcommittee finds that the bioassay is of reasonably good quality, and that useful results for risk assessment can be obtained from it. The Subcommittee disagrees with the Agency's interpretation of the data that increases in either renal tubular cell neoplasia or mononuclear cell leukemias in F334 rats were associated with perchloroethylene exposure. The Subcommittee agrees with the conclusion in the document that perchloroethylene inhalation is associated with a significant increase in the frequency of liver carcinoma in B6C3F1 mice. This result provides experimental verification of an assumed extrapolation between routes of administration from a gavage study, as described in the Health Assessment Document.

The Subcommittee believes it is reasonable to describe the weight of the epidemiological evidence in humans as conforming to the EPA guideline for carcinogen risk assessment definition of "inadequate." The Subcommittee concludes that the animal evidence of carcinogenicity is "limited" because of positive results in only one strain of mouse of a type of tumor that is common and difficult to interpret. Thus, the Subcommittee concludes that perchloroethylene belongs in the overall weight-of-the-evidence category C (possible human carcinogen).

In the opinion of some members of the Subcommittee, a quantitative assessment of perchloroethylene is desirable, and the mouse data are adequate for this purpose. Treatment of this assessment as a "what-if" calculation, as presented in the original Health Assessment Document, is desirable. Such a quantitative assessment probably will show that an increase in cancer would not be detected in the groups most exposed to perchloroethylene at current exposure levels. This inference deserves mention in the executive summary. The analysis of pharmacokinetics in the draft Addendum is commendable and will support further estimates of the possibility of cancer in exposed populations.

The Subcommittee requests that the Environmental Health Committee address the question of whether one-tailed or two-tailed statistical tests of significance are appropriate for the routine analysis of bioassay data. Agency staff reported at the meeting that one-tailed tests are routinely used. This use assumes that chemical substances can only increase the frequency of cancer, but this assumption seems contrary to empirical observations. Resolution of this issue will influence the conclusions regarding perchloroethylene. In addition, the Subcommittee requests that the Environmental Health Committee arrange for a detailed review of the physiological-pharmacokinetic model used in the analysis of perchloroethylene. The Subcommittee reviewed some results of the model but not the model per se. EPA is likely to use the model in the future to assess the risks of other substances.

In support of the review of perchloroethylene, the Subcommittee requests that the Agency provide the members with analyses of (1) human carcinogens and their effects in the rat and mouse, (2) human hepatotoxins and their effects in the rat and mouse, and (3) human renal toxins and their effects in the rat and mouse.

The Subcommittee believes that the final Addendum will enhance the value of the Health Assessment Document and that, contingent on the correction of the issues discussed in the attached report, the document will be scientifically adequate to meet its stated purposes. We appreciate the opportunity to comment on this public health issue and request a formal response to our advice.

Sincerely,

John Doull, M.D., Ph.D.
Chair, Halogenated Organics Subcommittee

Seymour Abrahamson, Ph.D.
Vice-Chair, Halogenated Organics Subcommittee

# REPORT OF THE HALOGENATED ORGANICS SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE ON A DRAFT ADDENDUM TO THE HEALTH ASSESSMENT DOCUMENT FOR TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

## Introduction

The Halogenated Organics Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board met on May 15, 1986 in Madison, Wisconsin, to review a draft Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene; Updated Carcinogenicity Assessment; EPA-600/8-82/005FA; March, 1986). The Environmental Health Committee previously reviewed the draft Health Assessment Document for perchloroethylene on May 9-10, 1984. A report on this draft was sent to the Agency on January 4, 1985. The draft Addendum primarily analyzes the results of a 1985 inhalational bioassay by the National Toxicology Program performed at Battelle Pacific Northwest Laboratories. The Subcomittee thanks the National Toxicology Program for sending a representative, Dr. John Minnear, to contribute to the discussion at the May 15th meeting.

The Subcommittee concludes that the Addendum improves the scientific foundation of the existing Health Assessment Document and further improves the Agency's ability to perform a risk assessment for this compound. The Agency intends for the Health Assessment Document to serve as a multimedia source document. The Subcommittee believes that, contingent on the correction of the issues discussed below, the draft Addendum will also be scientifically adequate for this purpose.

## Quality Assurance of the Bioassay

The Subcommittee reviewed the available quality assurance information of the bioassay. It concludes that these audits were properly carried out and generally are consistent with each other. The quality assurance process identified discrepancies during the collection of in-life toxicology data, verification of analytical chemistry results, cage injuries, brief overexposure of the high dose group of rats, autolysis of some specimens, and the failure to section all lesions. Some animal escapes and confusion over animal identification were reported. However, there is little possibility that animals moved from control to test cages, or between test groups, because the animal housing in the Battelle inhalation chamber is well controlled, and the chambers are in rooms within a barrier facility. The Subcommittee also does not believe that resorting a few animals would likely create a positive result as an artifact with a rare tumor. The random movement of a few animals between cages is more likely to obscure the detection of a statistically positive finding of an infrequent lesion.

These problems are fairly common in bioassay work and do not impede the interpretation of clear, distinctive findings. The Subcommittee believes that the bioassay provided data that are adequate for risk assessment, unless EPA attempts to interpret small differences between groups of animals.

The Subcommittee recommends that the Agency summarize and assess the implications of the quality assurance information in the final Addendum.

Interpretation of the Carcinogenicity Results

The draft Addendum describes two lesions of potential interest that occurred in Fisher 334/N rats--renal tubular neoplasia and mononuclear cell leukemias. The Subcommittee concludes that the National Toxicology Program bioassay does not provide a scientific basis to associate either lesion with inhalational exposure to perchloroethylene. Both findings would result from small differences between control and treated groups, and they conflict with other bioassays of perchloroethylene in the rat and which are problematic in relation to the quality assurance conclusions. Both findings have multiple problems, any one of which overwhelms the interpretation. These problems include:

a) Perchloroethylene neither appeared to induce an increase in rare renal tubular neoplasia in male rats, nor was the trend in these tumors among the male rats dose-related. No renal tubular neoplasia were observed in female rats. The reported numbers of adenomas in male rats were 1/49 (control), 3/49 (200 ppm) and 2/50 (400 ppm). Renal tubular carcinomas occurred in 0/49 (control), 0/49 (200 ppm) and 2/50 (400 ppm) of the male rats. When results of both tumors are reported, the numbers of animals affected were 1/49 (control), 3/49 (200 ppm) and 4/50 (400 ppm). To attribute statistical significance to the findings in male rats, the analysis aggregated adenomas and carcinomas. However, the analysis of numbers of animals with adenomas or carcinomas as a group is not an obvious biological procedure.

The pathology of these tumors is not well-understood, and little background information is available in the literature. The diagnosis of renal tubular neoplasia in the rat is not a clearly understood procedure among experts. Whether or not conversion from adenoma to carcinoma occurs is not known, and the draft Addendum does not review this subject. In addition, the statistical analyses supporting conclusions in the text are in error. The Fisher exact test has been miscalculated, and trend has not been analyzed.

The Subcommittee recommends that the Agency develop better descriptions of (1) the pathology of the renal tubular neoplasia in rats (including speculations about progression or conversion), and (2) the rationale for aggregating the numbers of animals with adenomas or carcinomas. At a minimum, it should assess each data set independently before evaluating the aggregated data, and the results of statistical tests for any trends. For the benefit of potential non-expert readers, the final Addendum needs to clarify that the enumeration of rats with carcinoma or adenoma is subject to debate.

To analyze the renal tubular neoplasia results, the Agency has to address several competing hypotheses, such as an unusual occurence within: the specific group of F334 rats used in the bioassay, aberant housing conditions, historical underdetection of renal tubular neoplasia, induction of tumors by perchloroethylene, and so forth. Eight (8) out of 148 (5.4%) male rats had findings of adenoma or carcinoma. Either this frequency or the frequency for all untreated rats, male and female (8/296; 2.7%) can be compared to the reported historical frequency of 4/1,720 or 0.23%. (The note in the draft Addendum does not clearly state the basis of the historical observations.) The Addendum also needs to address the credibility of this number in the light of the probably variable search for lesions in the absence of cross observations that suggest a neoplastic response. Historically, renal tubular neoplasia in control rats tend to be under-reported.

Questions can be asked and then answered, about possible biological or statistical reasons for the differences in control and overall incidence. The Subcommittee suggests that the staff calculate the prior likelihood of the frequency of renal tubular neoplasia under different hypotheses about the average rate of occurrence, using the Poisson distribution. The staff can compare these results to each other and to the biological interpretations of each hypothesis.

b) Perchloroethylene did not appear to induce a marginal increase in mononuclear cell leukemia in rats. At the present time, the scientific community has a poor understanding of the pathology of mononuclear cell leukemia. The high frequency in all groups, including controls is not usual for F334 rats. The results suggest faulty pathological diagnoses or some unusual circumstances in the rat colony at the time. The extent of characterizing mononuclear cell leukemias was histopathological examination. Other means of characterization, which are necessary to distinguish neoplasia from leukocytic hyperplasias that may develop in older rats, were not used.

The results of the statistical analysis are not convincing. The Addendum presents the mononuclear cell leukemia data in terms of a progressive three stage classification which appears to be preliminary and ad hoc. The staging of diagnoses does not represent a consensus effort of the community of experienced pathologists. However, the draft Addendum states that the strength of the evidence for carcinogenicity in the F334 rat rests on the resolution of issues regarding the uncertainty in the assignment of frequency within the stages of mononuclear cell leukemia. No human analogue is known for mononuclear cell leukemia of the rat. This absence is not important for EPA's policies on carcinogenicity, although a lack of correspondence does concern some biologists. However, the absence of a human analogue is important, when staging is considered, since staging refers to the usually more extensive information on leukemic progression in humans.

If a two-tailed test is used, the most striking observation in the results occurred at 200 ppm, in which 18 of 50 female rats in the control group were reportedly diagnosed as having mononuclear cell leukemia in one of the three stages versus 30 of 50 of the perchloroethylene treated female rats. This comparison leads to a confidence limit of about $p = 0.03$ by the Fisher exact test (two-tailed). Regardless of the statistic, 18 versus 30 is not a striking observation and, given the generally high frequency of mononuclear cell leukemia diagnoses in all groups, it is worth inquiring what the chance is of finding such a result if two of six groups are drawn at random, each group being subject to the same high, random frequency of diagnoses (reported as 179 of 300 or about 60%).

In oral statements at the meeting, Agency staff reported that a statistically significant difference between untreated and perchloroethylene treated rats could be observed for mononuclear cell leukemia, if the time-to-tumor was analyzed. This may be the case, but these oral statements contradict the written statements in the draft Addendum regarding time-to-tumor. Some Subcommittee members have attempted to evaluate whether or not diagnosable mononuclear cell leukemia occurred earlier in perchloroethylene exposed rats than in unexposed.

The presentation of data in the draft Addendum is such that this comparison cannot be made because neither the actual data, nor the dependent probabilities, are presented. (See "statistical analyses," below.) However, the draft Addendum states anectodally at several points that this comparison is not worth making because of analyses contained in the National Toxicology Program report.

The draft Addendum does not review the analyses, and does not present the supporting data. However, if the oral comments are correct, then either the National Toxicology Program analysis, or the interpretation of this analysis in the draft Addendum, is in error.

The Subcommittee suggests that the Agency will experience difficulty in gaining scientific support for the conclusion that perchloroethylene exposure is associated with increased frequency of mononuclear cell leukemia in rats, based on the National Toxicology Program bioassay data. Any effort to do so should begin with an explanation of why the frequency of this rumor did not increase after perchloroethylene exposure of rats in the bioassays performed by the National Cancer Institute and by Rampy and co-workers.

The Subcommittee agrees with the statement in the draft Addendum that first generation hybrid mice of C57BI6 and C3H parental orgin (B6C3F1) exhibit statistically significant increases in carcinoma of the liver associated with exposure to perchloroethylene by inhalation. These results confirm the findings of a National Cancer Institute study with the same strain of mouse and administration of perchloroethylene by gavage. The Environmental Health Committee and its Subcommittees have consistently urged the Agency to calculate the potency of a carcinogen for all routes of administration when data are available for only one route (using the best general information about uptake, absorption, metabolism, distribution, elimination and mechanism). Once data has existed for one route, it has advised EPA to use the empirical evidence as the basis for decision-making and to forgo the hypothetical calculation. Perchloroethylene provides an example of experimental validation, both qualitatively and quantitatively, of the hypothetical extrapolation. However, this validation does not change the interpretation on which a decision might be based. No new, dispositive information has been gained.

Although the possibility exists that carcinomas arise de nova, the available evidence strongly supports the idea that the adenomas and carcinomas represent a single disease process to which scientists have applied an arbitrary division into two diagnostic terms. Since we usually don't know the rate at which the various lesions progress after exposure to a given test chemical, and because histologic evidence alone is not entirely a satisfying indicator of biological behavior, the Subcommittee recommends analyzing the lesions both separately and combined. It should be remembered that many mice with hepatic carcinomas also have adenomas that have not been included in the summary tallies.

Other Data from the National Toxicology Program Bioassay

The Subcommittee requests that Agency staff fully assess all of the information available from the National Toxicology Program study. The draft Addendum notes the occurrence of squamous cell metaplasia of the nasal cavity in male rats but does not provide statistical analysis of significance or trend with dose. The draft Addendum refers to a finding of renal tubular cell hyperplasia in rats, but no data are provided. Renal tubular karyomegaly is noted in rats and mice of both sexes, but no data are provided.

The Subcommittee also recommends that Agency staff thoroughly assess and interpret the significance of mortality outcomes for rodents chronically exposed to perchloroethylene in the National Toxicology Program bioassay. These data can be important in setting standards for drinking water. One interesting possibility is that the kidney also is a target organ. The draft Addendum notes excess mortality in mice at 100 ppm and 200 ppm but suggests that this result is caused by hepatic cancer. An appropriate statistical analysis of mortality will correct for this effect by correctng for deaths from hepatic cancer (a time-to-not-tumor calculation).

Statistical Analysis of the Bioassay Results

The display of data and statistical analysis of these data in the draft Addendum needs revision. The Subcommittee found some critical instances of misquotation and error.

While the statistical analyses reported in the Addendum can be reproduced by the Subcommittee, this can only be done if a one-tailed Fisher exact test is used. The use of a one-tailed test is appropriate, if perchloroethylene only can increase the frequency of cancer. This assumption is dubious when the background in the control group is high, and it is contrary to the general knowledge about the effects of chemicals on tumor frequency in rodents.* Instead, a two-tailed test seems appropriate. The Agency should state whether an analysis is one-tailed or two-tailed in the text.

Metabolism and Pharmacokinetics

The Subcommittee believes that the draft Addendum and the final Health Assessment Document provide a thoughtful response to the comments regarding pharmacokinetics made during the previous review. The data in the draft Addendum are adequate for evaluating potential metabolic mechanisms which pertain to possible carcinogenic effects perchloroethylene. Further, the Subcommittee commends the Agency for the discussion of the different mechanistic implications of perchloroethylene metabolites in the induction of cancer.

At present, the Subcommittee has only reviewed some results of the model used by Agency staff to analyze data for perchloroethylene. Because of the potential importance of such models for EPA risk assessments, the Subcommittee recommends that the Environmental Health Committee undertake a review of the general approach. However, the Subcommittee has developed a consensus regarding one issue that was subject to contention during the public meeting. EPA has not double counted the factor for interspecies extrapolation of metabolized dose. Because staff have modeled the absolute amount per unit volume (tissue specific concentration), some extrapolation between species is required. However, the Agency loses some of the power of the physiological-pharmacokinetic models when this approach is taken.

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* See, for example, J.K. HASEMAN, "Patterns of Tumor Incidence in Two-year Cancer Bioassay Feeding Studies in Fisher 334 Rats," Fundamental and Applied Toxicology 3 (1983), pp. 1-9.

Because of the implication that tetrachloroethylene oxide is a carcinogenic intermediate, discussion of the reactivity of various haloethylene oxides should be included. Agency staff should search for studies which correlate the chemical reactivity, hepatotoxicity and carcinogenicity of haloethylene oxides, such as those by Henschler or Van Duuren.

Most studies have attributed the metabolism of perchloroethylene to a proposed reactive metabolite, tetrachloroethylene oxide, which is converted by rearrangement to trichloroacetyl chloride. The latter will acylate rather than alkylate macromolecules. The acylation reaction could be followed by spontaneous hydrolysis and regeneration of the free macromolecules. Thus, no genetic effect may be observed. Indeed, Van Duuren and coworkers have concluded from their studies of the carcinogenicity of various halo-substituted ethylene oxides that tetrachloroethylene oxide is not carcinogenic when administered to rats by any of several routes.

The discussion in the addendum suggests that tetrachloroethylene oxide is the only reactive, carcinogenic metabolite formed following perchloroethylene administration. The Subcommittee recommends that other putative carcinogenic metabolites be described. For example, glutathione conjugation products should also be included. The role of these potential metabolites in eliciting effects, such as renal damage or carcinogenicity, should be discussed. Henschler has suggested glutathione conjugates of various haloethylene compounds as the proximal initiators of renal toxicity, particularly after hydrolysis in the kidney renal tubule.

Several authors have described the covalent binding of radioactive perchloroethylene to tissues after metabolic activation. This binding may be partially due to the formation of acyl derivatives after the formation of trichloroacyl chloride as an intermediate, as suggested by studies in which trichloroacetic acid was found after acidic hydrolysis of labelled macromolecules. The significance of the acylation reaction in genotoxicity is not clear. However, no covalent binding to deoxyribonucleic acid has been demonstrated, which is indicative of a protective or hydrolytic mechanism, perhaps accelerating the decomposition of tetrachloroethylene oxide to trichloroacetyl chloride before the oxide can gain access to deoxyribonucleic acid. Trichloroacetyl chloride can react with macromolecules to form various trichloroacetic acid esters which may undergo rapid enzymatic hydrolysis to yield trichloroacetic acid and regenerate the macromolecules. This hypothesis merits investigation.

Genotoxicity

The Subcommittee disagrees with the statement in the draft Addendum that perchloroethylene is genotoxic by implication because a metabolite of perchloroethylene is genotoxic. Tetrachloroethylene oxide, the metabolite in question, is not a demonstrated metabolite of perchloroethylene but a postulated metabolite, although the assumed pathway is reasonable. The hypothetical conversion of perchloroethylene to tetrachloroethylene oxide does not appear to account for the carcinogenic properties of perchloroethylene, because perchloroethylene is not mutagenic and because tetrachloroethylene oxide is apparently not carcinogenic. Perchloroethylene has been tested in many mutagenicity bioassays, a few of which show positive activity, but on balance the weight-of-the-evidence is borderline and not conclusive.

Mechanism

Given the current evidence, the Subcommittee hypothesizes that, operationally, perchloroethylene may be an indirect acting carcinogen or carcinogenic promoter of low potency. By promoter, the Subcommittee means that perchloroethylene alone does not induce tumors. Instead, perchloroethylene appears to act in concert with other substances, endogenous processes, viruses, oncogenes, or radiation, which can initiate cancer in the absence of promoters. Initiators are usually thought to be genotoxic substances, binding to deoxyribonucleic acid in order to cause initiating events. When perchloroethylene is present, however, tumors are observed when they would not otherwise be, even when the initiator is not known. Although definitive evidence is lacking, perchloroethylene appears to act at a later stage in the carcinogenic process.

The evidence which leads to the Subcommittee's hypothesis that perchloroethylene may act as an indirect acting carcinogen or a promoter is that perchloroethylene: (1) probably is not mutagenic; (2) does not bind to deoxyribonucleic acid; (3) increases the frequency of liver carcinomas in B6C3F1 mice when these tumors are commonly seen in the same strain not exposed to perchloroethylene; (4) induces liver carcinoma in a species and strain specific manner; (5) induces peroxisomes in the livers of B6C3F1 mice, which provides an alternative mechanism; and (6) acts consistently in comparative studies of halo-substituted ethylenes which indicate that asymmetrically substituted compounds generally are carcinogenic, whereas symmetrically substituted generally are not.

Epidemiology

The Environmental Health Committee has previously reviewed the epidemiological evidence as it was discussed in the Health Assessment Document. The Subcommittee finds no reason to alter the Committee's previous findings at this time. The National Cancer Institute may publish a new epidemiology study of perchloroethylene.* The Subcommittee recommends that the Agency evaluate these results in the Addendum, if they are available in a timely and satisfactory form.

Weight-of-the-evidence Category

Based on the National Toxicology Program bioassay results and the Agency's guidelines for carcinogen risk assessment, the Subcommittee concludes that "limited" evidence exists for the carcinogenicity of perchloroethylene in animals because the evidence arises only from a single strain of mouse and because the kind of tumor associated with perchloroethylene exposure in this mouse strain makes it difficult to create an inference regarding human carcinogenicity. The epidemiological evidence is described in the Health Assessment Document as "inadequate." Working from EPA's proposed guidelines, the Subcommittee concludes that the overall weight-of-the-evidence category is C ("possible human carcinogen"). The Subcommittee has carefully considered and rejected the position of some staff that positive evidence of liver carcinoma in the B6C3F1 mouse associated with exposure to perchloroethylene by two different routes of administration should change the weight-of-the-evidence category to B ("probable human carcinogen").

* See A. BLAIR, P. TOLBERT, T. THOMAS and D. GRAUMAN, (Abstract) Mortality among Dry Cleaners. Fourth International Symposium on Epidemiology in Occupational Health (September 10-12, 1985).

Quantitative Potency Estimate

Estimation of the upper bound of perchloroethylene potency will convey some of the implications of the bioassay results, and the data are adequate for this purpose. However, it is important to clarify for the lay reader that the range described is an upper bound estimation of risk, not a range of risk. Some Subcommittee members strongly advocate the usefulness of such "what-if" estimates for policy purposes, and on balance there are no strong reasons not to continue with this approach.

The Health Assessment Document has made a good start in comparing animal and human upper bound potency estimates, and the Subcommittee recommends that the final Addendum make a more detailed effort in this area, particularly if new epidemiology data are analyzed. Because a what-if calculation based on the mouse data will suggest that new cases of cancer could not be detected in the group most exposed to perchloroethylene, the conclusions from this comparison are important for Agency decision-making and should be placed in the executive summary.

Exposure and Risk

The draft Addendum does not contain exposure estimates for perchloroethylene. Because of the immediate possibility that human exposures can be estimated with good accuracy from urinary excretion levels of trichloroactic acid, the Subcommittee recommends that the final Addendum summarize the current published exposure information, make explicit the linkage to the pharmacokinetics of perchloroethylene and integrate the hazard and exposure information.

Editorial Quality

Some sections of the draft Addendum were of poor editorial quality. Some specific errors were unfortunate, such as confidence limits misquoted from the National Toxicology Program bioassay report and a topsy-turvy description of time-to-tumor data because they occurred at pivotal points. These errors tend to reduce confidence in the Agency's interpretation.

Miscellaneous Issues

The Subcommittee would like to receive a brief update on animal bioassays of perchloroethylene that are in progress or have recently been completed.

The draft Addendum does not note research needs. Bioassays of perchloroethylene in mouse strains with distant genetic relationships to the B6C3F1 mouse could be most informative. New data could refine the physiological-pharmacokinetic model.

Perchloroethylene is a widely distributed compound and enters breast milk in significant concentrations. It is not known whether or not infants are significantly more sensitive to this compound than are adults. EPA should identify this as an additional area of uncertainty.

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
Perchloroethylene Panel

May 15, 1986
Madison, Wisconsin

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Executive Secretary

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