UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
January 4, 1985

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

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Ruckelshaus:

On November 29, 1984, the Environmental Health Committee of EPA's Science Advisory Board received a report from its Chlorinated Organics Subcommittee, chaired by Dr. Seymour Abrahamson, following its November 8 review of a draft Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride), which was prepared by the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development [EPA-600/ 8-84-006A; April, 1984; External Review Draft]. The stated purposes of the draft document are to serve as a source document to support decision-making, initially for the Office of Air Quality Planning and Standards but subsequently for other program offices, and to place health effects in perspective with environmental concentrations of this chemical.

The Environmental Health Committee further reviewed the health assessment document and evaluated its Subcommittee's report. The document is intended to inventory the scientific literature and evaluate key studies regarding the toxicity and related characteristics of ethylene dichloride. The Committee finds that the draft document satisfies these objectives in a scientifically adequate manner. While the Committee contributed a few additional citations, these did not significantly alter the draft document's major conclusions.

The Committee's key conclusions regarding the health assessment document include:

o Concurrence that the available scientific information demonstrates that ethylene dichloride is not a teratogen but is a mutagen.

o Agreement that ethylene dichloride falls into category 2B (the chemical... is a probable human carcinogen) of the criteria established by the International Agency for Research on Cancer. This conclusion is based on data generated by studies using the oral route of administration. Similar studies using the inhaltion route of exposure gave negative results, and the Committee does not believe that present evidence supports the conclusion that ethylene dichloride is carcinogenic via inhalation.

We appreciate the opportunity to comment on the public health issues relating to ethylene dichloride. More detailed technical comments by individual Committee members have been communicated directly to OHEA. The Committee understands that new toxicology studies will reach completion in the near future. The Science Advisory Board stands ready, if requested, to review the Agency's analysis of this information, the exposure assessment, or the ecological effects of ethylene dichloride. We request a formal response to our advice in this report.

Sincerely,

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

Norton Nelson, Ph.D.
Chair, Executive Committee

cc: Alvin L. Alm (A-101)
Joseph A. Cannon (ANR-443)
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MAJOR CONCLUSIONS AND TECHNICAL COMMENTS BY THE ENVIRONMENTAL HEALTH COMMITTEE'S CHLORINATED ORGANICS SUBCOMMITTEE ON EPA's DRAFT HEALTH ASSESSMENT DOCUMENT FOR 1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE)

On November 8, 1984, the Chlorinated Organics Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board reviewed a draft Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride) which was prepared by the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development [EPA-600/8-84-006A; April, 1984; External Review Draft]. The Subcommittee's major conclusions and technical comments are discussed below.

Summary and Conclusions

The Subcommittee recommends that OHEA summarize the generally important information about the health effects of ethylene dichloride from the document for the reader. The current Summary is essentially a table of contents, in prose form, when an outline of the contents is already available. In particular, the essential conclusions for a user under time stress, as in the case of a transportation spill, should be immediately accessible.

Exposure

The Subcommittee received a companion summary of exposure information for 1,2-dichloroethane from the Office of Air Quality Planning and Standards (OAQPS) that summarizes the Agency's current understanding of ambient exposure levels. The Subcommittee wishes to express its appreciation for this information, since otherwise it would be impossible to compare observed effect levels or dose-response relationships with environmental levels.

The Subcommittee understands the difficulty that the Agency has in estimating exposures because those levels are in the process of changing. We point out, however, that the Subcommittee has not reviewed either the methodology or the data by which OAQPS arrived at its statements regarding exposure.

The health assessment document describes the analytical methodology used to detect ethylene dichloride and provides information on previous releases of this substance. Although releases change with time, this information is critically important in a source document because of the lag that can take place between exposure and the occurrence of chronic health effects. Similarly, the information in the draft document about fate and transport are of importance to the toxicologist's ability to understand the relevance of experiments using different routes of exposure. The Subcommittee reviewed the exposure data that was made available, but its expertise should not be regarded as thorough at this time.

Table 7-8 should be deleted, for it duplicates other tables in this section, and some of the data displayed may reflect double counting.

Ecological Effects

The Subcommittee did not comment on this issue.

Pharmacokinetics

The pharmacokinetics of ethylene dichloride are noteworthy in that, although the half-life of disappearance is dose-dependent, the rates of disappearance at specific doses are first order not zero order. The Subcommittee is at a loss to explain this phenomenon. Perhaps differing limitations to loss exist at different ethylene dichloride doses. However, the draft document has not interpreted the data correctly. The disappearance of ethylene dichloride clearly is zero-order with dose, as best shown in the 1982 article by Rietz. In addition, some dose-response data from a bioassay of ethylene dichloride are consistent with nonlinear metabolism in that the response has a linear relationship to some power of dose that is less than one (<1).

The pharmacokinetics of ethylene dichloride have important implications for the quantitative assessment of its carcinogenic risk. Since OHEA uses a "plausible upper bound" method based on administered dose to estimate risks, the pharmacokinetic information will not change the risk estimate used in the text. Although the pharmacokinetics of this compound suggest linearity, the Agency's method does not incorporate this information. The plausible upper bound method has its basis in an appropriate, protective policy for a public health agency. Because the prediction of actual risk at low doses exceeds the state of the art in risk assessment, the Subcommittee does not disagree with the use of this method. However, OHEA should not attempt to provide a scientific rationale for the use of this method in the draft document when the basis for its use is a risk management decision.

In contrast to the impact on the plausible upper bound estimate of risk, the justification of linearity and the uncertainty in risk will change from the description in the draft when non-linear pharmacokinetics are considered.

The pharmacokinetic information on ethylene dichloride was developed for purposes other than risk assessment. Different experimental designs will be necessary to obtain more relevant data. If ethylene dichloride becomes an important public health priority, then EPA may want to consider performing this research.

Much of the information on the metabolism of ethylene dichloride appears to be based on analogy to the metabolism of a similar chemical, ethylene dibromide. While it may be useful to compare these two substances, the text errs in confusing hypothetical metabolites with intermediates that have been isolated and analyzed. This occurred to such an extent that some publications are described in the text as supporting the existence of certain metabolic species, when in fact these papers did not study ethylene dichloride. OHEA should use a more critical approach regarding the pattern of ethylene dichloride metabolism.

Acute and Subchronic Effects

The Subcommittee does not understand why OHEA has emphasized Russian data on ethylene dichloride so extensively, particularly when the draft document explains why this information is not reliable. The document should delete or clarify most of these references. Further, the extensive textual tables of anecdotal data on clinical incidents reflect a misemphasis. The Subcommittee recommends that this information be placed into an appendix to which the main

text can refer.

Teratology and Reproductive Effects

The conclusions in the draft document are generally reasonable. The available information does not show that ethylene dichloride is a teratogen, nor is the epidemiological evidence sufficient to document these effects. The summary of this information on page 1-4 needs rewording, since it does not state that the research need is for epidemiology. By analogy to other halogenated organic chemicals, it is also reasonable to suspect testicular effects and, therefore, to suggest experimental animal research to confirm or deny this possibility.

Mutagenic effects

The document concludes that the available information shows that ethylene dichloride is a mutagen. The Subcommittee agrees with this finding. On page 1-4, the summary states that it is a "weak" and "direct-acting" mutagen in prokaryotes. The Subcommittee prefers that OHEA avoid the use of qualifiers such as weak and strong to refer to potency in this context since it potentially confuses potency with severity of effect. It would be better to state in the summary that, for example, at a certain dose, DNA alkylation in the rat corresponds to a five-fold increase in bacterial rate. It is helpful to describe potency on a relative basis in comparison to other mutagenic chemicals. The induced mutation rate obtained with the given dose of ethylene dichloride in Drosophila (described on page 9-151) is of the same order as that which would be induced by a dose of two to three thousand rad of x-rays. The Subcommittee does not agree that this potency is "weak." Similarly, direct-acting appears to mean that no cytosolic activation was required, in which case it seems better to state "not requiring metabolic activation in cell culture experiments."

The Subcommittee agrees with the statement in the document that it is reasonable to do an animal experiment to test for mutagenesis in gonads.

The Subcommittee believes that the statement on page 9-149, ninth line from the bottom, is wrong. The experiment illustrated in the table of page 9-155 does not describe (and needs) mating data. This is not a good experiment, and OHEA should not rely on it to conclude that non-disjunction occurs. Similar problems exist with the data in Table 9-31 on page 9-156.

Carcinogenicity

Prior to the Subcommittee's review, OHEA scientists committed to make some revisions in the text. The "boilerplate" is to be brought up to the current standard for other chemicals reviewed by the Agency. The definition of "unit risk" is to be corrected. OHEA will update the table on page 9-230. The weight of the evidence sections on ethylene dichloride will be reworked.

The document concludes that ethylene dichloride falls into category 2B (the chemical...is a probable human carcinogen) of the criteria established by the International Agency for Research on Cancer (IARC). The Subcommittee agrees with this finding for the oral route of exposure but disagrees for

the inhalation route. For oral administration, tumors occurred with two species of rodents (both rats and mice), for both males and females and in multiple studies. However, the evidence for the inhalation route is negative.

The document should clarify whether the doses in the inhalational study by Maltoni were comparable to the doses in the National Cancer Institute study which used the oral route of administration. Information on page 68 of the Banbury Report on ethylene dichloride indicates that the doses are about the same. The similarity (or lack thereof) of doses is critical to an understanding of inhalational carcinogenicity.

The draft document has used the occurence of DNA alkylation and mutagenicity by ethylene dichloride to support the classification of ethylene dichloride as a probable carcinogen. However, when ethylene dichloride is inhaled, alkylation occurs in the same tissues as when the chemical is given orally, and no tumors are found. The document needs to point out this fact and address its implications.

In addition to quantitative differences in levels of metabolites or in distribution, qualitative differences in toxicity with the route of administration are known for some chemicals. It often is true that bioassay evidence for a specific route of administration is missing for a chemical. In these cases, the evidence from other routes of administration must be assumed to apply. For ethylene dichloride, however, negative evidence from an inhalation bioassay exists. The general assumption regarding inhalation carcinogenesis does not overrule this specific fact. Since the health assessment document was developed primarily to serve as a basis for a decision on whether to regulate air emissions, this is a critical point.

The Subcommittee encourages OHEA to make "what-if" calculations in support of its analysis of uncertainty in the health assessment document. The estimate of a potential quantitative risk for inhalation of ethylene dichloride, by assuming linear proportionality to carcinogenic incidence of ethylene dibromide, is an example that is already in the draft. The Subcommittee believes that this calculation helps to highlight the uncertainties in the data base. The Subcommittee also commends OHEA for using time to tumor models to estimate risk. If the data can be obtained, OHEA should extend the time to tumor analysis to Maltoni's inhalation bioassay. Although an hypothesis regarding the expected incidence of inhalation tumors will not outweight the actual data, the Subcommittee suggests that OHEA go even further to compare the observed number of tumors found with inhaled ethylene dichloride to the expected number, as if the inhalation bioassay were consistent with the data from ingestion.

The Subcommittee recommends that OHEA not sum data from statistically positive sites of tumor occurrence. Unless a biological rationale or a prior hypothesis from epidemiological studies exists, the Agency should use data from the most sensitive site.

The document analyzes the occurence of stomach cancer, but the Subcommittee suggests that this calculation be deleted since stomach cancer is not a remote site with respect to ethylene dichoride carcinogenicity, and the explanation of incidence at lower doses will require a different rationale. The document also makes the assumption that animals aquiring hemangiosarcoma died of this tumor. The Subcommittee agrees that this is a good assumption, since vascular tumors tend to kill quickly.

The analysis of carcinogenicity relies heavily on the National Cancer Institute study for which the dosed animals exhibited high mortality, showed signs of a murine virus, and were co-housed with another bioassay. The Agency may want to consider recommending an audit for this study to more fully appraise the quality of the data. The Subcommittee recommends that the Agency formally inquire whether or not the National Toxicology Program has performed (or plans to perform) an audit of the National Cancer Institute study. The reasons for the high mortality in this study are not known but may be discovered. Whatever the case, the document should address this uncertainty.

Literature Review

The draft document has reviewed the available scientific literature relatively completely. A few additional citations could be added, but these will not change the draft's major conclusions.

The Subcommittee requests that all future health assessment documents identify the date at which the literature review was completed. Only citations which substantially affect critical issues should be introduced beyond this date (perhaps in an addendum). Further, the Subcommittee requests that future documents describe the general nature of the information cited, including peer-reviewed articles, primary data from industry-sponsored toxicity studies, or otherwise.

Editorial Quality

The draft document was also written in an uneven and piecemeal style. This problem was particularly troublesome in that pharmacokinetic information needed by authors of other sections was not available to them in a timely manner.