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

March 9, 1988

SAB-EHC-88-012

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:

The Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee met on August 13-14 1987 to evaluate the scientific adequacy of the Office of Research and Development's July 1987 Draft Addendum to the Health Assessment Document for Trichloroethylene. The attached report completes the Subcommittee's evaluation of this document.

The Subcommittee's conclusions and recommendations for the major issues in the review include the following:

- In general, the document has evaluated the relevant studies and presented their strengths and weaknesses in a balanced manner.

- The evidence for the carcinogenicity of trichloroethylene in animals is appropriately discussed in the draft Addendum. However, the Addendum should place greater emphasis upon such issues as: the inconsistency among many experiments because of the number of apparent negative as well as positive results; the possibility that the parent compound is a tumor inducing agent: and, in the context of metabolism and pharmacokinetic data, discussion of the in vitro and in vivo data that suggest that trichloroethylene is a weakly genotoxic agent.

- The overall weight of evidence lies on the continuum between the categories B_2 and C of EPA's risk assessment guidelines for cancer. The Subcommittee's major concern with the Addendum, and with the classification system of the guidelines, is that the relatively moderate tumor responses and the uncertainties regarding most of the assumed endpoints are not adequately presented.

- Trichloroethylene has the potential to cause cancer in humans, but its potency is low. Current scientific evidence reports liver tumors in two strains of mice by two routes of administration, lung tumors in mice by inhalation and renal tumors in rats following gavage. There is also limited evidence for lymphomas in rats and mice, forestomach tumors in mice and testicular interstitial cell tumors in rats.

We appreciate the opportunity to conduct a scientific evaluation of this compound. In behalf of the Subcommittee, we request that the Agency formally respond to the scientific advice provided in the attached report.

Sincerely,

Norton Nelson, Chair
Executive Committee

Richard A. Griesemer, Chair
Environmental Health Committee

John Doull, Chair
Halogenated Organics Subcommittee

Report of the Halogenated Organics Subcommittee of the
Office of Research and Development's July 1987 Draft
Addendum to the Health Assessment Document for Trichloroethylene

Major Conclusions and Recommendations

1. The draft addendum appropriately evaluated the relevant studies and presented their strengths and weaknesses. The scientific evidence for the carcinogenicity of trichloroethylene in animals is appropriately discussed in the draft addendum.

2. Current scientific evidence reports liver tumors in two strains of mice by two routes of administration (oral and inhalation). There is also evidence of lung tumors in mice by inhalation, for renal tumors in rats following gavage, limited evidence for lymphomas in rats and mice, forestomach tumors in mice and testicular interstitial cell tumors in rats.

The draft addendum needs to place greater emphasis upon the inconsistency among reported observations across many experiments. There are as many negative as positive study results, and interpretation of the results requires careful examination of factors such as: the varying purity of the test substances (some contain epichlorhydrin, for example); the difficulty in setting a maximum tolerated dose (MTD) because of cumulative and delayed toxic effects (many studies used dose rates that were either too high or too low); varying ages at the start of exposure; differing durations of exposure; lack of adjustment for early mortality; and under reporting of the extent of histopathological examinations. As a result, it is not clear from the draft addendum if the scattered reports of leukemias and testicular and forestomach tumors are false positive errors or indicators of widespread effects.

The endpoints with the most biological plausibility, based upon what is known about the effects of structurally related compounds, are liver and lung tumors in mice and renal tumors in rats. Liver tumors (benign and malignant) in mice appear unequivocally related to compound administration by two routes of exposure in one inbred and one outbred strain of mice. The incidences in the National Toxicology Program (NTP) 1982 assay are 76 per cent in male mice compared to about 35 per cent expected (some male control groups yield 55 or 60 per cent tumors) and 39 per cent in female mice compared to 10 per cent as an approximate expected rate. While clearly in excess, they do not approach the incidence of 100 per cent that occurred for chloroform, for example. This suggests a lower or more moderate potency for trichloroethylene. Three other studies in mice gave negative results, although all were flawed to some degree. The flaws involve small group sizes, testing in only one sex, short duration of treatment, overdosing and unexpectedly low tumor incidences in control mice.

Lung tumors did not increase in Swiss mice (slight increase in the low dose males but not in the high dose males), while in the B6C3F1 mice increases in the males were observed only at the high dose (if adenomatous hyperplasia is combined). In a replicate study in the same laboratory, increases were observed in high dose female but not in male mice. The Subcommittee considers

these types of results as suggestive but not definitive for the mouse lung. Renal tumors in rats are reported for F344 and S-D rats but not for CM rats. In F344 male rats, renal adenomas or carcinomas were 0/48 in controls, 2/49 in low dose and 3/49 in the high dose group. In S-D rats, only 5 of 129 high dose male rats had renal tumors. The Subcommittee does not view these reported results as indicative of a potent effect, and recommends that this viewpoint be expressed in the draft addendum.

3. The significant body of in vitro and in vivo data that suggest that trichloroethylene is, at best, only weakly genotoxic have not received appropriate weight of evidence consideration, particularly when considered in the context of metabolism and pharmacokinetic data. The draft addendum has also not seriously evaluated several significant studies implicating the potential role of hepatic peroxisome proliferation in mediating trichloroethylene carcinogenicity. Instead, it stresses the view of direct acting genotoxic mechanisms of carcinogenicity. An expanded presentation of these points should be included.

4. Although there is an impressive weight of evidence implicating the metabolites of trichloroethylene in tumor induction, the possibility should not be discounted that the actual tumor inducing agent is the parent compound. To enhance the completeness of the draft addendum, this possibility should be discussed at greater length.

5. Unpublished experimental data should either be subjected to quality assurance checks and external peer review or used in only a limited way, if at all, as a basis for quantitative risk assessment. The report of studies by Maltoni using trichloroethylene are incomplete and, thus, of questionable value. However, his observations of lung tumors in mice, Leydig cell tumors in rats and kidney tumors in rats may be considered to be in agreement with the Henschler and Fukuda mice studies and the NTP rat studies.

6. The Subcommittee has also reviewed the draft addendum with respect to genotoxicity (mutagenicity, chromosome aberations and DNA damage) endpoints. The very limited additional data does not lead to a clearer understanding of potential genotoxicity than previously existed.

7. The Subcommittee concludes that trichloroethylene has the potential to cause cancer in humans, but that its potency is low. The conclusion in the draft addendum should be qualified by stating the moderateness of the tumor responses and the uncertainties of most of the supposed endpoints. It should be emphasized that chlorinated hydrocarbons are difficult to test because of the cumulative effects of toxicity and that the weight of evidence is not necessarily an either/or judgment among the current categories of EPA's risk assessment guidelines for cancer. The Subcommittee concludes that the interpretation of the weight of evidence falls on the continuum between sufficient and limited evidence and could be reasonably judged either way. In the case of tetrachloroethylene, the mouse liver tumor response was more

exaggerated, and a committee of the International Agency for Research on Cancer (IARC) judged it to have sufficient evidence for carcinogenicity. The same committee concluded that the animal evidence for trichloroethylene was limited, although it is not clear whether all of the studies reviewed by EPA were considered by IARC.

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
Roster for August 13-14, 1987 Review of the Draft
Addendum to the Health Assessment Document for Trichloroethylene

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