File EDC

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

October 29, 1984

Dr. Daniel Byrd, III
Executive Secretary
Science Advisory Board (A-101F)
U.S. Environmental Protection Agency
Washington, D.C. 20460

Dear Dr. Byrd:

Public comments submitted on the First External Review Draft of the EPA Health Assessment Document for Ethylene Dichloride have been reviewed by EPA's Office of Health and Environmental Assessment (OHEA).

Attached please find a position paper prepared by OHEA which summarizes the major issues raised by public comments in relation to the draft document. The issues highlighted in the enclosed paper are those perceived as being among the most crucial to be discussed at the upcoming November 8, 1984, SAB subcommittee meeting on the Ethylene Dichloride External Review Draft (EPA-600/8-84-006A, April 1984). Major emphasis was on the carcinogenicity, mutagenicity and reproductive toxicity; however, some comments were made on the air quality and toxicity sections of the document.

Public comments, received before the close of business on Friday, June 22, 1984, or shortly thereafter, are available upon request from the Environmental Criteria and Assessment Office and copies will also be available at the November 8, 1984, meeting.

Please feel free to contact me (919/541-4173) or Dr. Robert Bruce (919/541-4154) for any further assistance regarding this matter.

Sincerely yours,

Michael A. Berry

Lester D. Grant, Ph.D.
Director, Environmental Criteria
and Assessment Office (MD-52)

Enclosure

Hos Shah
P08B EDC Program Panel
Date 12/6/84

SL 039341

THE OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT (OHEA) POSITION PAPER ON PUBLIC COMMENTS REGARDING THE ETHYLENE DICHLORIDE DOCUMENT

This paper summarizes the Office of Health and Environmental Assessment (OHEA's) responses to key issues raised by the public review comments on the Health Assessment Document for Ethylene Dichloride, external review draft, April, 1984. All of the comments listed below were received from either the Chemical Manufacturers Association (ethylene dichloride panel) or from Imperial Chemical Industries.

I. OHEA'S RESPONSES TO COMMENTS REGARDING CARCINOGENICITY OF ETHYLENE DICHLORIDE

Comment 1:

The National Cancer Institute (NCI) (1978) cancer bioassay study on 1,2-dichloroethane (EDC) in rats and mice is inadequate evidence for its carcinogenicity.

Response:

The NCI cancer bioassay, in which EDC was administered to rats and mice by gavage, produced a clear positive carcinogenic response. The NCI clearing house panel, as well as the Carcinogen Assessment Group (CAG), have considered this study to be adequate in supporting the carcinogenic effects of EDC. In rats, EDC produced a statistically significant increase in the incidence of squamous cell carcinomas of the forestomach, hemangiosarcomas of the circulatory system, and fibromas of subcutaneous tissue in male rats. There was also a statistically significant increased incidence of adenocarcinomas of the mammary gland in female rats. In mice EDC produced statistically significant increased incidence of alveolar/bronchiolar adenomas, mammary carcinomas, endometrial tumors in female mice, and hepatocellular carcinomas in male mice. This study meets the criteria for the technical adequacy of animal carcinogenicity studies published by the NTP (1984).

Comment 2:

The Theiss and Van Duuren mouse studies, characterized in the Health Assessment Document (HAD) as supportive evidence, do not support the conclusion that EDC is carcinogenic. Neither study produces statistically significant elevation in tumor response related to the administration of EDC.

Response:

The CAG agrees that neither the Theiss study nor the Van Duuren mouse study produced statistically significant tumor response. However, increased incidence of lung tumors in the Theiss study and increased incidence of skin carcinomas in the Van Duuren study cannot be disregarded.

Comment 3:

No reactive metabolites have been isolated and verified in EDC metabolism studies.

Response:

It is extremely difficult to isolate and verify the reactive metabolites. Therefore, it is not unusual that no reactive metabolites have been isolated and verified in EDC metabolism studies. However, there is indirect evidence that metabolism of EDC results in the production of reactive metabolites of an electrophilic nature such as those proposed to be formed in the metabolic scheme (figures in 9-5 to 9-7) in the Health Assessment Document. The metabolites such as chloroacetaldehyde, putative 1-chloroso-2-chloroethane, the half-mustard S-(2-chloroethyl) glutathione and its episulfonium ion provide a theoretical basis for the covalent binding of labeled material to cellular macromolecules such as proteins and DNA after administration of labeled EDC, a possible consquence of this binding is damage to cellular integrity and genetic apparatus. DNA adduct formations are known to be related to carcinogenesis.

Comment 4:

A major problem of the technical adequacy of the 1978 NCI long-term animal study is that it was conducted simultaneously with gavage studies on 17 other organic (mostly halogenated) chemicals in the same room at the Hazleton Laboratory. This greatly increases the possibility that the wrong compound was administered to the test animals because all the tested materials were stored together.

Response:

The NCI clearing house committee that reviewed the NCI EDC bioassay report (1978) was aware of this problem. It was concluded, however, that this short coming was not significant enough to invalidate the clear positive carcinogenic response observed in the EDC bioassay study.

Comment 5:

The comparison of unit risk estimates of 1,2-dichloroethane (EDC) to 1,2-dibromoetheane (EDB) based on a loose structural relationship has little scientific validity.

Response:

Both 1,2-dichloroethane and 1,2-dibromoethane are halogenated aliphatic hydrocarbons. Both are alkylating and mutagenic agents. The degree of alkylation is closely associated with the reactivity (electronegativity) of halogen atoms. In this case bromide is more reactive than chloride. Both EDC and EDB produced stomach tumors and hemangiosarcomas in rats by gavage. Therefore, it is reasonable to assume that the relative potency of EDC and EDB, as determined from inhalation vs. gavage data, is a valid comparison.

Comment 6:

The unit risk estimate for the EDC low-dose linear model is applied to the NCI data without regard to current knowledge about the pharmacokinetics and metabolism of EDC.

Response:

The CAG is aware of the available information about the pharmacokinetics and metabolism of EDC described in the HAD. Relevant information published by Reitz et al. (1982), who measured and compared levels of DNA alkylation of EDC administered to Osborne-Mendel rats after inhalation and after exposure by gavage, has been used to estimate risk by inhalation on the basis of gavage data.

Comment 7:

The inhalation studies of Maltoni are not adequately or objectively assessed in terms of their significance as a basis for human health assessment.

Response:

Available information on the Maltoni EDC inhalation studies in rats and mice was critically evaluated and described in the HAD. No significant incidences of tumors were seen in any of the target organs. Several factors may have contributed to those findings, such as differences in the pharmacokinetics and metabolism by inhalation vs. gavage. Maximum tolerated dose may not have been reached. In dose-response extrapolation to human health risk assessment, all biologically and statistically positive data sets are assessed with due regard to biological relevance and appropriateness of route of exposure with a view that human sensitivity is as high as the most sensitive responding animal species.

REFERENCES

1. National Toxicology Program. (1984) Report of the Ad Hoc panel on chemical carcinogen testing and evaluation of the national toxicology program board of scientific counselors.

2. Reitz, R. H., T. R. Fox, J. C. Ramsey, J. F. Quast, P. W. Languardt, and P. G. Watanabe. (1982) Pharmacokinetics and macromolecular interactions of ethylene dichloride in rats after inhalation or gavage. Toxicol. Appl. Pharmacol. 62: 190-204.

II. OHEA'S RESPONSES TO COMMENTS REGARDING NON-CARCINOGENIC HEALTH EFFECTS ASPECTS OF ETHYLENE DICHLORIDE

Comments regarding mutagenicity and reproductive toxicity are listed below. Responses will be made available at the November 8, 1984 SAB meeting by the Reproductive Effect Assessment Group of OHEA.

Comment 1. Sec. 9.4:

It is suggested that the conclusion that EDC is a mutagen in prokaryotic systems is overstated, since only the study of Rannug et al. demonstrated an adequate positive response. It was also considered inappropriate to discredit negative studies for not using positive class controls.

Comment 2. Sec. 9.4:

The plant systems used to assess the mutagenicity of EDC are not recognized test systems and should not be considered as relevant in evaluating the mutagenicity of EDC as recognized assays. In addition, the response in mammalian cells has not been corroborated or repeated.

Comment 3. Sec. 9.4:

The case for the mutagenicity of EDC has been overstated.

1. The evidence in bacteria is weak.
2. Of the four assays in Drosophila, one was designed for method development only, another showed only a slight, although statistically significant, increase, and two were inadequate.
3. The suggested metabolites of EDC that have been shown to be mutagenic have not yet been isolated from EDC-treated animals.
4. Cytogenic and host-mediated assays are negative, providing a weight of evidence evaluation that EDC is no more than a weak mutagen.

III. OHEA'S RESPONSES TO COMMENTS REGARDING THE AIR QUALITY AND TOXICITY SECTIONS OF THE DOCUMENT

Comment 1. Ch. 1; p. 3:

Concerning the statement on this page dealing with exposure levels associated with acute effects, it was suggested that rephrasing the statement would add to a clearer reflection of the available data.

Response:

The proposed change is considered appropriate when modified to state: Several papers describing human health surveys appear in the literature; adverse effects are largely associated with the gastrointestinal and nervous systems. The exposure information in these studies is not well documented, but taken together indicates that adverse effects have likely occurred in humans at EDC levels below 100 ppm, although probably not as low as 10 ppm.

Comment 2 Sec. 5; pp. 9-11, including Table 5-6:

EDC emissions to the environment are greatly overstated since they are based on old monitoring data and outmoded engineering controls. EPA possesses more recent information as a result of the Clean Air Act section 114 questionnaire.

Response:

This section is intended to provide background information from the published literature and not information contained in EPA files. In the event regulation is indicated, EPA will publish a separate exposure document that presents their data. Furthermore, it is stated in the document that the information presented is based on dated (1979 mostly) data, but that these are the best available. The document also states that "the impact of current

control technology may not have been adequately assessed" because it was not available. Since the data are presented as dated, no change is recommended.

Comment 3 Sec. 7:

Monitoring data do not reflect current control practices and, hence, are not representative of current levels.

Response:

The dates that all the monitoring data were published are clearly presented in the document. That more recent levels are lower cannot be confirmed since more recent studies either have not been performed or are not available. Since the data are not represented as being indicative of current levels, but rather as being indicative of the conditions prevailing at the time of sampling, no change is recommended.

Comment 4 Sec. 7; p. 7-20, Table 7-8:

Data presented in the chapter do not support Table 7-8.

Response:

A horizontal brace, which summed the three columns (<1.0, 1.0-5, >5-10), was inadvertently omitted. The brace will be included.

Comment 5 Sec. 9.1:

It was commented that the pharmacokinetic section was an objective review.

Comment 6 Sec. 9.3:

It was concurred that EDC has not been demonstrated to produce adverse effects on reproduction.

Response:

No response required.

Comment 7 Sec. 9; pp. 11 and 13:

The study of Urosova was considered inadequate on page 9-128, but was used here to indicate that EDC accumulates in breast milk.

Response:

Caveats will be placed on these data to indicate to the reader the shortcomings of this study.

Comment 8 Sec. 9; p. 51:

Comparison of EDC with other compounds, such as EDB, are inappropriate for inclusion in a HAD.

Response:

Comparison between compounds with similar structures is appropriate when these data add perspective to the topic, or when the inferences from these comparisons are clearly indicated as speculative.

Comment 9 Sec. 9; pp. 76-79:

Studies of workers exposed to EDC, reported in the Russian literature, are given too much weight since these studies cannot be critically evaluated.

Response:

The deficiencies in these studies are described in order to make the reader aware of their limitations. It is considered inappropriate to delete these reports from this survey of literature on EDC.

SL 039347

SUMMARY OF EXPOSURE INFORMATION FOR 1,2-DICHLOROETHANE

Emission rates and source characteristics were determined by engineering study as a part of the source assessment effort for all significant categories of stationary sources. For point sources (such as chemical plants, etc.), ambient air concentrations were estimated by atmospheric dispersion modeling of emissions. This methodology, known as the Human Exposure Model (HEM), initially provides a rapid, inexpensive, and generally conservative estimate of population exposure, principally for use in priority setting and problem scoping. As additional information is obtained, subsequent refinements of the exposure assessment may also play a role in regulatory determinations on candidate pollutants.

The HEM requires source location (latitude/longitude), relevant source parameters (emission rates, stack heights, etc.), and meteorological data. Where the number of sources in a particular category is very large or the available data too sparse to permit a source-by-source assessment (e.g., emissions associated with gasoline marketing), exposure is estimated using an area source approach. In this case, estimates of emissions can be distributed throughout a specified area. This approach employs a dispersion algorithm (Hanna and Gifford, 1973) that has proved to be a simple but reasonable model for estimating concentrations in high source density areas such as cities.

The predicted ambient concentrations obtained from modeling the source types are combined with census data to provide estimates of the exposed populations and exposure levels. Unless otherwise noted, concentrations are estimated and exposure modeled within a radius of 50 km from a specific point source or within a prescribed area for area sources.

Table 1 summarizes preliminary results from the HEM. At this time, emissions from chemical plants (accounting for 99.6 percent of 1,2-dichloroethane uses), publicly owned treatment plants and evaporative losses from leaded gasoline have been examined. Chemical plants include those that either use 1,2 dichloroethane or produce it as a by-product. These processes using 1,2-dichloroethane include vinyl chloride monomer, ethyl chloride, methyl chloroform, ethyleneamines, perchloroehylene, and trichloroethylene production. Emissions from publicly owned treatment works arise from the secondary emissions of 1,2-dichloroethane resulting from the disposal of wastewater that is contaminated with it. Emissions from gasoline marketing arise because 1,2-dichloroethane is in leaded gasoline as a lead scavenger. Information on emissions and risks associated with gasoline marketing are discussed in detail in EPA reports.

TABLE 1. PRELIMINARY HEM ESTIMATES OF HUMAN EXPOSURE TO 1,2-DICHLOROETHANE

Source Category	Number of Sources	Current Emissions (Mg/yr)	Maximum Annual Average ($\mu g/m^3$)
Chemical Plants	25	3,930	540
Publicly Owned Treatment Works	95*	7,300	18
Evaporative Emissions	**	100	0.01-0.02

* 95 publicly owned treatment works are estimated to emit greater than 10 megagrams per year.

**All U.S. vehicles using leaded gasoline.

TABLE 2. SUMMARY OF 1,2-DICHLOROETHANE MONITORING INFORMATION

Air Quality Measure	Concentration[1] ($\mu g/m^3$)	Number of Observations
Maximum[1]	651[2]	1
Remote and Rural Areas[3]	0	9
Urban and Suburban[3]	0.5	1,230
Source Dominated Areas[3]	5	436

[1]Based on 24-hour averages
[2]Lake Charles, LA (2 sources nearby)
[3]Based on quarterly averages