# REPORT ON ETHYLENE DICHLORIDE TO THE SCIENTIFIC REVIEW PANEL

## PART C - COMMENTS, RESPONSES, AND SUPPORTING MATERIAL

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AB 1807

# Assembly Bill No. 1807

## CHAPTER 1047

An act to add Article 1.5 (commencing with Section 14021) to Chapter 3 of Division 7 of the Food and Agricultural Code, and to add Chapter 3.5 (commencing with Section 39650) to Part 2 of Division 26 of the Health and Safety Code, relating to air pollution.

[Approved by Governor September 23, 1983. Filed with Secretary of State September 23, 1983.]

### LEGISLATIVE COUNSEL'S DIGEST

AB 1807, Tanner. Air pollution: toxic air contaminants.

(1) Under existing law, the State Air Resources Board is required to adopt ambient air quality standards for each air basin in the state. Standards relating to health effects are required to be based upon the recommendations of the State Department of Health Services. Air pollution control districts and air quality management districts are required to adopt and enforce rules and regulations which assure that reasonable provision is made to achieve and maintain ambient air quality standards. The Department of Food and Agriculture has general authority to regulate pesticides.

This bill would require, upon request of the state board, the State Department of Health Services, in consultation with and with the participation of the state board, to evaluate and prepare recommendations on the health effects of substances, other than pesticides in their pesticidal use, emitted into the ambient air which may be determined to be toxic air contaminants, and would require the state board, in consultation with and with the participation of, the State Department of Health Services, to prepare a report which would serve as the basis for regulatory action and to determine, by regulation, whether a substance is a toxic air contaminant. The Director of Food and Agriculture, in consultation with the State Department of Health Services and the state board, would be required to evaluate health effects of pesticides which may be or are emitted into the ambient air and may be hazardous to human health. It would define the terms "toxic air contaminant," "airborne toxic control measure," and "pesticide." The state board would be required to adopt airborne toxic control measures to reduce emissions of toxic air contaminants from nonvehicular sources below the threshold exposure level, if any, at which no significant adverse health effects are anticipated.

The Director of Food and Agriculture would be required to determine which pesticides are toxic air contaminants and to determine, in consultation with the State Department of Health Services, the state board, and districts, the appropriate degree of control measures needed for pesticides identified as toxic air

contaminants. The director, in consultation with county agricultural commissioners and districts in the affected counties, would be required to develop and adopt control measures designed to reduce emissions from those pesticide sources.

The bill would require the state board, based on its determination of toxic air contaminants, to determine whether revisions are needed in vehicular emission standards and motor vehicle fuel additives standards to prevent harm to the public health from vehicular emissions.

The bill would impose a state-mandated local program by requiring districts to propose regulations enacting airborne toxic control measures on nonvehicular sources not later than 120 days after their adoption by the state board, except that districts would be authorized to adopt and enforce equally effective or more stringent control measures. A district would be required to adopt regulations implementing airborne toxic control measures on nonvehicular sources within 6 months after adoption by the state board. District new source review rules and regulations would be required to control emissions of toxic air contaminants, except that processors of food and fiber operating 6 months or less in any calendar year would be exempt until January 1, 1987.

The bill would require the appointment of a 9-member Scientific Review Panel on Toxic Air Contaminants to advise the state board in its evaluation of the health effects toxicity of substances.

The bill would make any person who violates any rule or regulation, emission limitation, or permit condition adopted to control a toxic air contaminant liable for a civil penalty not exceeding $10,000 per day.

(2) The bill would declare legislative intent that the state board, the State Department of Health Services, and the Department of Food and Agriculture perform functions required by the bill in the 1983–84 fiscal year within their existing resources and budgetary authorizations.

(3) Article XIII B of the California Constitution and Sections 2231 and 2234 of the Revenue and Taxation Code require the state to reimburse local agencies and school districts for certain costs mandated by the state. Other provisions require the Department of Finance to review statutes disclaiming these costs and provide, in certain cases, for making claims to the State Board of Control for reimbursement.

However, this bill would provide that no appropriation is made and no reimbursement is required by this act for a specified reason.

*The people of the State of California do enact as follows:*

SECTION 1. Chapter 3.5 (commencing with Section 39650) is added to Part 2 of Division 26 of the Health and Safety Code, to read:

## CHAPTER 3.5. TOXIC AIR CONTAMINANTS

### Article 1. Findings, Declarations and Intent

39650. The Legislature finds and declares the following:

(a) That public health, safety, and welfare may be endangered by the emission into the ambient air of substances which are determined to be carcinogenic, teratogenic, mutagenic, or otherwise toxic or injurious to humans.

(b) That persons residing in California may be exposed to a multiplicity of toxic air contaminants from numerous sources which may act cumulatively to produce adverse effects, and that this phenomenon should be taken into account when evaluating the health effects of individual compounds.

(c) That it is the public policy of the state that emissions of toxic air contaminants should be controlled to levels which prevent harm to the public health.

(d) That the identification and regulation of toxic air contaminants should utilize the best available scientific evidence gathered from the public, private industry, the scientific community, and federal, state, and local agencies, and that the scientific research on which decisions related to health effects are based should be reviewed by a scientific review panel and members of the public.

(e) That, while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health.

(f) That the state board has adopted regulations regarding the identification and control of toxic air contaminants, but that the statutory authority of the state board, the relationship of its proposed program to the activities of other agencies, and the role of scientific and public review of the regulations should be clarified by the Legislature.

(g) That the Department of Food and Agriculture has jurisdiction over pesticides to protect the public from environmentally harmful pesticides by regulating the registration and uses of pesticides.

(h) That while there is a statewide program to control levels of air contaminants subject to state and national ambient air quality standards, there is no specific statutory framework in this division for the evaluation and control of substances which may be toxic air contaminants.

(i) That the purpose of this chapter is to create a program which specifically addresses the evaluation and control of substances which may be toxic air contaminants and which complements existing authority to establish, achieve, and maintain ambient air quality standards.

(j) That this chapter is limited to toxic air contaminants and nothing in the chapter is to be construed as expanding or limiting the

authority of any agency or district concerning pesticides which are not identified as toxic air contaminants.

(k) That a statewide program to control toxic air contaminants is necessary and desirable in order to provide technical and scientific assistance to the districts, to achieve the earliest practicable control of toxic air contaminants, to promote the development and use of advanced control technologies and alternative processes and materials, to identify the toxic air contaminants of concern and determine the priorities of their control, and to minimize inconsistencies in protecting the public health in various areas of the state.

## Article 2. Definitions

39655. For purposes of this chapter, "toxic air contaminant" means an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health. Substances which have been identified as hazardous air pollutants pursuant to Section 7412 of Title 42 of the United States Code shall be identified by the state board as toxic air contaminants. Toxic air contaminants which are pesticides shall be regulated in their pesticidal use by the Department of Food and Agriculture pursuant to Article 1.5 (commencing with Section 14021) of Chapter 3 of Division 7 of the Food and Agricultural Code.

39656. For purposes of this chapter, "airborne toxic control measure" means recommended methods, and where appropriate a range of methods, of reducing the emissions of a toxic air contaminant, including, but not limited to, emission limitations, control technologies, the use of operational and maintenance conditions and closed system engineering.

39657. For purposes of this chapter, "pesticide" means any economic poison as defined by Section 12753 of the Food and Agricultural Code.

## Article 3. Identification of Toxic Air Contaminants

39660. (a) Upon the request of the state board, the State Department of Health Services, in consultation with and with the participation of the state board, shall evaluate the health effects of and prepare recommendations regarding substances, other than pesticides in their pesticidal use, which may be or are emitted into the ambient air of California which may be determined to be toxic air contaminants.

(b) In conducting this evaluation, the State Department of Health Services shall consider all available scientific data, including, but not limited to, relevant data provided by the state board, the Occupational Safety and Health Division of the Department of

Industrial Relations, international and federal health agencies, private industry, academic researchers, and public health and environmental organizations.

(c) The evaluation shall assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, of the substance.

The evaluation shall also contain an estimate of the levels of exposure which may cause or contribute to adverse health effects and, in the case where there is no threshold of significant adverse health effects, the range of risk to humans resulting from current or anticipated exposure.

(d) The State Department of Health Services shall submit its written evaluation and recommendations to the state board within 90 days after receiving the request of the state board pursuant to subdivision (a). The State Department of Health Services may, however, petition the state board for an extension of the deadline, not to exceed 30 days, setting forth its statement of the reasons which prevent the department from completing its evaluation and recommendations within 90 days. Upon receipt of a request for extension of, or noncompliance with, the deadline contained in this section, the state board shall immediately transmit to the Assembly Committee on Rules and the Senate Committee on Rules, for transmittal to the appropriate standing, select, or joint committee of the Legislature, a statement of reasons for extension of the deadline, along with copies of the department's statement of reasons which prevent it from completing its evaluation and recommendations in a timely manner.

(e) The state board or a district may request, and any person shall provide, information on any substance which is or may be under evaluation and which is manufactured, distributed, emitted, or used by the person of whom the request is made, in order to carry out its responsibilities pursuant to this chapter. To the extent practical, the state board or a district may collect the information in aggregate form or in any other manner designed to protect trade secrets.

Any person providing information pursuant to this subdivision may, at the time of submission, identify a portion of the information submitted to the state board or a district as a trade secret and shall support the claim of a trade secret, upon the written request of the state board or district board. Information supplied which is a trade secret, as specified in Section 6254.7 of the Government Code, and which is so marked at the time of submission, shall not be released to any member of the public. This section shall not be construed to prohibit the exchange of properly designated trade secrets between public agencies when those trade secrets are relevant and necessary to the exercise of their jurisdiction provided that the public agencies exchanging those trade secrets shall preserve the protections afforded that information by this paragraph.

Any information not identified as a trade secret shall be available

to the public unless exempted from disclosure by other provisions of law. The fact that information is claimed to be a trade secret is public information. Upon receipt of a request for the release of information which has been claimed to be a trade secret, the state board or district shall immediately notify the person who submitted the information, and shall determine whether or not the information claimed to be a trade secret is to be released to the public. The state board or district board, as the case may be, shall make its determination within 60 days after receiving the request for disclosure, but not before 30 days following the notification of the person who submitted the information. If the state board or district decides to make the information public, it shall provide the person who submitted the information 10 days' notice prior to public disclosure of the information.

(f) The State Department of Health Services and the state board shall give priority to the evaluation and regulation of substances based on factors related to the risk of harm to public health, amount or potential amount of emissions, manner of usage of the substance in California, persistence in the atmosphere, and ambient concentrations in the community.

39661. (a) Upon receipt of the evaluation and recommendations prepared pursuant to Section 39660, the state board, in consultation with and with the participation of the State Department of Health Services, shall prepare a report in a form which may serve as the basis for regulatory action regarding a particular substance pursuant to subdivisions (b) and (c) of Section 39662.

The report shall include and be developed in consideration of the evaluation and recommendations of the State Department of Health Services.

(b) The report, together with the scientific data on which the report is based, shall, with the exception of trade secrets, be made available to the public and shall be formally reviewed by the scientific review panel established pursuant to Section 39670. The panel shall review the scientific procedures and methods used to support the data, the data itself, and the conclusions and assessments on which the report is based. Any person may submit any information for consideration by the panel which may, at its discretion, receive oral testimony. The panel shall submit its written findings to the state board within 45 days after receiving the report. The panel may, however, petition the state board for an extension of the deadline, which may not exceed 15 working days.

(c) If the scientific review panel determines that the health effects report is seriously deficient, the report shall be returned to the state board, and the state board, in consultation with and with the participation of the State Department of Health Services, shall prepare revisions to the report which shall be resubmitted, within 30 days following receipt of the panel's determination, to the scientific review panel which shall review the report in conformance with

subdivision (b) prior to a formal proposal by the state board pursuant to Section 39662.

39662. (a) Within 10 working days following receipt of the findings of the scientific review panel pursuant to subdivision (c) of Section 39661, the state board shall prepare a hearing notice and a proposed regulation which shall include the proposed determination as to whether a substance is a toxic air contaminant.

(b) After conducting a public hearing pursuant to Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the state board shall list, by regulation, substances determined to be toxic air contaminants.

(c) If a substance is determined to be a toxic air contaminant, the regulation shall specify a threshold exposure level, if any, below which no significant adverse health effects are anticipated.

(d) In evaluating the nature of the adverse health effect and the range of risk to humans from exposure to a substance, the state board shall utilize scientific criteria which are protective of public health, consistent with current scientific data.

(e) Any person may petition the state board to review a determination made pursuant to this section. The petition shall specify the additional scientific evidence regarding the health effects of a substance which was not available at the time the original determination was made and any other evidence which would justify a revised determination.

Article 4. Control of Toxic Air Contaminants

39665. (a) Following adoption of the determinations pursuant to Section 39662, the executive officer of the state board shall, with the participation of the districts, and in consultation with affected sources and the interested public, prepare a report on the need and appropriate degree of regulation for each substance which the state board has determined to be a toxic air contaminant.

(b) The report shall address all of the following issues, to the extent data can reasonably be made available:

(1) The rate and extent of present and anticipated future emissions and estimated levels of human exposure.

(2) The stability, persistence, transformation products, dispersion potential, and other physical and chemical characteristics of the substance when present in the ambient air.

(3) The categories, numbers, and relative contribution of present or anticipated sources of the substance, including mobile, industrial, agricultural, and natural sources.

(4) The availability and technological feasibility of airborne toxic control measures to reduce or eliminate emissions, and the anticipated effect of airborne toxic control measures on levels of exposure.

(5) The approximate cost of each airborne toxic control measure

and the magnitude of risks posed by the substances as reflected by the amount of emissions from the source or category of sources.

(6) The availability, suitability, and relative efficacy of substitute compounds of a less hazardous nature.

(7) The potential adverse health, safety, or environmental impacts that may occur as a result of implementation of an airborne toxic control measure.

(c) The staff report, and relevant comments received during consultation with the districts, affected sources, and the public, shall be made available for public review and comment at least 45 days prior to the public hearing required by Section 39666.

39666. (a) Following a noticed public hearing, the state board shall adopt airborne toxic control measures to reduce emissions of toxic air contaminants from nonvehicular sources.

(b) For toxic air contaminants for which the state board has determined, pursuant to Section 39662, that there is a threshold exposure level below which no significant adverse health effects are anticipated, the airborne toxic control measure shall be designed, in consideration of the factors specified in subdivision (b) of Section 39665, to reduce emissions sufficiently so that the source will not result or contribute to ambient levels at or in excess of the threshold exposure.

(c) For toxic air contaminants for which the state board has not specified a threshold exposure level pursuant to Section 39662, the airborne toxic control measure shall be designed, in consideration of the factors specified in subdivision (b) of Section 39665, to reduce emissions to the lowest level achievable through application of best available control technology or a more effective control method, unless the state board or a district board determines, based on an assessment of risk, that an alternative level of emission reduction is adequate or necessary to prevent an endangerment of public health.

(d) Not later than 120 days after the adoption by the state board of an airborne toxic control measure pursuant to this section, the districts shall propose regulations enacting control measures on nonvehicular sources within their jurisdiction which meet the requirements of subdivisions (b), (c), and (e), except that a district may, at its option, adopt and enforce equally effective or more stringent control measures than the airborne toxic control measures adopted by the state board. A district shall adopt rules and regulations implementing airborne toxic control measures on nonvehicular sources within its jurisdiction in conformance with the requirements of subdivisions (b), (c), and (e), not later than six months following the adoption of airborne toxic control measures by the state board.

(e) District new source review rules and regulations shall require new or modified sources to control emissions of toxic air contaminants consistent with subdivisions (b), (c), and (d) except for processors of food and fiber that operate for six months or less in

any calendar year. The exception for processors of food and fiber shall become inoperative on January 1, 1987. On or before January 1, 1986, the state board, in consultation and with the participation of the Department of Food and Agriculture, shall report to the Legislature on the feasibility of implementation and the economic impact of this section on processors of food and fiber.

39667. Based on its determinations pursuant to Section 39662, the state board shall determine if revisions are needed in the emission standards for vehicular sources, or in the standards for motor vehicle fuel additives, adopted pursuant to Part 5 (commencing with Section 43000), in order to prevent harm to the public health from vehicular emissions.

### Article 5. Scientific Review Panel

39670. (a) A nine-member Scientific Review Panel on Toxic Air Contaminants shall be appointed to advise the state board and the Department of Food and Agriculture in their evaluation of the health effects toxicity of substances pursuant to Article 3 (commencing with Section 39660) of this chapter and Article 1.5 (commencing with Section 14021) of Chapter 3 of Division 7 of the Food and Agricultural Code.

(b) The members of the panel shall be highly qualified and professionally active or engaged in the conduct of scientific research, and shall be appointed as follows for a term of three years:

(1) Five members shall be appointed by the Secretary of the Environmental Affairs Agency, one of whom shall be qualified as a pathologist, one of whom shall be qualified as an oncologist, one of whom shall be qualified as an epidemiologist, one of whom shall be qualified as an atmospheric scientist, and one who shall have relevant scientific experience and shall be experienced in the operation of scientific review or advisory bodies.

(2) Two members shall be appointed by the Senate Committee on Rules, one of whom shall be qualified as a biostatistician and one of whom shall be a physician or scientist specializing in occupational medicine.

(3) Two members shall be appointed by the Speaker of the Assembly, one of whom shall be qualified as a toxicologist and one of whom shall be qualified as a biochemist.

(4) Members of the panel shall be appointed from a pool of nominees submitted to each appointing body by the President of the University of California. The pool shall include, at a minimum, three nominees for each discipline represented on the panel, and shall include only individuals who hold, or have held, academic or equivalent appointments at universities and their affiliates in California.

(c) The panel may establish ad hoc committees, which may include other scientists, to assist it in performing its functions.

(d) Members of the panel, and any ad hoc committee established by the panel, shall submit annually a financial disclosure statement that includes a listing of income received within the preceding three years, including investments, grants, and consulting fees derived from individuals or businesses which might be affected by regulatory actions undertaken by the state board or districts pursuant to this chapter. The financial disclosure statements submitted pursuant to this subdivision are public information. Members of the panel shall be subject to the disqualification requirements of Section 87100 of the Government Code.

(e) Members of the panel shall receive one hundred dollars ($100) per day for attending panel meetings, and shall be reimbursed for reasonable and necessary travel and other expenses incurred in the performance of their duties.

(f) The state board and the State Department of Health Services, and, in the case of pesticides, the Department of Food and Agriculture shall provide technical and clerical staff support to the panel.

### Article 6. Penalties

39674. (a) Any person who violates any rule or regulation, emission limitation, or permit condition adopted pursuant to Article 4 (commencing with Section 39665) is liable for a civil penalty not to exceed ten thousand dollars ($10,000) for each day in which the violation occurs.

(b) There is no liability under subdivision (a) if the person accused of the violation alleges by affirmative defense and establishes that the violation is caused by an act which was not the result of intentional or negligent conduct.

SEC. 2. Article 1.5 (commencing with Section 14021) is added to Chapter 3 of Division 7 of the Food and Agricultural Code, to read:

### Article 1.5. Pesticides

14021. (a) As used in this article, "pesticide" means any economic poison as defined in Section 12753.

(b) For purposes of this article, "toxic air contaminant" means an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health. Pesticides which have been identified as hazardous air pollutants pursuant to Section 7412 of Title 42 of the United States Code shall be identified by the director as toxic air contaminants.

14022. (a) In consultation with the State Department of Health Services and the State Air Resources Board, the director shall evaluate the health effects of pesticides which may be or are emitted into the ambient air of California and which may be determined to

be a toxic air contaminant which poses a present or potential hazard to human health. Upon request of the State Air Resources Board, the director shall include a pesticide for evaluation.

(b) In conducting this evaluation, the director shall consider all available scientific data, including, but not limited to, relevant data provided by the State Department of Health Services, the Occupational Safety and Health Division of the Department of Industrial Relations, international and federal health agencies, private industry, academic researchers, and public health and environmental organizations. At the request of the director, the State Air Resources Board shall document the level of airborne emissions and the State Department of Health Services shall provide an assessment of related health effects of pesticides which may be determined to pose a present or potential hazard and each agency shall provide technical assistance to the department as it conducts its evaluation.

(c) The director may request, and any person shall provide, information on any substance which is or may be under evaluation and which is manufactured, distributed, or used by the person to whom the request is made, in order to carry out his or her responsibilities pursuant to this chapter. Any person providing information pursuant to this subdivision shall, at the request of the director, identify that portion of the information submitted to the department which is a trade secret and, upon the request of the director, shall provide documentation to support the claim of the trade secret. Information supplied which is trade secret, as specified in Section 6254.7 of the Government Code, and which is so marked at the time of submission shall not be released to the public by the director, except in accordance with Section 1060 of the Evidence Code and Section 21160 of the Public Resources Code.

(d) The director shall give priority to the evaluation and regulation of substances based on factors related to the risk of harm to public health, amount or potential amount of emissions, manner of usage of the pesticide in California, persistence in the atmosphere, and ambient concentrations in the community.

14023. (a) Upon completion of the evaluation conducted pursuant to Section 14022, the director shall, in consultation and with the participation of the State Department of Health Services, prepare a report on the health effects of the pesticide which may be determined to be a toxic air contaminant which poses a present or potential hazard to human health due to airborne emission from its use. The report shall assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, of the substance. The report shall also contain an estimate of the levels of exposure which may cause or contribute to adverse health effects and, in the case where there is no threshold of significant adverse health effects, the range of risk to humans, resulting from current or anticipated exposure. The report shall

include the findings of the State Department of Health Services. The report shall be made available to the public, subject to subdivision (c) of Section 14022.

(b) The report prepared pursuant to subdivision (a) shall be formally reviewed by the scientific review panel established according to Section 39670 of the Health and Safety Code. The director shall also make available the data deemed necessary to the scientific review panel, according to departmental procedures established to ensure confidentiality of proprietary information. The panel shall review, as appropriate, the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based.

(c) If the scientific review panel determines that the health effects report is seriously deficient, the report shall be returned to the director who shall revise and resubmit the report to the panel prior to development of emission control measures.

(d) The director shall determine which pesticides are toxic air contaminants.

(e) The director shall determine, in consultation with the State Department of Health Services, the State Air Resources Board, and the air pollution control districts or air quality management districts in the affected counties, the need for and appropriate degree of control measures for each pesticide identified as a toxic air contaminant in subdivision (d). Any person may submit written information for consideration by the director in making his determinations pursuant to subdivisions (d) and (e).

14024. (a) For those pesticides for which a need for control measures has been determined pursuant to subdivision (e) of Section 14023 and pursuant to provisions of this code, the director, in consultation with the agricultural commissioners and air pollution control districts and air quality management districts in the affected counties, shall develop and adopt control measures designed to reduce emissions sufficiently so that the source will not expose the public to the levels of exposure which may cause or contribute to significant adverse health effects. Where no demonstrable safe level or threshold of significant adverse health effects has been established by the director, the control measures shall be designed to adequately prevent an endangerment of public health through the application of best practicable control techniques.

(b) Best practicable control techniques may include, but are not limited to, the following:

(1) Label amendments.
(2) Applicator training.
(3) Restrictions on use patterns or locations.
(4) Changes in application procedures.
(5) Reclassification as a restricted material.
(6) Cancellation.

14025. Any person may petition the department to review a determination made pursuant to this article. The petition shall specify the additional scientific evidence regarding the health effects of a pesticide which was not available at the time the original determination was made and any other evidence which would justify a revised determination.

14026. Nothing in this article shall be construed to limit or expand the department's authority regarding pesticides which are not determined to be toxic air contaminants.

SEC. 3. It is the intention of the Legislature, in the enactment of this act, that the State Air Resources Board, the State Department of Health Services, and the Department of Food and Agriculture shall perform the functions required by this act within their respective existing resources and budgetary authorizations during the 1983–84 fiscal year, by appropriating sufficient funds in Items 3400-001-001, 3400-001-044, 4260-001-001, 4260-001-044, 4260-001-455, 8570-001-001, 8570-001-111, 8570-001-890, 8570-101-001 and 8570-101-111 of the Budget Act of 1983 (Ch. 324, Stats. 1983).

SEC. 4. No appropriation is made and no reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution or Section 2231 or 2234 of the Revenue and Taxation Code because the local agency or school district has the authority to levy service charges, fees, or assessments sufficient to pay for the program or level of service mandated by this act.

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# REQUEST FOR INFORMATION

STATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

May 31, 1984

Dear Sir or Madam:

Subject: Request for Information Regarding Ethylene Dichloride

I am writing to request information on the health effects of ethylene dichloride as part of our toxic air contaminant program. This program is based on legislation enacted in September 1983, Assembly Bill 1807 (Tanner). AB 1807 (Health and Safety Code Sections 39650, et seq.) requires the ARB to identify compounds as toxic air contaminants and once identified to develop and adopt control measures for such compounds. After consultation with the staff of the Department of Health Services (DHS), we have selected ethylene dichloride as a candidate toxic air contaminant to be evaluated in accordance with the provisions of AB 1807.

Before the ARB can formally identify a compound as a toxic air contaminant, several steps must be taken. First, the ARB must request the Department of Health Services to evaluate the health effects of candidate compounds. Second, the ARB staff must prepare a report which includes the health effects evaluation and then submit the report to a Scientific Review Panel for its review. The report submitted to the Panel will be made available to the public. Information submitted in response to this request will be considered in the ARB report to the Panel. Although, any person may also submit information directly to the Panel for its consideration, I urge you to submit all information at this time for our consideration in the development of the report for the Panel. The Panel reviews the sufficiency of the information, methods, and data used by the DHS in its evaluation. Lastly, after review by the Scientific Review Panel, the report with the written findings of the Panel will be considered by the Air Resources Board and will be the basis for any regulatory action by the Board to officially identify a compound as a toxic air contaminant.

Prior to formally requesting the DHS to prepare a health effects evaluation of ethylene dichloride, we are providing, pursuant to the provisions of Section 39660(e) of the Health and Safety Code, an opportunity to interested parties to submit information on the health effects of ethylene dichloride

which he or she believes would be important in DHS's evaluation of ethylene dichloride as a candidate toxic air contaminant.

In May 1984, ARB staff received a reference search on ethylene dichloride health effects using the MEDLARs II and DIALOG Information Services. These information services include material available to the public on or before November 1983. The attached bibliography lists the references from this information search. We are requesting pertinent information on ethylene dichloride health effects, including any material that may not be available to the public, that is not included in the attached bibliography.

I would appreciate receiving any relevant information you wish to submit by June 30, 1984. To expedite the review process, we ask that any information which you believe should be regarded as "trade secret" be clearly marked and separated from other information. Your help in expediting our review will be greatly appreciated.

You may identify portions of the information you submit as "trade secret" in accordance with Health and Safety Code Section 39660(e). The claim of trade secrecy must be supported upon the request of the Air Resources Board. Other information claimed to be trade secret and information otherwise claimed to be exempt from disclosure may be identified as confidential in accordance with Section 91011, Title 17, California Administrative Code. Section 91011 requires that the claim of confidentiality be accompanied by specified supporting information.

Pursuant to the provisions of the Public Records Act (Government Code Sections 6280 et seq.), the information you provide will be a public record and subject to public disclosure, except for trade secrets which are not emission data or other information which is exempt from disclosure or the disclosure of which is prohibited by law. The information may also be released to the Environmental Protection Agency, which protects trade secrets and confidential information in accordance with federal law, and to other public agencies, which are also required to protect such information.

Please send the information to the attention of:

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Ethylene Dichloride
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

If you have any further questions regarding health effects information, please contact Mr. John Batchelder at (916) 323-1505. For any other questions, please contact Mr. Don Ames at (916) 322-8285.

If you are not the person to whom this request should be addressed, please forward it to the appropriate person in your organization. Also, please let us know whether you would like to continue to receive information inquiries for other candidate compounds, and if not, if there is anyone in your organization to whom such requests should be sent.

Sincerely,

Peter D. Venturini, Chief
Stationary Source Division

cc: Alex Kelter, DHS
Lori Johnston; DFA
Wayne Morgan, President CAPCOA
Jan Bush, Executive Secretary CAPCOA
David Howekamp, EPA Region IX
Assemblywoman Tanner
APCO's

Attachment

1. Alumot, E. et al (1976) Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet Toxicol. 14:105-110.

2. Ames, B., Infante, P. F. and Reitz, R. H. (1980) Ethylene dichloride: A potential health risk?. Banbury Report. 5:350pp.

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BARNES-HIND HYDROCURVE INC.
A Revlon Vision Care Company

895 Kifer Road
Sunnyvale, California 94086

408 736-5462

June 4, 1984

William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Reference: Ethylene Dichloride

Regarding May 31, 1984 ARB request for information on the health effects of Ethylene Dichloride. We have no data to submit at this time. Presently, we only purchase and use approximately 20 gallon of Ethylene Dichloride per year for QC lab testing purposes.

We would like to continue to receive information inquiries, etc. for other potential toxic air contaminants.

Sincerely,

Dale Hanson

Dale B. Hanson
Director, Engineering

DBH/dpc

cc: P. Charley
G. Sweeney

Bill 7/6 (12)

SDS Biotech

June 28, 1984

Peter D. Venturini, Chief
Stationary Source Division
Air Resource Board
1102 Q Street
Sacramento, CA 95812

Dear Mr. Venturini:

Per your letter of May 31, 1984 requesting information on ethylene dichloride (EDC), I wish to respond with a couple of comments. The recent draft Health Assessment Document (HAD) for the EPA provides a good review of the literature and list of references. However, there are some major flaws with the document and some points you may wish to consider. The Chemical Manufacturers Association (CMA) has recently responded with comments to EPA about this document. The table of major manufacturers of EDC and capacities has been updated (enclosed); the environmental release of EDC has been greatly reduced due to: 1) a major reduction in usage of EDC in other than vinyl chloride monomer [VCM] production (e.g., paints, paint and varnish removers, coatings, adhesives, and lead scavengers) and 2) the industry compliance with the USEPA/NESHAPS Standard (40 CFR61) which regulates EDC/VCM manufacture.

Concerning the carcinogenicity data from the National Cancer Institute (NCI) bioassay (1978), the results of this study have been questioned because of the problems with the technical adequacy. A major problem with this 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. Currently, CMA is scheduling an audit of this study to determine the quality of conduct; in addition NTP is considering a bioassay of EDC via drinking water or microencapsulation. Other bioassays have not shown a carcinogenic response and in addition the mutagenicity data is negative or weakly positive.

Please place my name on the list to continue to receive informational inquiries for other candidate compounds.

If you have any questions, please contact me at (216) 357-3764.

Sincerely,

Ross E. Jones

Ross E. Jones, Ph.D.
Senior Research Toxicologist

RECEIVED
JUL 6 1984
Stationary Source Division
Air Resources Board

kms/6.38

xc: Has Shah (CMA)
T. Robinson (Vulcan Chemical, EDC Chairman)

TABLE 5-1

Major Manufacturers of Ethylene Dichloride[a]

| Manufacture | Plant Sites | Annual Capacity[c] (Millions of Metric Tons) |
|---|---|---|
| Atlantic Richfield (ARCO) | Port Arthur, TX | 0.200 |
| OD→ DIAMOND SHAMROCK | DEER PARK, TX | 0.084 |
| ~~Borden, Inc.~~ | ~~Geismar, LA~~ | ~~0.230~~ (NO LONGER IN EDC PROD |
| Dow Chemical USA | Freeport, TX | 0.725 |
| | Oyster Creek, TX | 0.500 |
| | Plaquemine, LA | 0.840 |
| E.I. duPont (Conoco) | Lake Charles, LA | 0.525 |
| Ethyl Corp. | Baton Rouge, LA[b] | 0.320 |
| | Pasadena, TX | 0.110 |
| ~~Formosa Plastics Corp.~~ | ~~Baton Rouge, LA~~ | ~~0.240~~ (EDC PRODUCTION DISCONTIN |
| | ~~Point Comfort, TX~~ | ~~0.385~~ |
| Georgia-Pacific Corp. | Plaquemine, LA | 0.735 |
| B.F. Goodrich Co. | ~~Deer Park, Tx~~[b] | ~~0.110~~ (NOT USED, Tolled OR MADE) |
| | La Porte, TX | 0.720 |
| | Calvert City, KY | ~~0.450~~ 0.720 |
| | Convent, LA | 0.360 |
| PPG Industries | Lake Charles, LA | 1.230 |
| Shell Chem. Co. | Deer Park, TX | 0.620 |
| | ~~Norco, LA~~[b] | ~~0.540~~ (PERMANENTLY CLOSED) |
| Union Carbide Corp. | Taft, LA[d] | 0.070 |
| | Texas City, TX[d] | 0.070 |
| Vulcan Materials Co. | Geismar, LA | 0.160 |
| | Total | ~~0.140~~ 7.989 |

Note: Capacities are flexible depending on finishing capacities for vinyl chloride and chlorinated solvents.

[a] SRI, 1983; CMR, 1983

[b] ~~Operated under a toll agreement with Diamond Shamrock Corp.~~

b ← Closed for an indefinite time period because of the temporary closing of Shell's vinyl chloride monomer plant located there.

c ← Captive use ~~only~~ Applies To majority of 27 plants

STATE OF CALIFORNIA—THE RESOURCES AGENCY GEORGE DEUKMEJIAN, Governor

CALIFORNIA ENERGY COMMISSION
1516 NINTH STREET
SACRAMENTO, CALIFORNIA 95814

June 28, 1984

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Ethylene Dichloride
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Per your request for information on ethylene dichloride, I am forwarding the following items for your consideration.

- Significant indoor emissions of ethylene dichloride should be considered in estimating not only total emissions to the atmosphere but also current body burdens. Ulsamer, et. al. (1981) reported that building materials in the home and the work environment emit significant levels of ethylene dichloride, i.e., 3 $mg/m_3$ measured above the building material. Indoor ethylene dichloride sources include various building materials and cleaning products. Common commercial solvents such as 1, 1, 1 - trichloroethane may contain EDC as a contaminant (see reference No. 53 in your EDC References). Little data exists on indoor air EDC concentrates, but Molhave (1983) and Girman (1984) may have some useful unpublished data on this topic.

- Alcohols, which reach people via emissions from many consumer products, and many widely consumed beverages, have a synergistic adverse health effect with solvents such as ethylene dichloride (Henschler, et. al., 1980).

- The National Toxicology Program recently completed a full audit of carcinogen testing for 1, 1, 1,- trichloroethane testing, which is structurally related to ethylene dichloride and may be found in the same commercial products. The audit's results should have been released last winter for public review (Birnbaum, 1983), and may influence the interpretation of studies on other hydrocarbons such as ethylene dichloride.

- NIOSH (1978) recommended taking into account the oxidative decomposition of ethylene dichloride in the presence of lighted cigarettes, open flames, or hot metals. Oxidative decomposition products include the toxic substances phosgene, hydrochloric acid, and dichloro acetylene.

- o Occupational exposure to ethylene dichloride is an important component of the total population exposure. NIOSH (1978) estimated the number of exposed U.S. workers at 2.9 million in 1972-1974, and the annual production at 8 billion pounds in 1976.

The references mentioned above are listed in the attachment. I hope that this information will assist ARB and the Department of Health Services in evaluating the health effects of ethylene dichloride. Please contact me at (916) 324-3603, if you have any further questions. In addition, please continue to send me information inquiries for other candidate compounds.

Sincerely,

Thomas J. Phillips (by Judith Gaumon)

THOMAS J. PHILLIPS
Planner I
Siting and Environmental Division

TJP:nwb
Attachment

## References


Birnbaum, L., 1983. Chemical Manager, National Institute for Environmental Health Sciences, Research Triangle Park, NC (919) 541-3798. Personal communication with T. Phillips, December 9.

Girman, J., 1984. Staff Scientist, Lawrence Berkeley Laboratory, Berkeley, CA. Personal communication with T. Phillips, June 25. (415) 486-5057.

Henschler, et. al., 1980. As cited in Ulsamer et. al., 1981.

Molhave, L., 1983. Indoor air pollution due to organic gases and vapors of solvents in building materials. Env. Intl. 8: 117-127.

National Institute for Occupational Safety and Health - NIOSH, 1978. NIOSH Current Intelligence Bulletin 27, Chlorethanes: Review of Toxicity. August 21. DHEW (NIOSH) No. 78-181.

Ulsamer, A.G., K.C. Gupta, and H. Kang, 1981. Organic Indoor Air Pollutants. Workshop on Indoor Air Quality Research Needs. Interagency Research Group on Indoor Air Quality, U.S. Department of Energy and U.S. Environmental Protection Agency, Washington, D.C.: pp. 102-111. NTIS.

# CALIFORNIA STATE UNIVERSITY
LONG BEACH

OFFICE OF STAFF PERSONNEL
(213) 498-4031


June 14, 1984

Mr. William V. Loscutoff, Chief
Toxic Pollulants Branch
RE: Ethylene Dichloride
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

California State University, Long Beach is not conducting any scientific evaluations involving the health effects of ethylene dichloride and its impact on the environment. Therefore, I am unable to provide you with any information that could be submitted to the Scientific Review Panel for its consideration.

I have reviewed your bibliography on ethylene dichloride and cannot add to it. I appreciate you providing the opportunity to review and comment on the study being conducted.

Sincerely,

Dick Hunt

Dick Hunt
Environmental Health &
Occupational Safety Officer

DH:pj
cc: President Horn
Vice President Cooper



LONG BEACH CALIFORNIA 90840
THE CALIFORNIA STATE UNIVERSITY AND COLLEGES

CHEMICAL MANUFACTURERS ASSOCIATION

July 2, 1984

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Re: Ethylene Dichloride

Dear Mr. Loscutoff:

By notice dated May 31, 1984, you requested information as to the health effects of ethylene dichloride. The bibliography attached to your notice lists the draft health assessment document on ethylene dichloride prepared by the U.S. Environmental Protection Agency. CMA's Ethylene Dichloride Panel recently submitted comments on this document to EPA, along with a suggested revision. These materials are enclosed for your review.

Please let me know if we can be of further assistance to you in evaluating the health effects of this important industrial chemical.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager
EDC Program Panel

Enclosure

c.c. EDC Panel

Note: CMA enclosed annotated copies of EPA 600/6-8-84-006A,B (2 vol. Draft Assess. Doc. for EDC. Sent to Jim Batchelder



Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.
2501 M Street, NW • Washington, DC 20037 • Telephone 202/887-1100 • Telex 89617 (CMA WSH)

CHEMICAL MANUFACTURERS ASSOCIATION

GERALDINE V. COX, Ph.D.
Vice President
Technical Director

June 22, 1984

Project Officer for Ethylene Dichloride
Environmental Criteria and Assessment Office (MD-52)
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

Dear Sir:

The Ethylene Dichloride Panel of the Chemical Manufacturers Association ("CMA") is pleased to submit the enclosed comments on the draft Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride). 49 Fed. Reg. 11878 (March 28, 1984). As part of these comments, and for the convenience of EPA staff, we also submit the enclosed revised version of the Health Assessment Document reflecting the changes that are necessary for it to be technically accurate and scientifically sound.

The major point addressed in these comments is the need for a more balanced and objective evaluation of the carcinogenicity of ethylene dichloride. The Health Assessment Document overemphasizes the gavage bioassay conducted for the National Cancer Institute ("NCI") in the early 1970s, while understating the importance of other long-term studies, including a more recent inhalation bioassay that showed no tumorigenic response. Because of questions that have been raised as to the adequacy of the gavage bioassay, CMA intends to conduct an audit for quality assurance. Until the gavage bioassay is reevaluated, and the results of an upcoming long-term drinking water study become available, no conclusive judgment can be made as to the carcinogenicity of ethylene dichloride.

Given the conflicting data presently available as to the carcinogenicity of ethylene dichloride and the questionable adequacy of the NCI bioassay, mechanical application of a linear mathematical risk model to the data from the NCI bioassay is inappropriate. Scientific judgment should be applied to the



Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.
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range of metabolic, pharmacokinetic, and other data on ethylene dichloride, in order to produce a more realistic estimate of health risk.

There is also a need for a more balanced discussion of mutagenicity, greater selectivity in the use of certain foreign data, and revision of the sections on sources and levels of ethylene dichloride in the environment.

If you have any questions relating to these comments, please do not hesitate to contact Dr. Has Shah of my staff at 202-887-1192.

Sincerely,

Enclosures

cc: SAB Environmental Health Committee

BEFORE THE U.S. ENVIRONMENTAL PROTECTION AGENCY

# COMMENTS OF THE CMA ETHYLENE DICHLORIDE PANEL ON EPA'S DRAFT HEALTH ASSESSMENT DOCUMENT FOR ETHYLENE DICHLORIDE


Geraldine V. Cox, Ph.D.
Vice President
Technical Director
Chemical Manufacturers Association

David F. Zoll, Esq.
Vice President
General Counsel
Chemical Manufacturers Association

Hasmukh C. Shah, Ph.D.
Manager
Ethylene Dichloride Panel
Chemical Manufacturers Association

Of Counsel:

W. Caffey Norman, III
Cleary, Gottlieb, Steen & Hamilton
1752 N Street, N.W.
Washington, D.C. 20036

Chemical Manufacturers Association
2501 M Street, N.W.
Washington, D.C. 20037
(202) 887-1100


June 22, 1984

The Ethylene Dichloride ("EDC") Panel of the Chemical Manufacturers Association ("CMA") represents all the U.S. manufacturers of EDC and most U.S. manufacturers of vinyl chloride, which is derived from EDC.

These comments on the EDC Health Assessment Document ("HAD") fall under the following headings:

A. Biological Effects
   1. Carcinogenicity
      a. Qualitative assessment
      b. Quantitative assessment
   2. Mutagenicity
   3. Reproductive Effects
   4. Pharmacokinetics
   5. Other

B. Current Uses

C. Environmental Levels and Exposure

D. Conclusion

## A. Biological Effects

### 1. Carcinogenicity

#### a. Qualitative assessment

The weight of the evidence does not support the conclusion reached in the HAD that EDC is a probable human carcinogen (pp. 1-5, 9-235). This conclusion is based essentially on a bioassay conducted in the early 1970s by Hazleton

Laboratories America Inc. for the National Cancer Institute ("NCI"), reported in 1978. Because of concerns that this study is not technically adequate and has not been quality assured, CMA has requested permission from the National Toxicology Program ("NTP") to conduct an in-depth audit of the study. In contrast to the NCI bioassay, a more recent inhalation bioassay in rats and mice produced negative results. The treatment of carcinogenicity in the HAD should be more balanced, with negative studies given equal weight to a purportedly positive one.

The technical adequacy of the 1978 NCI study has been questioned for several reasons. A major problem 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. Moreover, a significant proportion of a volatile halogenated organic chemical administered orally is expired unchanged. It is not appropriate to attribute a positive result to a chemical administered by gavage when all the test subjects may have received inhalation doses of one or more of the 17 other chemicals. This problem is addressed in the proceedings of an important scientific conference on the carcinogenicty of EDC (the "Banbury EDC Conference"), where Dr. Harry B. Plotnick of the National Institute for Occupational Safety and Health

stated, "I won't challenge your results, but you have an awful lot of faith in a study that you considered not to be flawed, and which I consider to be so utterly flawed that you can't rely upon it." Banbury Report 5, Ethylene Dichloride: A Potential Health Risk?, 50-51 (Cold Spring Harbor Laboratory 1980).

The observation of tumors in the 1978 NCI gavage bioassay is contradicted by the negative results obtained by Maltoni in a more recent inhalation bioassay on rats and mice. There is no reason to believe, as suggested in the HAD (p. 9-196), that the Maltoni study was conducted at less than maximum tolerated dose. An analysis presented at the Banbury EDC Conference concluded that "the two highest dose levels in the inhalation study were entirely comparable on a mg/(kg·day) basis to those yielding a strongly positive result in the NCI study." Hooper, K., Gold, L.S., Ames, B.N., The Carcinogenic Potency of Ethylene Dichloride in Two Animal Bioassays: A Comparison of Inhalation and Gavage Studies, in Banbury Report 5, Ethylene Dichloride: A Potential Health Risk?, 67.

The discrepancy in results between the 1978 NCI study and the 1980 Maltoni bioassay was addressed at the Banbury EDC Conference. One likely explanation is that the route of exposure (gavage v. inhalation) makes a real difference with regard to the carcinogenic potential of EDC. See id., at 77. Maltoni has suggested that other factors may have contributed to the difference in results, including:

- the purity of the EDC tested;
- the animal laboratory cross-contamination, discussed above;
- the performance of the experiment with particular reference to the probability of mix-up of chemicals during treatment, and to the professionalism of the team carrying on treatment, control of animals, and autopsies;
- the size of both treated and control animal groups.

Maltoni, C., Valgimigli, L., and Scornato, C., Long-Term Carcinogenic Bioassays on Ethylene Dichloride Administered by Inhalation to Rats and Mice, in Banbury Report 5, Ethylene Dichloride: A Potential Health Risk?, 23.

Other scientists have concluded that "[a]dditional long-term oral ingestion studies employing several species of animals are needed to determine if DCE [EDC] is a carcinogen." Drinking Water and Health 3, 111 (National Academy Press 1980). We understand that NTP has recently decided, because of the major difference in response between dosage by gavage and dosage by inhalation, to conduct a multi-strain rodent bioassay on EDC in drinking water (or by microencapsulation, if a drinking water study is not technically feasible). The upcoming NTP study should provide data useful in evaluating the significance of the existing gavage and inhalation data and in assessing the carcinogenicity of EDC.

The Theiss and Van Duuren mouse studies characterized in the HAD as "supportive evidence" (pp. 1-5, 9-235) in fact do not support the conclusion that EDC is carcinogenic. Neither

study produced a statistically significant elevation in tumor response related to the administration of EDC (pp. 9-202, 9-203).

In summary, leaving aside the question whether EPA should be using the IARC weight-of-evidence criteria, it is premature and inappropriate to classify EDC according to those criteria until the questions raised as to the technical adequacy of the 1978 NCI bioassay are resolved.

b. Quantitative assessment

In calculating a unit risk estimate for EDC, the HAD uses statistics in place of scientific judgment. Rather than investigating the difference in results between the NCI bioassay and the Maltoni study, the HAD simply states that "[t]he reason for this nonresponsiveness by inhalation is not known." (P. 9-218.) The HAD then applies a linear mathematical model to the NCI data, without regard to current knowledge about the pharmacokinetics and metabolism of EDC. This is ironic, because the HAD contains a thorough review of the extensive information available on the pharmacokinetics of EDC.

Use of data on ethylene dibromide (EDB) to calculate a carcinogenic potency for EDC is even more objectionable scientifically than the mechanical use of the 1978 NCI data on EDC described above. The comparison (p. 9-227) of EDC to EDB based on a loose structural relationship has little scientific validity. Many studies have noted major differences between

the various halogenated organic compounds. There are numerous other compounds as closely related (judging by the number of carbon or halogen atoms) to EDC as is EDB. The HAD contains no criteria or analysis justifying the choice of EDB, as opposed to any of a number of other compounds, as a surrogate for EDC.

Because of the use of questionable or irrelevant data and the many conservative assumptions incorporated in the mathematical model used by EPA, neither of the unit risk estimates for EDC can be used to predict actual risk. Use of these estimates is inappropriate even for the limited purposes, e.g., providing a rough comparison to other chemicals, stated in the HAD. In any event, whatever qualifications the HAD places on the use of the unit risk estimates are likely to be disregarded by the public and regulatory officials who need guidance. Recent public comments before the EPA Science Advisory Board (the "SAB") have emphasized this problem, and EPA itself has stated that it is concerned about the tendency of regulatory decision-makers to latch onto the numbers and ignore the qualitative evidence, which Dr. Anderson has called the "heart" of the risk assessment.

One solution to this problem is to integrate the qualitative and quantitative data and to use scientific judgment to characterize the risk in a quantitative or semi-quantitative way. When using modeling results as part of the data for assessing risk, the most likely estimate of each model

used should be presented, along with both the upper and the lower confidence limits, a discussion of the statistical fit of the models, and a discussion of any assumptions or uncertainties. If more than one data base is available, the range of numbers should reflect all the available data bases, with appropriate comments on the quality and relevance of the data. Such a method not only would make better use of all the data, but would also produce estimates of greater value to the regulatory decision-maker than unit risk estimates which overstate the true risk and are dependent on assumptions that can affect the prediction by several orders of magnitude.

Unless EPA is willing to prepare a comprehensive scientific risk assessment for EDC, integrating all the available data on mechanism, pharmacokinetics, metabolism, and other relevant data, no unit risk estimate should be provided and the comparison to the alleged carcinogenic potencies of other chemicals should be deleted. For the reasons given above, the 1978 NCI study and the purported similarity of EDC to EDB are altogether too fragile a foundation to support calculations that will be used as precise estimates of incremental human cancer risk from exposure to EDC.

2. Mutagenicity

When metabolically activated, EDC is at most a very weak mutagen. The tone of the discussion of mutagenicity in the HAD should be more balanced. For example, the HAD presents

an overstated case for the mutagenic potential of EDC in bacterial systems. The McCann study is described in the HAD (p. 9-134) as "negative or at best only marginal positive." In fact, induced revertants were only 25 above background, so that the study could not appropriately be considered even marginally positive.

The four assertedly positive studies on Drosophila melanogaster reported in the HAD (p. 9-146) are inadequate to draw any firm conclusion as to the mutagenicity of EDC. Two were inadequately reported Russian studies in which the purity of the EDC is apparently unknown. The third study showed a statistically significant increase in lethal recessive mutations, but the actual increase was only 1.73 percent over the untreated flies. The fourth Drosophila study was conducted for purposes of method development and should not be used to assess the mutagenicity of EDC.

Other data considered in the HAD to be supportive evidence for the mutagenicity of EDC (pp. 9-139, 9-140) in fact relate to the mutagenic potency of certain suggested reactive metabolites. These metabolites have not been isolated in EDC studies.

The HAD acknowledges that two cytogenetic studies of EDC were negative (p. 9-154). All host mediated assays were negative. Considering all the data on mutagenicity, EDC cannot be considered as anything more than a very weak mutagen in

metabolically activated systems, and in vivo mutagenicity in mammals has not been shown.

3. Reproductive Effects

The HAD concludes that "the available studies indicate that EDC has little ability to adversely affect the reproductive or developmental processes in laboratory animals except at maternally toxic levels." (P. 9-130.) This is a scientifically valid conclusion. Viewed collectively, all reproductive studies on rats, mice, and chickens and all teratology studies on rats, mice, and rabbits show no reproductive effects or teratogenicity related to EDC.

4. Pharmacokinetics

The pharmacokinetics section of the HAD presents a fairly objective review of the work done by Spreafico and Reitz, and acknowledges that EDC does not bioaccumulate (p. 9-32). The level of DNA alkylation and chemical binding of EDC is extremely low.

5. Other

The HAD cites a study by Urosova several times in the discussion of absorption and distribution (pp. 9-11, 9-13, 9-19). This seems entirely inappropriate given the conclusion reached in another section of the HAD that the Urosova study "cannot be accepted as scientific evidence," because of a number of listed inadequacies (p. 9-128). This kind of selective

use of reported information reflects an unfortunate willingness to overuse or stretch data when it supports an author's purposes.

Another example of misuse of information in the HAD is the lengthy discussion of a 1957 health and morbidity survey of Russian aircraft industry workers (pp. 9-76 to 9-79). This study suffers from the same shortcomings as the Urosova study and other Russian studies which, according to the HAD, "are presented with insufficient detail for critical scientific review." (P. 9-127.) In fact, no major health problems have been associated with exposure to EDC in the workplace in the United States.

At various locations in the HAD, EDC is compared to other compounds, such as EDB (e.g., p. 9-51). This comparison is scientifically inappropriate. Overall, the comparisons are inconsistent and generally do not add to the EDC data base. Speculation based on loose structural relationships has no place in an HAD.

B. Current Uses

EDC emissions to the environment are greatly overstated in Section 5 (Sources in the Environment) relative to 1984 production practices and EDC uses. The data presented in Table 5-6 reflect 1979 and prior years. Today approximately 90 percent of all EDC produced is used captively as feedstock for the manufacture of other chemicals. EDC exports have increased

substantially since 1979 and domestic use in paints, coatings, adhesives and gasoline has decreased substantially. The National Paint and Coatings Association recently informed us that no EDC is currently used in paints, strippers, and coatings. Similarly, communications with the Adhesives and Sealants Council indicate that little, if any, EDC is currently used in adhesives and sealants in the United States. The changed usage pattern has, without question, decreased the amount of EDC released to the environment from 1979 levels.

Clean air laws and regulations, both state and federal, have become substantially more stringent since the emissions estimates in the HAD were made. EDC emissions from the manufacture of EDC and vinyl chloride monomer ("VCM") have been significantly reduced as a result of industry compliance with these new laws and regulations, including the national emission standard for vinyl chloride under Section 112 of the Clean Air Act (40 C.F.R. §§ 61.60-61.71), which also indirectly limits EDC emissions in many cases. 1983 data on EDC emissions from the manufacture of EDC and VCM are on file at EPA as a result of an early 1984 industry response to a Clean Air Act Section 114 questionnaire. While CMA does not have access to all the Section 114 questionnaire responses, we estimate, based on member company data, that 1983 environmental emissions of EDC are up to 90 percent less than the 6,154 metric tons indicated in Table 5-6.

C. Environmental Levels and Exposure

The environmental levels set forth in Section 7 (Environmental Levels and Exposure) should be updated to reflect current control practices and the changes described above in EDC usage. In particular, ambient air levels given in the HAD are not representative of current exposure. The ambient concentration data presented in Table 7-1 relate to the period from 1976 to 1978. They do not reflect reduced emissions resulting from industry compliance with the national emission standard for vinyl chloride. Thus, the data presented are so dated as to be no longer applicable.

There are also inconsistencies between the exposure data in the HAD and the conclusions drawn from the data. Of primary concern is the discussion of the multiple surveys of ground and surface waters and the conclusions drawn relative to the total estimated population exposed to EDC in drinking water as shown in Table 7-8. This table indicates that 195,595,000 persons, approximately 80 percent of the U.S. population, are exposed to 1.0 to 5.0 ug/l of EDC in their drinking water. Letkiewicz (1982) is cited as the reference source even though this author is also quoted (p. 7-20) that "most [ground and surface water systems in the United States] are below 1.0 ug/l." This is an inconsistency that should be corrected.

A summary of the data reflecting positive responses for the presence of EDC in the six national surveys of ground

and surface water contamination is given below. The three phases of the National Organics Monitoring Survey are presented as three separate surveys.

Summary of EDC Identification in Water

| | Ground Water | Surface Water |
|---|---|---|
| National Organics Reconnaissance Survey | 0/16 | 6/64 |
| National Organics Monitoring Survey - I | 0/18 | 1/87 |
| II | 1/18 | 1/87 |
| III | 0/18 | 1/87 |
| National Screening Program for Organics in Drinking Water | 1/13 | 1/107 |
| Community Water Supply Survey | 3/312 | 1/110 |
| Ground Water Supply Survey | 6/466 | ----- |
| | 9/479 | ----- |
| Rural Water Survey | 5/633 | 1/47 |
| TOTAL | 25/1973 | 12/589 |
| | 1.3% | 2.0% |

The above table shows that only 1.3 percent of ground water sources and 2.0 percent of surface water sources were found to contain EDC. The relatively low percentage of samples containing EDC found in the surveys, combined with the acknowledgement in the HAD that "most [sources] are below 1 ug/l" of EDC, would appear to refute the contention that 196 million

people are at risk of exposure to at least 1.0 ug/l of EDC in their drinking water.

D. Conclusion

The thoroughness of the HAD overall, and particularly the review of pharmacokinetic data, is commendable. Substantive revisions are needed, as described above, to indicate the inconclusiveness of the available data as to carcinogenicity and to provide greater objectivity in the discussion of mutagenicity. We share the concern recently expressed by Dr. Herman Collier of the SAB with regard to another document in this series -- that the HAD is written in a manner that leads the public and perhaps the scientific community to view EPA as having structured its rationale to reach the preferred conclusion that a chemical is a human carcinogen. This apparent predisposition on the part of the Cancer Assessment Group should not be reflected in these important documents.

Because of questions that have been raised as to the adequacy of the NCI gavage bioassay, CMA intends to conduct an audit for quality assurance. Until the NCI bioassay is reevaluated, and the results of the upcoming NTP drinking water study become available, no conclusive judgment can be made as to the carcinogenicity of EDC. Given the conflicting data presently available as to the carcinogenicity of EDC and the questionable adequacy of the NCI bioassay, mechanical application of a linear mathematical risk model to the data from the NCI

bioassay is inappropriate. Scientific judgment should be applied to the range of metabolic, pharmacokinetic, and other data on EDC, in order to produce a more realistic estimate of health risk.

Finally, it is important that the HAD's discussion of sources and environmental exposure be as accurate as possible. In this regard, we would be pleased to assist EPA in obtaining more up-to-date information on sources and uses of EDC.

State of California

# Memorandum

To : William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Date : July 20, 1984

Place : Sacramento

From : **Department of Food and Agriculture**

Subject: Response to Request for Information Relevant to DOHS Evaluation of Ethylene Dichloride as a Candidate Toxic Air Contaminant

In response to your request, I am enclosing a copy of the print-out of references in the Department of Food and Agriculture's Registration Library. Please be advised that some of these references may be confidential access and as such may fall under the Department's policy on such matters.

Lori Johnston

Lori Johnston, Assistant Director
Pest Management, Environmental
Protection & Worker Safety
(916) 322-6315

Attachment

cc Hans Van Nes
Olaf Leifson



SURNAME
SO-106

PESTICIDE DATA REPORT California State Dept. Food & Agriculture 07/11/84

ETHYLENE DICHLORIDE
**********

CAS NUMBER: 107-06-2
MANUFACTURER:
MANUFACTURER'S REG NO:
DATA PACKAGE NUMBER: 1007
CHEMICAL CODE: 00274
CHEMICAL ACTION CODE: FUMIGANTS
DATE OF THIS ENTRY:
TECHNICAL NAME:
1.2 DICHLORDETHANE
TRADE NAME(S):
EDC

REFERENCES FOR Acute oral (TEST ID 011 )
CHLORASOL FUMIGANT TOXICOLOGICAL SUMMARY (1007-001) 12/53
(DATA IN SUPPORT OF GAS-O-CIDE)
SKIN ABSORPTION LD50 RABBITS
INHALATION-RATS
PRIMARY TISSUE IRRITATION-RABBITS
EYE INJURY TO RABBITS
S/TOXICOLOGY STUDIES-ETHYLENE DICHLORIDE (1007-001) 02/62
SINGLE ORAL DOSE LD50-RATS
SINGLE SKIN PENETRATION-RABBITS
SINGLE INHALATION-RATS
THRESHOLD LIMIT VALUE
SKIN IRRITATION-RABBIT
EYE INJURY-RABBIT

REFERENCES FOR Oncogenicity stu (TEST ID 832 )
BIOASSAY OF 1,2-DICHLORDETHANE FOR POSSIBLE (1007-002) 01/78
CARCINOGENICITY (PUB RPT FROM NATIONAL
CANCER INSTITUTE)
NO DATA FOUND FOR TEST-TYPE 100.
NO DATA FOUND FOR TEST-TYPE 300.

PACIFIC GAS AND ELECTRIC COMPANY

PG&E — 77 BEALE STREET • SAN FRANCISCO, CALIFORNIA 94106 • (415) 781-4211 • TWX 910-372-6587

July 3, 1984

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Ethylene Dichloride
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Information Inquiries Mailing List
Requests for Public Health Information

Pacific Gas and Electric Company received your May 31, 1984 request for additional public health information regarding ethylene dichloride. We reviewed the bibliography and concluded that we are unaware of any additional information which would be of use to you.

Please send all future information inquiries to me at the above address.

Thank you.

Sincerely,

J. F. McKENZIE

PPG Industries, Inc. One PPG Place Pittsburgh, Pennsylvania 15272 (412) 434-2801

**A. Philip Leber, Ph.D.**
Manager of Industrial Toxicology
Environmental Affairs
Industrial Chemical Division

July 3, 1984

William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Dr. Loscutoff:

Re: Ethylene Dichloride

This is in response to your request for information on the chemical ethylene dichloride (EDC). In reviewing our toxicology files for this material, only one relevant reference was found that was not included in your reference list. A copy of this article is attached to this letter.

PPG appreciates the opportunity to contribute to California's efforts in developing rational assessments of hazards from airborne chemicals.

Sincerely,

A. Philip Leber

mec

Attachment

cc: S. Angrist
R. Davis

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(Requests for reprints should be addressed to:-
Universitäts-Frauenklinik
78 Freiburg, Germany)



# Clinical Features, Pathogenesis and Management of Dichloroethane Poisoning[1]

G. Martin, K. Knorpp, K. Huth, F. Heinrich and C. Mittermayer

Department of Medicine (Joint Directors: Prof. H. J. Dengler, Prof. H. A. Kühn and Prof. H. G. Lasch) and the Department of Pathology (Director: Prof. W. Sandritter), University of Giessen

Summary:- A 57-year-old man died of therapy-resistant cardiovascular failure 24 hours after ingestion of an dichloroethane-containing embrocation. Apart from gastro-enterocolitis and hepatic necrosis he developed a severe haemorrhagic diathesis. The complex disturbance of the haemostatic mechanism, which included thrombocytopenia and reduced activity of all clotting factors examined (Factor I, II, V, VII and XIII), was ascribed to consumption ("using up") of these substances by disseminated intravascular coagulation ("Verbrauchskoagulopathie") and secondar hyperfibrinolysis. Therapeutic principles for the management of oral dichloroethane poisoning are suggested taking into account the likely pathogenesis. They include prompt gastric lavage with addition of paraffin (in which dichloroethane dissolves), measures to protect the liver, continuous supervision and adjustment of blood gases. Incipient consumption of the clotting factors is counte acted by heparin infusions. Cardiovascular function is supervised by continuous registration of th electrocardiogram, even after apparent improvement in the patient's condition or subsidence of th initial stupor. Should renal failure occur, treatment is the same as for other types of acute renal failur

Some analgesic and anti-inflammatory embrocations include dichloroethane ($CH_2$-Cl-$CH_2$-Cl) as their main hyperaemia-inducing constituent. Accidental or deliberate ingestion of such embrocations which are meant solely for external use, may result in severe and sometimes fatal dichloroethane poisoning (2, 3, 13).

To the few reports of poisoning by swallowing dichloroethane a further case is added here. It was characterized by very severe cardiac arrhythmias and disturbances of the clotting mechanism causing a haemorrhagic diathesis due to intravascular consumption of clotting factors.

## Case Report

At about 18.30 on November 4, 1966, patient R., a 57-year-old man, swallowed, presumably with suicidal intent, about 40 ml of an initially unidentified embrocation used by him for the relief of rheumatic complaints. He was admitted to hospital at 20.00 on the same day in a somnolent condition. As the patient could not be roused, information about the poison swallowed was unobtainable. Relatives could not be contacted. The expired air smelled stron of camphor. A few minutes after admission to hospital the pati vomited about 300 ml of a bilious liquid smelling of camphor about 30 minutes later voided copious, apparently normal, faeces three occasions. Otherwise there were no alarming signs of sev poisoning.

## Clinical Features and Course

Apart from a postgastrectomy scar external appearance was r mal. There were no demonstrable neurological defects, cyanc dyspnoea, oedema, jaundice, skin rash or haemorrhagic diathe Blood pressure was constant at 140/80 mm Hg. The electrocar gram (ECG) showed sinus tachycardia of about 100/minute ventricular extrasystoles but normal A-V conduction.

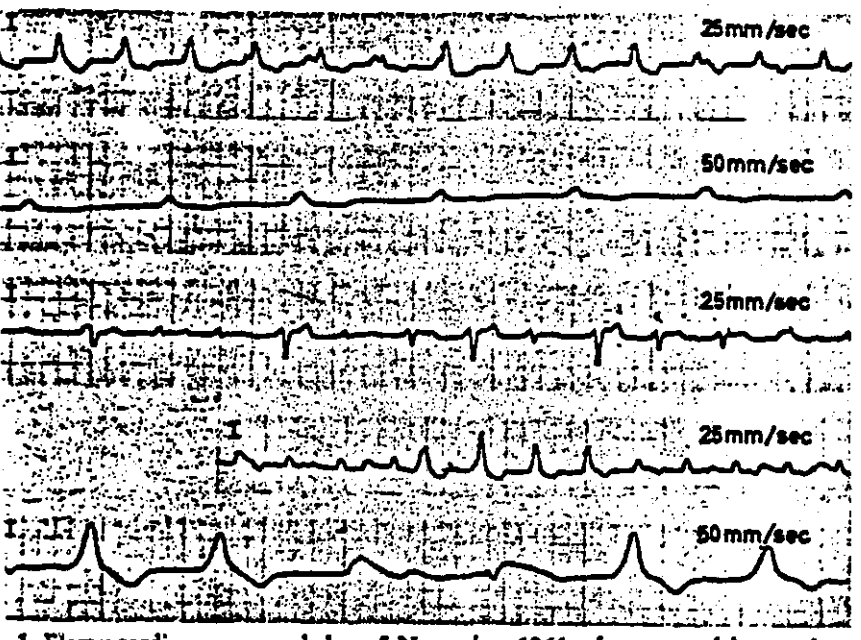
Serum glutamic-oxaloacetic transaminase (SGOT) and se glutamic-pyruvic transaminase (SGPT) activities were normal (4.5 and 6.7 IU, respectively). After gastric lavage, which produced small quantities of food residue, infusion of a 5% Ringer-laevu solution combined with strophanthin and antibiotics was institu Oral paraffin, which binds ethane dichloride and in this way vents or delays its absorption, was not given as there was no formation on the type of poison (9). A gas analyser which w have immediately detected the presence of halogenated hydrocarb

[1] Translated from Dtsch. med. Wschr. 93 (1968), 2002.

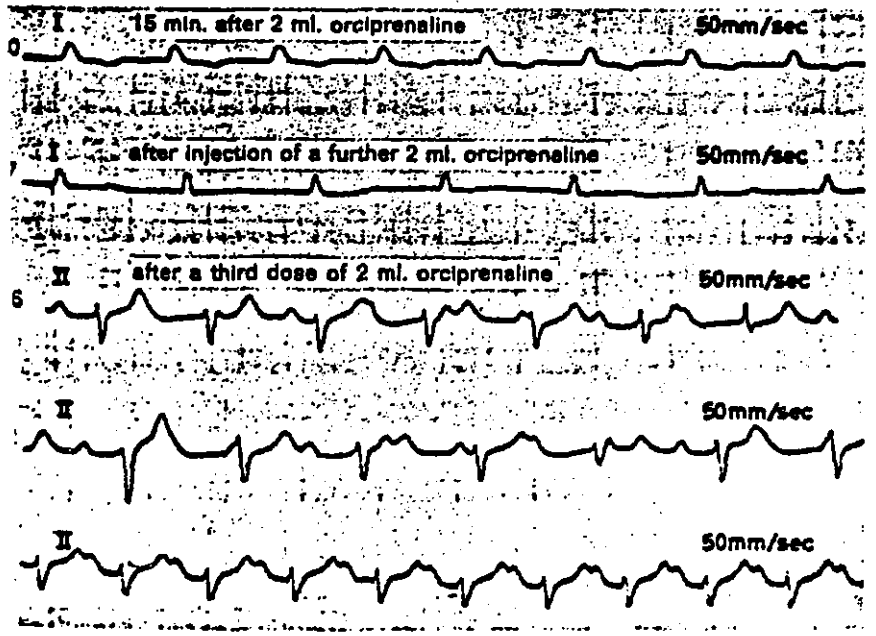
the expired air was not available at that time. In view of the continued improvement in the patient's condition no further therapeutic measures were adopted.

On the morning of November 5th, twelve hours after admission to hospital, the patient responded to stimuli. It was only then, 14 hours after the accident, that the patient and relatives who had since been summoned by telephone provided the information that he had swallowed Marament®. This embrocation is made up of: 100 g dichloroethane, 2.0 g oil of pine-needles, 0.2 g methyl salicylate, 0.05 mg cobra (Naja tripudians) toxins and an unspecified emulsifier in 100 ml of the liquid.

At about 8.30, almost immediately after the toxic nature of the remedy had become known, the patient's condition suddenly deteriorated with dyspnoea, orthopnoea and progressive clouding of consciousness. Blood pressure could no longer be recorded. At 8.40, during attempts at improving the circulation, cardiac arrest supervened.




1. Electrocardiogram recorded on 5 November 1966, after successful resuscitation: probably complete atrio-ventricular dissociation with changing site of pacemaker.




2. Electrocardiogram recorded at 10.10–10.47 a. m. on 5 November 1966: sinus cardia after injection of a total of 6.0 ml of orciprenaline (Alupent®).

After successful resuscitation by external cardiac massage for 25 minutes and artificial respiration with oxygen (by intubation) the ECG showed complete atrio-ventricular block with a regular idioventricular rate of 70/minute. The P-waves, so far as they were discernible, indicated an atrial rate of 75/minute (Fig. 1).

The ventricular and atrial rates responded to the intravenous injection of 1.0 mg orciprenaline with a rise to 85/minute and 120/minute respectively. Finally, complete A-V block subsided and a regular rhythm of 110/minute returned (Fig. 2).

Rapid infusion of Haemaccel®, sodium bicarbonate, 5% Ringer-laevulose solution and noradrenaline succeeded at about 10.40 (two hours after cardiac arrest) in restoring the circulatory state to normal. Unaided by adrenergic agents the blood pressure rose to 105/85 mm Hg and the patient responded to stimuli.

ECG recordings (precordial leads) showed episodes of right bundle branch block. 17 hours after the accident the sinus rhythm was again disturbed by occasional ventricular extrasystoles which became more frequent in the course of the next half hour (Fig. 3). After a further two hours, P-waves were no longer discernible; but the possibility that they were fused with the preceding T-waves could not be excluded.

During the day the ventricular extrasystoles became more frequent and changes in the site of impulse origin resulted in episodes of parasystole. 24 hours after ingestion of the poison the blood pressure fell rapidly within 30 minutes and cardiac arrest occurred.

During resuscitation attempts prolonged bleeding from venipunctures drew attention to an increased bleeding tendency.

At 10.40, after nodal rhythm and stable circulatory conditions had become re-established and consciousness was gradually returning, massive haematemesis occurred, presumably due to profuse bleeding from the gastro-intestinal mucosa. It effectively precluded oral administration of paraffin which even then might still have proved beneficial. Up to 14.00 a total of 1,500 ml of blood-containing gastric contents had been evacuated, partly by vomiting and partly by suction catheter. An analysis of the clotting factors (at 15.00) showed maximal reduction of Factors II, V, VII and XIII and complete defibrination, fibrinogen being no longer demonstrable in the tyrosine-tryptophan test (12). The platelet count had dropped to 14,300/mm³, fibrinolysis (Piper's method [10]) was increased to four times its normal value and pro-activator levels were below 10%. The thrombelastogram showed the blood to be incoagulable. Thrombin time after fibrinogen substitution was 59 seconds instead of the normal 12 seconds.

The complex coagulation disorder with thrombocytopenia and reduced activity of all coagulation factors was attributed to the consumption of these substances in a process of disseminated intravascular coagulation ("Verbrauchskoagulopathie") and to secondary hyperfibrinolysis (5, 7). The patient was given 5,000 U heparin by intravenous drip over a period of two hours and he was also given intravenously Cohn's fraction as a fibrinogen substitute, 4.0 g of ε-amino-caproic acid as an anti-fibrinolytic agent and 2.0 ml Vitamin $K_1$ (phytomenadione).

A further estimation of clotting factors at 18.00 showed a rise in fibrinogen level to 16 mg/100 ml and in the platelet count to 20,000/mm³. Factors II, V and VII remained low. As was subsequently confirmed at necropsy, the liver at that time was already irretrievably damaged. The steep rise of SGOT to 1,860 IU, of SGPT to 450 IU and of

lactate dehydrogenase to 4,555 IU and the reduction of serum-albumin concentration to 1.59 g/100 ml and of plasma-cholesterol to 76 mg/100 ml were presumably attributable to fulminating yellow atrophy of the liver. The abnormally high lactate-dehydrogenase activity may have possibly been due to haemolysis.

Blood-gas analysis (Astrup's method) after massive infusion of a total of 920 mEq. of sodium bicarbonate revealed extreme acidaemia (pH 6.8) which was partly of metabolic (reduced base excess and standard bicarbonate) and partly of respiratory origin (marked increase in $CO_2$ tension). At the time the blood samples were taken the patient was already moribund. He died at approximately 20.00, about 24 hours after ingestion of the poison, of irreversible cardiac and circulatory failure.

### Necropsy Findings

The most striking feature was acute yellow atrophy of the enlarged (1,800 g) and flabby liver. The cut surface showed irregular yellowish-brown mottling. Through the microscope the lobular structure was discernible only as a shadow outline.

The portal canals were crowded closely together. Goldner's stain revealed very dark, homogeneous and lumpy hepatic cells with only a few nuclei. Distended cells, hyaline bodies and large intracellular fat droplets were also seen. Only a few hepatic cells were of normal appearance.

Both ventricles were hypertrophied and the right one was also dilated. On microscopic examination the myocardial fibres were thickened and the cell nuclei enlarged and irregular. There were also recent, predominantly perivascular, focal necroses of the myocardial fibres (Fig. 4*). The coronary arteries were slightly arteriosclerotic but not narrowed.

The lungs showed bilateral chronic emphysema, membranous pleural adhesions, considerable congestion and oedema. Microscopic examination revealed both occluding and non-occluding thrombi in the small lung arteries and capillaries, of not quite recent origin (Figs. 5 and 6).

The haemorrhagic diathesis manifested itself in haemorrhages into the mucosae of oesophagus, stump of the stomach (after a Billroth II gastrectomy) and rectum, and into the subepicardial, subendocardial and myocardial tissues. Bleeding into the intestinal wall was noticeable in some jejunal loops. The attempts at resuscitation had resulted in fracture of several ribs, subpleural haematoma and haemothorax of minor degree on the left side.

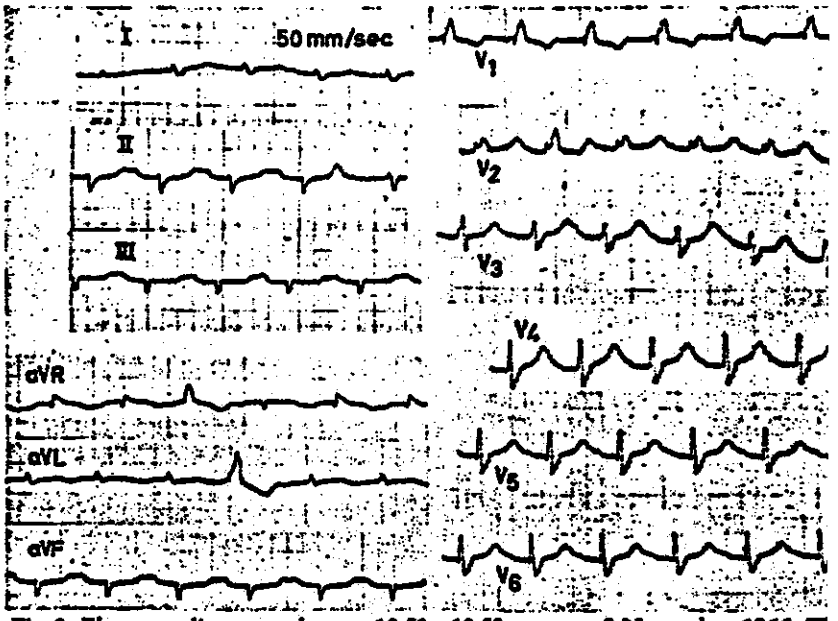



Fig. 3. Electrocardiogram taken at 10.53—10.58 a.m. on 5 November 1966. T tracings (the leads were not recorded simultaneously) show, first, sinus tach cardia with some extrasystoles; on the reight: complete right bundle branch blo has developed which may indicate acute cor pulmonale.

## Discussion

The signs and symptoms presented by this case of dichloroethane poisoning corresponded closely to the clinical picture described by others. Characteristic features were an initial stage of stupor followed by the development of gastro-enterocolitis, hepatic necrosis, haemorrhagic diathesis and cardiogenic shock within 48 hours. The frequently observed involvement of the kidneys was absent in our case. Toxic effects of dichloroethane resemble those produced by other halogenated hydrocarbons, especially carbon tetrachloride, chloroform and ethane tetrachloride. All these agents have in common that, being fat-soluble, they have narcotic effects and taken orally they cause gastrointestinal damage and necrosis of the liver and kidneys. The renal lesions generally do not develop until after a latent period of 24–48 hours (9 Cardiac arrhythmias and particularly ventricular fibrill tions have been observed after poisoning with chlorofor and carbon tetrachloride (4) and Friese (3) also notice in a case of ethane dichloride poisoning a transient i version of the T-wave in leads $V_3$–$V_5$ such as occurs rudimentary infarction of the anterior wall. The haemo rhagic tendency that accompanies carbon tetrachlori and dichloroethane poisoning has been ascribed to a ma sive reduction in prothrombin concentration.

The post-mortem examination in our case revealed n only the signs of haemorrhagic diathesis but also throm in the pulmonary arterioles and capillaries. Taking in account the complex changes in the haemostatic mecha ism and the not unfavourable effects of heparin admi istration, the assumption appears justified that the dram tic reduction in the platelet count and clotting factors w a sign of their marked depletion, the substrates havi been consumed in the process of coagulation (8). This i terpretation receives support from the fact that fibrinog has a half-life of 3–4 days (1): the drop in the plate count and plasma Factor I could not, therefore, be counted for by the onset of hepatic necrosis and the sulting interference with the formation and synthesis plasma clotting factors. As to the accompanying hyp fibrinolysis, this was presumably a reactive process to d solve the fibrin thrombi as is frequently observed in gen alized intravascular clotting (7).

Whether dichloroethane can trigger intravascu clotting is so far unknown. Being a fat solvent it mi damage the platelet membrane and thereby release p telet Factor III; or it might activate the clotting process inducing haemolysis and thereby releasing pro-coagul erythrocytic lipoproteins (erythrocytin [11]). The sn venom in the embrocation (snake bites may cause int

* Figs. 4–6 are on p. 66.

For the article by Turina et al. (pp. 49–50)

## Crohn's Disease of the Oesophagus

Fig. 1. Crohn's disease of the oesophagus. Oesophagram: severe degree of stenosis with thread-like irregular lumen immediately above the diaphragm. Conical narrowing of the oesophagus above the stenosis.


Fig. 2. Same case as Fig. 1. Resected specimen of the distal oesophagus and proximal part of the stomach showing a 2 cm long granulomatous stenosis (S) below the upper margin of the resection.

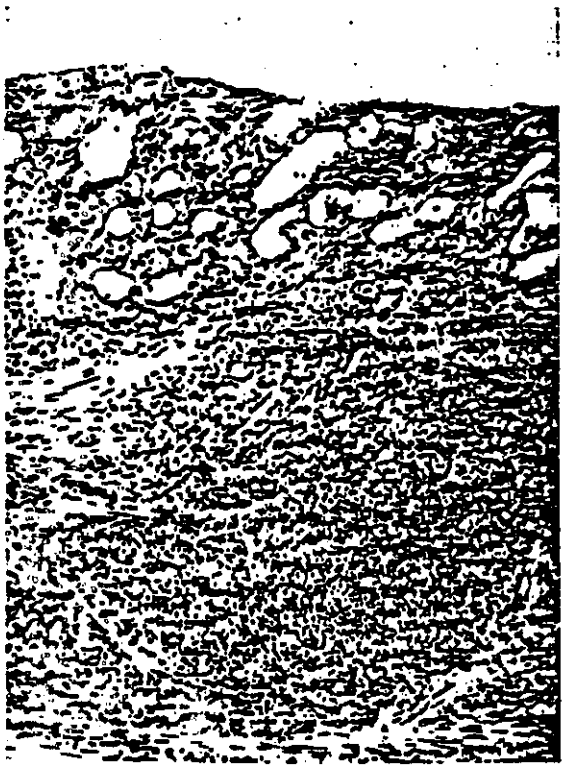


Fig. 3. Same case. Ulcer floor with non-specific granulation tissue and compact lymph follicles in the residual parts of the tunica propria, also in the submucosa which is fibrotic and hyperaemic. Magnification × 35.

Fig. 4. Same case. Muscularis propria with compact lymph follicles. Magnification × 88.

6

or the article by Martin et al. (pp. 62–67)

## Clinical Features, Pathogenesis and Management of Dichloroethane Poisoning

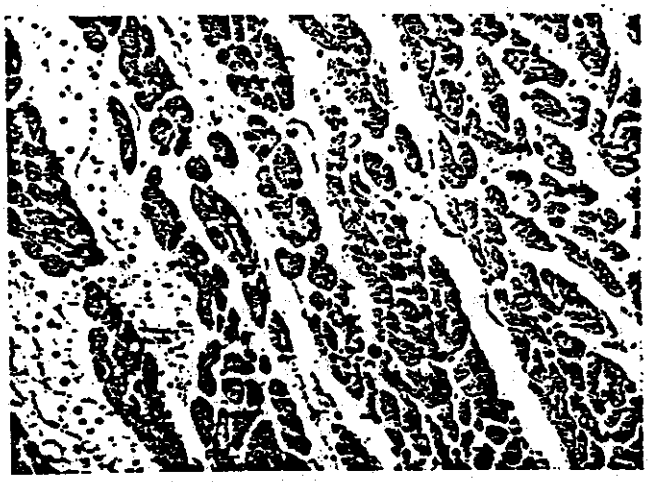


Fig. 4. Heart-muscle necrosis. Goldner's trichome stain. Magnification × 140.

Fig. 5. Hyaline thrombi in lung vessels. Goldner's trichome stain. Magnification × 140.

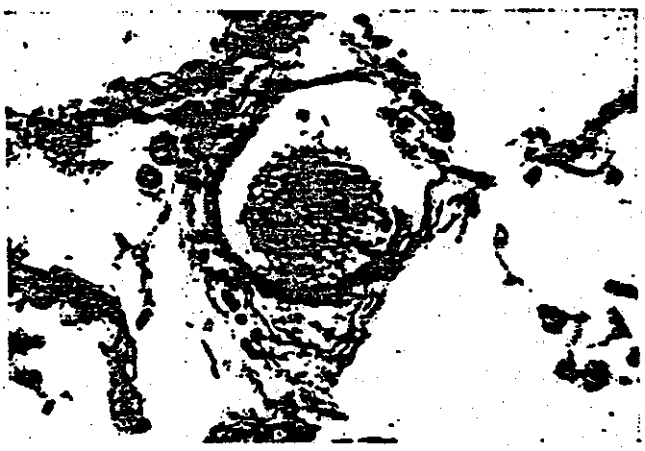


Fig. 6. Hyaline thrombus in lung vessels. Goldner's trichome stain. Magnification × 240.

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For the article by Gedigk et al. (pp. 68–77)

## The Morbid Anatomy of Marburg Virus Disease

Fig. 1. Irregularly arranged areas of necrosis (dark) affecting single cells and cell groups in the liver. Case 1 (PM No. 378/67). Formalin, Goldner, × 100.

cular clotting) can be excluded as a causal factor as poison was taken by mouth. The severe damage to the ans induced by dichloroethane could possibly bring ut the release of tissue thromboplastins which, in con- ction with the excessive acidaemia and circulatory fail-, could cause a shift in the physiological balance be- en fibrinolysis and clotting towards the latter.

There is also the possibility that the cardiac arrhythmia l the consequent reduction in cardiac output (cardio- ic shock) played a causal role in the pathogenesis of avascular clotting. On the other hand, the dilatation the right ventricle and development of acute cor pul- nale with cardiac arrhythmia, cardiogenic shock and ocardial necroses could equally well originate from avascular coagulation and the resulting, histologically ven, blocking of the pulmonary circulation by thrombi. his latter hypothesis is accepted the haemorrhagic dia- sis, the cardiac arrhythmia and the disseminated ne- se: in the intestine and kidneys could be attributed to action of a single mechanism since the fully developed drome of intravascular coagulation is characterized by arction of, and haemorrhages into, various organs.

## nclusions

The clinical picture presented by dichloroethane soning is determined by the quantity of poison ingest- In man the tolerated single dose is not more than ml, with a maximal daily dose of 3.0 ml (9). As there o known specific antidote, measures to counteract the cts of orally taken dichloroethane are primarily con- d to attempts at reducing or slowing down absorption the poison from the gastro-intestinal tract. Further rapeutic measures aim at preventing acute hepatic ure and at restoring the disordered haemostatic mecha- n, acid-base balance and cardiovascular function. Selec- therapy directed to the restoration of a particular ctional system is impossible. From considerations of pathogenetic mechanism, published reports and our observations some general principles for dealing with dichloroethane poisoning emerge:

) Alertness to the possibility of dichloroethane poi- ing is important. Inadequate specification of some loroethane-containing preparations as potentially gerous is liable to mislead patients, relatives and the nding physician.

) Analysis of the expired air by a gas analyser for the ence of chlorinated hydrocarbons, unless this type of on can be absolutely ruled out.

) Prompt gastric lavage, provided there is no contra- cation, with addition of paraffin; then administration 100–150 ml of paraffin and saline purges, either by ith or indwelling stomach tube. Paraffin administration peated every 6–8 hours for the first 24–48 hours.

4) Prompt measures to protect the liver similar to those employed in acute yellow atrophy (6). Repeated laboratory tests.

5) Supervision and constant adjustment of blood gases and steps to ensure excretion of an alkaline urine. Sodium bicarbonate administration should be supplemented by THAM, because the latter is more effective in counteracting intracellular acidosis.

6) Prompt and continuous analysis of the clotting factors to ensure that an incipient consumption of platelets and fibrinogen is immediately checked by an infusion of heparin (20,000 U in 24 hours). This therapy is applicable even in the presence of gastro-intestinal haemorrhage. If defibrination has already occurred, heparin combined with Cohn's fraction I as a fibrinogen substitute is given by infusion.

7) Continuous supervision of cardiovascular function with continuous recording of the ECG.

8) Administration of water and electrolytes as required and symptomatic treatment of the gastro-enterocolitis which is an almost invariable complication. Intestinal haemorrhages resulting in a critical reduction in haemoglobin concentration may require blood transfusion.

9) Renal failure setting in 24–48 hours after ingestion of the poison is a potential complication of the third stage of dichloroethane poisoning. Its occurrence depends on the quantity swallowed, the interval between ingestion and beginning of treatment and the success of the antecedent therapeutic measures. Treatment is the same as for acute failure from other causes.

10) An apparent improvement in the patient's condition after the initial stuporous stage has subsided must not lead to premature slackening of the therapeutic efforts.


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(Authors' addresses:- Dr. G. Martin
Universitäts-Frauenklinik
Humboldtalle, 34 Göttingen;
Dr. K. Knorpp; Privatdozent Dr. K. Huth; Dr. F. Heinrich
Medizinische Kliniken und Polikliniken
Klinikstr. 32b, 63 Giessen;
Dr. C. Mittermayer
Pathologisches Institut der Universität
78 Freiburg/Br., Germany)

# PUBLIC REVIEW OF DRAFT REPORTS

STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

February 19, 1985

Dear Sir/Madam:

Subject: Reports on Ethylene Dichloride (EDC)

In my May 31, 1984, letter requesting health effects information on EDC, I indicated that we would prepare a report on EDC for review by the Scientific Review Panel (SRP). Also in that letter, I stated that the report submitted to the Panel will be made available to the public upon its submittal to the Panel.

This letter is to inform you of an opportunity we are providing to review and comment on the report on EDC prior to its submittal to the SRP. The report will have three parts. Part A, by the ARB staff, discusses the uses, emissions, and ambient air concentrations of EDC. Part B, by the Department of Health Services (DHS) discusses the effects of EDC on health and the risks associated with ambient EDC exposure. A draft Part A and the DHS Part B will be available by February 21, 1985. A new Part C containing public written comments on Parts A and B and responses to those comments by our staff and the DHS respectively will be included in the report to the SRP.

I am issuing this notice now to facilitate distribution and review of the report. We will provide thirty days for review. Therefore, reviewers will have until March 25, 1985 to submit written comments to:

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

After responding to public comments, we plan to send the report to the Scientific Review Panel for their review. The report will contain all comments by reviewers, responses by the ARB staff to comments on Part A, our revisions to the text of Part A, responses by DHS to comments on Part B, and DHS' revisions to Part B.

Please indicate on Attachment I which reports you wish to receive by mail, or you may pick up a copy of the appropriate reports in person at our Public Information Office. As I stated, the draft of Part A and Part B will be available February 21. Please call Don Ames at 916-322-8285 if you have any questions.

Sincerely,

Peter D. Venturini, Chief
Stationary Source Division

Attachment

cc: Alex Kelter, DHS
Raymond Neutra, DHS

## Requests for Reports on EDC

Please indicate which and how many reports you want. For each mailing, two copies of each Part will be free; for additional copies of Parts A or B, you may be billed $1.50 each; the cost of additional copies of Part C is not yet known.

| | Number of Copies |
|---|---|
| Draft Part A (available now) | _____ |
| Part B (available now) | _____ |
| Parts A, B, C (SRP package available at time submitted to SRP) | _____ |
| Report to ARB[1] (available in future, at least 45 days prior to Board hearing) | _____ |

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1 summary, revised (if necessary) Parts A, B and C, and findings of the SRP

Agency or Company: _____

Address: _____

City, State, Zip Code: _____

Mail this request by March 8, 1985 to:

Toxic Pollutants Branch
Attention: Ethylene Dichloride
Air Resources Board
P. O. Box 2815
Sacramento, Ca 95812

DOW CHEMICAL U.S.A.

WESTERN DIVISION
POST OFFICE BOX 1398
PITTSBURG, CALIFORNIA 94565
415 · 432-5000

March 25, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

We have reviewed draft Part A and Part B of the "Report on Ethylene Dichloride to the Scientific Review Panel." Please include our comments which follow into draft Part C of this report.

The EDC Technical Panel of the Chemical Manufacturers Association has prepared written draft comments on the "Report on Ethylene Dichloride to the Scientific Review Panel, Parts A and B." A copy of these draft comments are attached. We wish to incorporate the draft comments of the Chemical Manufacturers Association into our comments and request that they be included in Part C of the report.

In addition, we wish to add the following comment concerning Part A of the report.

On pages C-2, C-3, and C-4, there are inconsistencies in the data presented. On C-2, tetraethyl lead to EDC ratio is 1.0: 0.034 yet in equation the figure 0.304 is used instead of 0.034. On page C-3 the leaded gas production in 1983 is quoted as 119,472 bbls. yet in equation on Page C-4, 119,472,000 bbls. is used. In the last equations on C-4, two different values for tons of EDB per year are used. Also in a number of places on the three pages, EDB has been used where it should be EDC.

We appreciate the opportunity to comment on these reports.

Sincerely yours

Bryant C. Fischback,
Manager
Environmental Services

BCF:cs

Attachment

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

The EDC Technical Panel of the Chemical Manufactures Association wishes to submit comments on the "Report on Ethylene Dichloride to the Scientific Review Panel, Parts A and B". The Technical Panel requests that these comments be incorporated into Part C and be submitted to the Scientific Review Panel for their consideration.

PART A: USE, EMISSIONS, EXPOSURE

The Part A discussion of usage and emissions indicates that the dominant use of EDC nationwide is as a reactant in the production of vinyl chloride, perchloroethylene, trichloroethylene, methyl chloroform, and vinylidene chloride. While it is true that EDC is a reactant in the production of vinyl chloride, this substance is not used to produce methyl chloroform. Certain processes use vinyl chloride to produce methyl chloroform but none of the US producers use EDC per se to make methyl chloroform. While EDC can be used as a feedstock for the production of perchloroethylene and trichloroethylene, this usage is undertaken only when the market is "long" for this material. Normally, less expensive feedstocks are used for the production of these solvents.

It was noted that 2.7 tons of EDC was applied as a pesticide in 1983. Although it is unclear as to the form of pesticide used, it should be noted that at the end of 1985, EDC will no longer be used in liquid grain fumigants. Nevertheless, even if the use of EDC were to continue at the rate of 2.7 tons per year, this represents a trivial amount of material which would be undetectable in the ambient air of ithe State of California.

In the discussion on stationary sources, it is stated that "other potentially significant sources of EDC emissions include waste landfills and publically owned treatment works (POTWs)." and that "large sewage treatment plants can emit significant amounts of EDC." However, it was previously stated that the dominant source of EDC in California was in leaded gasoline. The next most common source was considered to be the use of EDC as a solvent or constituent of chemical products. This source category results in emissions totalling 124 tons per year. This usage, like the pesticide uses of EDC, consists of a relatively small amount of material on an annual basis. Consequently, one is uncertain as to the source of the EDC that is alleged to be emitted from hazardous waste landfills and POTWs. Surely, leaded gasoline is not being discarded in California's hazardous waste

landfills and POTWs. The other two major uses of EDC, industrial solvents and pesticides, do not constitute a sufficient quantity of material to be considered as "significant".

It is necessary to comment on Figure I-1 (pI-3), which presents a projection of emissions for the period from 1984 to 2000. The first data point contained in the graph is for the year 1984 and the remainder of the graph is presumably extrapolated from this one "single" data point. It is difficult not to question the scientific validity of such a procedure.

FATE IN THE ATMOSPHERE

This discussion correctly indicates that EDC in the atmosphere is attacked by hydroxy radicals and consequently, EDC is not a persistent air contaminant.

AMBIENT AIR EXPOSURE TO EDC

This section is probably the most significant portion of Part A insofar as it defines the extent of the ARB data base. It is essential to note that HSL's minimum value for reporting was 100 ppt(v). It is also essential to note that only 13 percent of the 566 analyses were above this minimum value of 100 ppt. and that the remaining 87 percent of the analyses were below this minimum value and are consequently undefined. In an attempt to use this minimal data base, the ARB staff assumed that any data point below the minimum value would be equivalent to 50 ppt.

Table III-1 contains the summary of the 24-hour EDC monitoring data and indicates that in the South Coast Air Basin, the average of four site means for 1983 was 67.5 ppt. This table also indicates that the average of the same four site means for 1984 was 53.1 ppt. A review of the data points for each of the four sites indicates that none of the sites experienced an exposure above the HSL's minimum value for the years 1983 or 1984. Since any value below the minimum value is undefined, none of the data points for the years 1983 or 1984 have any factual basis. At best, one would be able to say that one or more of the data points used to establish the site mean was above 100 ppt. In reviewing the data for 1984, it is noteworthy that only one of four sites had an exposure above the ARB's floor value of 50 ppt. Consequently, with the possible exception of Riverside, EDC was essentially not detected in the South Coast Air Basin during 1984. Nevertheless the document indicates that the annual average concentration to which most of the population of the South Coast Air Basin is exposed is 68 ppt. The scientific basis for this conclusion escapes our understanding.

Table III-3 lists the ambient air concentrations of EDC near landfills. Little if any significance should be given to the Ascon site since the data represents a single day's sampling and this was conducted over four years ago.

This section ends with the conclusion that "This analysis indicates that air is the major medium for exposure to EDC in the SCAB." We would suggest that based on the 1984 date, the air exposure to EDC is minimal and perhaps nonexistent.

Finally, this section indicated that a network of 16 monitoring stations would begin to monitor for EDC in early 1985. When one considers the facts that the use of EDC in leaded gasoline is decreasing; the use of EDC as a pesticide isalso probably on the decline; and that the emissions of EDC from landfills is thought to be decreasing, one must ask why is the ARB fostering the monitoring of a substance which is currently unquantifiable and whose concentration is expected to further decrease over the next few years.

In summary, Part A establishes a strong arguement for the position that it is not necessary to monitor EDC in the State of California. The ARB data base adequately demonstrates that EDC is not present in the atmosphere in measurable levels and is sufficiently low as to preclude any health hazards to the populace.

PART B: HEALTH EFFECTS OF EDC

The Technical Panel agrees with the summary statement that adverse health effects, such as systemic and reproductive effects, would not be expected to result from exposure to ambient levels of EDC in California urban environments. Moreover, we find the evidence for the designation of EDC as a probable human carcinogen less than convincing and do not believe that the populace of California is at risk from the exposure to the ambient levels of EDC found in California.

NCI GAVAGE BIOASSAY

While it is recognized that IARC has designated EDC as an animal carcinogen and as a probable human carcinogen, the NCI gavage bioassay on rats and mice was severely flawed in regard to the exceedance of the maximum tolerated dose in the rat study.

Although the Part B discussion of the bioassays mentioned the necessity of resorting to "cyclical dosage regime" during the NCI rat bioassay, it should be noted that even with the regime of four weeks on test, followed by one week without any dosing, all high dose rats died before the end of the study. This dosage modification was started after the animals had been on study for only 35 weeks. All dosing was discontinued for both rats and mice after 78 weeks. Due to the extraordinary toxicity experienced by the rats, we believe that the rat portion of the EDC bioassay was compromised and is unsatisfactory for the evaluation of carcinogenic effect.

As the result of our concern as to the conduct of the NCI bioassay, the Technical Panel conducted an audit of the in-life phase of the bioassay. A copy of this audit is enclosed with these comments.

MALTONI INHALATION BIOASSAY

Although the DHS staff is obviously doubtful as to the merits of the Maltoni inhalation bioassay, we believe that the study contributes significantly towards the understanding of the toxicological effects of this chemical. It would appear that the EPA's Science Advisory Board is of a similar opinion. In the SAB's recommendations to the Administrator on the EPA's Health Assessment Document for EDC, it was noted that while the SAB concurred with the assessment that EDC was a carcinogen by gavage, the SAB did not find EDC to be a carcinogen by the inhalation route of exposure.

The discussion of the Maltoni study contains the following conclusion regarding the DHS' evaluation of the inhalation bioassay:

> The staff of DHS believes that the calculations given here demonstrate that the Maltoni et al (1980) study did not employ sufficiently high concentrations to induce the expected tumor in either mice or rats. The negative finding of the expected tumor incidence at the highest dose level can be explained by a relatively small difference to response between the strains used in the NCI study and those in the Maltoni study. For these reason(sic), DHS does not see the need to modify the gavage doses for projected inhalation doses.

The EDC Technical Panel was a cosponsor of the Maltoni inhalation bioassay and while this was not a perfect study, we must disagree with the position taken by the DHS staff that the Maltoni studies are of little consequence.

DIFFERENCES IN RAT STRAINS

The staff stated as fact an assumption made earlier in the discussion that the Sprague-Dawley strain is less sensitive than the Osborne-Mendel strain in responsing to carcinogenic agents. It was stated that "It is possible, however, that these strains may have quantitative differences in their carcinogenic susceptibility since they were different from the strains used in the NCI bioassay." However, the DHS staff did not document the basis for this speculation. The Sprague-Dawley rat was used by Maltoni in his studies of vinyl chloride and a very definite carcinogenic response was observed in these animals.

DOSE EQUIVALENCY

Although the bioassay discussion does state that "The highest dose level for the male and female rats and themale mice in the two studies were comparable.", Dr. Kim Hooper in his comparative analysis of the two bioassays goes even further in his recognition of the dose equivalency when he states "Calculations show, however, that the two highest dose levels in theinhalation study were entirely comparable on a mg/(Kg*day)(sic) basis to those yielding a strongly positive result in the NCI study." (Kim hooper, Lois Swirsky Gold, and Bruce N. Ames, The Carcinogenic Potency of Ethylene Dichloride in Two Animal Bioassays: A Comparison of Inhalation and Gavage Studies. Banbury Report: Ethylene Dichloride: A Potential Health Risk?, Cold Spring Harbor Laboratory, 1980)

The DHS staff report also stated that "An additional point implied by Hooper et al. (1980) is that the two lower dose levels used in the Maltoni et al. study are too low to provide a carcinogenic response for the number of animals at each dose." and "It is concluded, therefore, that the number of animals in the inhalation study were too low at the lower dosages to provide for a positive carcinogenic response." The DHS staff failed to recognize that in a cancer bioassay, not all dose levels need to elicit a carcinogenic response. The two lower dose levels are an order of magnitude lower than the high dose levels and could be considered as an attempt to identify a no-observed-effect-level. This would be an appropriate action when the carcinogenic potency of the substance is unknown. Moreover, it would establish a potential theshold level if the substance were considered to be a "promoter" as compared to an "initiator" relative to its carcinogenic properties.

In its review of the Maltoni study, the DHS almost recognized that there may be basic differences in the manner in which the animal model responded to EDC via gavage exposure as compared to the inhalation exposure. This fundamental difference is seen in the level of in vivo binding of radioactive labeled EDC to rat DNA in the gavage exposure as compared to the inhalation exposure.(Reitz et al.1982) The level of DNA binding after gavage exposure was 2 to 5 times that seen after inhalation exposure. This would suggest that there are fundamental differences in metabolic mechanisms arising from the two exposure routes.

RISK ASSESSMENT

The DHS staff recommended the use of a lifetime excess risk value between 53 and 88 per million for community exposure to 1 ppb EDC. This is equivalent to a risk value of 5 to 9 per million for a lifetime exposure to 100 ppt EDC in the ambient atmosphere. While the Technical Panel may not agree fully with the DHS risk assessment, an acceptable risk of 5 to 9 per million

at 100 ppt EDC would indicate that the current ambient air levels of EDC of <53 ppt do not represent an unreasonable hazard to the populace of the State of California.

CONCLUSION

Based on the extremely low levels of EDC found in the ambient atmosphere in the South Coast Air Basin and on the expectation that emission sources of EDC will continue to decrease in the future, a lifetime risk value of 5 to 9 per million for the exposure to 100 ppt EDC indicates that is unnecessary for the Air Resources Board to initiate any additional air emission regulations for EDC at this time.

*Southern California Edison Company*

P. O. BOX 800
2244 WALNUT GROVE AVENUE
ROSEMEAD, CALIFORNIA 91770

EDWARD J. FAEDER, Ph.D.
MANAGER OF ENVIRONMENTAL OPERATIONS

TELEPHONE
(818) 302-2069

March 22, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Mr. Loscutoff:

Subject: Report on Ethylene Dichloride to the Scientific Review Panel: Part B - Health Effects of 1,2 Dichloroethane

Southern California Edison Company (SCE) has reviewed the "Report on Ethylene Dichloride to the Scientific Review Panel: Part B - Health Effects of 1,2-Dichloroethane" and would like to submit these brief comments.

Table 1 of the report (page 3) presents lifetime excess cancer risks from ambient exposure to ethylene dichloride (EDC). These risk estimates are calculated using five different dose response models, including the gamma multihit (GMH) model. Haseman et al.(1) have shown that the GMH model produces what appears to be unrealistically high risk estimates with some sets of data, and in other cases produces extremely low risk estimates. We feel that the Department of Health Services (DHS) should reconsider the use of this model even for purposes of comparison as it is used in this report.

DHS should also describe their criteria for selecting the recommended range of risk estimates which are presented in the EDC report and in other risk assessment reports as well. As an example, in the ethylene dibromide report, the lower bound selected was the maximum likelihood estimate (MLE) of risk calculated using the multistage model for hemangiosarcomas in mice. The upper bound selected was the 95% upper confidence limit (UCL) for risk calculated using the Weibull-multistage model for nasal cavity malignancies in rats. The upper and lower bounds were, therefore, selected from different estimates (MLE versus UCL) and models, using data from different species and tumor sites. In the EDC report the upper and lower bounds for risk selected were the MLE and UCL for risk using the same model, tumor site and species. Without an explanation of the criteria used to select the upper and lower bounds which are suggested for regulatory purposes, this selection process appears arbitrary.

We appreciate the opportunity to provide comments to the Air Resources Board on this and other important issues.

Sincerely,

Edward J. Zaebst

REFERENCE

1) Haseman, J. K., Hoel, D. G. and Jennrich, R. I., Some practical problems arising from use of the gamma multihit model for risk estimation. Journal of Toxicology and Environmental Health, Vol. 8, pp. 379-386, (1981).

CHEMICAL MANUFACTURERS ASSOCIATION

GERALDINE V. COX, Ph.D.
Vice President
Technical Director

Rick

March 22, 1985

William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

The Ethylene Dichloride Program Panel of the Chemical Manufacturers Association wishes to submit the attached comments on the "Report on Ethylene Dichloride to the Scientific Review Panel, Parts A and B". The EDC Panel requests that these comments be incorporated into Part C of the Report and be submitted to the Scientific Review Panel for their consideration.

If you have comments or questions, please do not hesitate to contact Dr. Robert Romano of my staff at 202/887-1198.

Sincerely yours,

Geraldine V. Cox

Enclosure



Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.
2501 M Street, NW • Washington, DC 20037 • Telephone 202/887-1260 • Telex 89617 (CMA WSH)

COMMENTS
of the
ETHYLENE DICHLORIDE PROGRAM PANEL
of the
CHEMICAL MANUFACTURERS ASSOCIATION

on

Report on Ethylene Dichloride
to the
Scientific Review Panel, Parts A and B

PART A: USE, EMISSIONS, EXPOSURE

The discussion in Part A of usage and emissions indicates that the dominant use of ethylene dichloride (EDC) nationwide is as a reactant in the production of vinyl chloride, perchloroethylene, trichloroethylene, methyl chloroform, and vinylidene chloride. While it is true that EDC is a reactant in the production of most of these chemicals, this substance is not used to produce methyl chloroform. Certain processes employ vinyl chloride to produce methyl chloroform but none of the US producers use EDC per se to make methyl chloroform.

It was noted that 2.7 tons of EDC were applied as a pesticide in 1983. Although the form of pesticide used is unclear, it should be noted that by the end of 1985, EDC will no longer be used in liquid grain fumigants. Nevertheless, even if the use of EDC were to continue at the rate 2.7 tons per year, this represents a small amount of material when compared to the overall VOC emissions in the State of California and would be undetectable in the ambient air.

In the discussion on stationary sources, it is stated that "... other potentially significant sources of EDC emissions include waste landfills and publicly owned treatment works (POTWs)," and "... large sewage treatment plants can emit significant amounts of EDC." However, it was previously stated that the dominant use of EDC in California is in leaded gasoline. The next most common use was indicated to be as a solvent or constituent of chemical products. This latter use category consumes an estimated 124 tons per year, which is a relatively small amount of material on an annual basis. Consequently, one is uncertain as to the source of the EDC that is alleged to be "significantly" emitted from hazardous waste landfills and POTWs. Surely, leaded gasoline is not being discarded in California's hazardous waste landfills and POTWs. The other two major uses of EDC, industrial solvents and pesticides, do not constitute a sufficient quantity of material to be considered as "significant".

It is necessary to comment on Figure I-1 (pI-3), which presents a projection of emissions for the period from 1984 to 2000. The first data point contained in the graph is for the year 1984 and the remainder of the graph is presumably extrapolated from this "single" data point. We must question the scientific validity of such a procedure.

FATE IN THE ATMOSPHERE

This discussion correctly indicates that EDC in the atmosphere is attacked by hydroxyl radicals and consequently, EDC is not a persistent air contaminant.

AMBIENT AIR EXPOSURE TO EDC

This section is probably the most significant portion of Part A in as much as it defines the extent of the ARB data base. It is essential to note that HSL's minimum value for reporting was 100 ppt(v). It is also noteworthy that only 13 percent of the 566 analyses were above this minimum value of 100 ppt., and that the remaining 87 percent of the analyses were below the minimum value and are consequently undefined. In an attempt to use this tiny data base, the ARB staff assumed that any data point below the minimum value would be equivalent to 50 ppt. This use of 50 ppt as a minimum value lacks a scientific basis and is misleading.

Table III-1 contains the summary of the 24-hour EDC monitoring data and indicates that in the South Coast Air Basin, the average of four-site means for 1983 was 67.5 ppt. The Table also indicates that the average of the same four-site means for 1984 was 53.1 ppt. A review of the data points for each of the four sites indicates that none experienced an exposure above the HSL's minimum value for the years 1983 or 1984. Since any value below the minimum value is undefined, none of the data points for the years 1983 or 1984 have any factual basis. At best, one would be able to say that one or more of the data points used to establish the site mean was above 100 ppt. In reviewing the data for 1984, it is noteworthy that only one of four sites, Riverside, had an exposure above the ARB's floor value of 50 ppt. Consequently, with the possible exception of Riverside, EDC was essentially not detected in the South Coast Air Basin during 1984. Nevertheless the document indicates that the annual average concentration to which most of the population of the South Coast Air Basin is exposed is 68 ppt. The scientific basis for this conlusion escapes our understanding.

Table III-3 lists the ambient air concentrations of EDC near landfills. Little if any significance should be given to the Ascon site since the data represents a single day's sampling and this was conducted over four years ago.

This section ends with the conclusion that, "This analysis indicates that air is the major medium for exposure to EDC in the SCAB." We would suggest that based on the 1984 data, the air exposure to EDC is minimal and perhaps nonexistent.

Finally, this section indicated that a network of 16 monitoring stations would begin to monitor for EDC in early 1985. When one considers the facts that the use of EDC in leaded gasoline is decreasing; the use of EDC as a pesticide is also probably on the decline; and that the emissions of EDC from landfills is thought to be decreasing, one must question the purpose of monitoring a substance which is currently unquantifiable and whose concentration is expected to further decrease over the next few years.

In summary, Part A establishes a strong argument for the position that it is not necessary to monitor EDC in the State of California. The ARB data base adequately demonstrates that EDC is not present in the atmosphere in measurable levels and is sufficiently low to preclude any health hazards to the population.

PART B: HEALTH EFFECTS OF EDC

The EDC Panel agrees with the summary statement that adverse health effects, such as systemic and reproductive effects, would not be expected to result from exposure to ambient levels of EDC in California urban environments. Moreover, we find the evidence for the designation of EDC as a probable human carcinogen less than convincing and do not believe that the population is at risk from exposure to the ambient levels of EDC found in California.

NCI GAVAGE BIOASSAY

While it is recognized that IARC has designated EDC as an animal carcinogen and as a probable human carcinogen, the NCI gavage bioassay on rats and mice was severely flawed in regard to exceeding the maximum tolerated dose in the rat study.

The discussion in Part B of the bioassays mentioned the necessity of resorting to "cyclical dosage regime" during the NCI rat bioassay. But, it should be noted that even with the regime of four weeks on test, followed by one week without any dosing, all rats in the high dose group died before the end of the study. This dosage modification was started after the animals had been on study for only 35 weeks. All dosing was discontinued for both rats and mice after 78 weeks. Due to the extraordinary toxicity experienced by the rats, we believe that the rat portion of the EDC bioassay was compromised and is unsatisfactory for the evaluation of carcinogenic effect.

As a result of our concern about the conduct of the NCI bioassay, the EDC Panel conducted an audit of the in-life phase of the bioassay. A copy of this audit is enclosed with these comments.

MALTONI INHALATION BIOASSAY

Although the DHS staff is obviously doubtful as to the merits of the Maltoni inhalation bioassay, we believe that the study contributes significantly toward the understanding of the toxicological effects of this chemical. It appears that EPA's Science Advisory Board is of a similar opinion. In the SAB's recommendations to the EPA Administrator on the Health Assessment Document for EDC, it was stated that while the SAB concurred with the assessment that EDC was a carcinogen by gavage, the SAB did not find EDC to be a carcinogen by the inhalation route of exposure.

The discussion of the Maltoni study contains the following conclusion regarding the DHS' evaluation of the inhalation bioassay:

> "The staff of DHS believes that the calculations given here demonstrate that the Maltoni et. al. (1980) study did not employ sufficiently high concentrations to induce the expected tumor in either mice or rats. The negative finding of the expected tumor incidence at the highest dose level can be explained by a relatively small difference to response between the strains used in the NCI study and those in the Maltoni study. For these reason(sic), DHS does not see the need to modify the gavage doses for projected inhalation doses."

The EDC Panel was a cosponsor of the Maltoni inhalation bioassay. While this study was not perfect, we must disagree with the position taken by the DHS staff that the Maltoni studies are of little consequence.

DIFFERENCES IN RAT STRAINS

The staff stated as fact an assumption made earlier in the discussion that the Sprague-Dawley strain is less sensitive than the Osborne-Mendel strain in responsing to carcinogenic agents. It was added that, "It is possible, however, that these strains may have quantitative differences in their carcinogenic susceptibility since they were different from the strains used in the NCI bioassay." However, the DHS staff did not document the basis for this speculation. The Sprague-Dawley rat was used by Maltoni in his studies of vinyl chloride and a very definite carcinogenic response was observed in these animals.

DOSE EQUIVALENCY

The bioassay discussion does state that, "The highest dose level for the male and female rats and the male mice in the two studies were comparable." However, Dr. Kim Hooper in his comparative analysis of the two bioassays, went even further in his recognition of the dose equivalency when he stated that, "Calculations show, however, that the two highest dose levels in the inhalation study were entirely comparable on a mg/(Kg . day)(sic) basis to those yielding a strongly positive result in the NCI study." (Kim Hooper, Lois Swirsky Gold, and Bruce N. Ames, The Carcinogenic Potency of Ethylene Dichloride in Two Animal Bioassays: A Comparison of Inhalation and Gavage Studies. Banbury Report: Ethylene Dichloride: A Potential Health Risk?, Cold Spring Harbor Laboratory, 1980)

The DHS staff report also stated that, "An additional point implied by Hooper et. al. (1980) is that the two lower dose levels used in the Maltoni et. al. study are too low to provide carcinogenic response for the number of animals at each dose," and further, "It is concluded, therefore, that the number of animals in the inhalation study were too low at the lower dosages to provide for a positive carcinogenic response." The DHS staff failed to recognize that in a cancer biassay, not all dose levels need elicit a carcinogenic response. The two lower dose levels are an order of magnitude lower than the high dose levels, and could be considered as an attempt to identify a no-observed-effect-level. This would be an appropriate action when the carcinogenic potency of the substance is unkown. Moreover, it would establish a potential threshold level if the substance were consdiered to be a "promoter," as compared to an "initiator," relative to its carcinogenic properties.

In its review of the Maltoni study, the DHS almost recognized that there may be basic differences in the response of the animal model to EDC via gavage exposure as compared to the response from inhalation exposure. This fundamental difference is seen in the level of <u>in vivo</u> binding of radioactive labeled EDC to rat DNA in the gavage exposure, when compared to that from inhalation exposure. (Reitz et al. 1982). The level of DNA binding after gavage exposure was 2 to 5 times that seen after inhalation exposure. This would suggest that there are fundamental differences in metabolic mechanisms arising from the two exposure routes.

RISK ASSESSMENT

The DHS staff recommended the use of a lifetime excess risk value between 53 and 88 per million for community exposure to 1 ppb EDC. This is equivalent to a risk value of 5 to 9 per million for a lifetime exposure to 100 ppt EDC in the ambient atmosphere. While the EDC Panel may not agree fully with the DHS risk assessment, an acceptable risk of 5 to 9 per million at 100 ppt EDC would indicate that current ambient air levels of EDC,

which are less than 53 ppt., do not represent an unreasonable hazard to the people of the State of California.

## CONCLUSION

Only extremely low levels of EDC are currently found in the ambient atmosphere in the South Coast Air Basin and it is expected that emission sources of EDC will continue to decrease in the future. The calculated lifetime risk value of 5 to 9 per million for exposure to 100 ppt. EDC is therefore quite conservative and indicates that it is unnecessary for the Air Resources Board to initiate any additional air emission regulations for EDC at this time.

# REPORT OF THE AUDIT FINDING OF THE NATIONAL CANCER INSTITUTE (NCI) CARCINOGENESIS BIOASSAY OF 1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE; EDC) PERFORMED UNDER THE AUSPICES OF THE CHEMICAL MANUFACTURERS ASSOCIATION (CMA)

Report of the audit findings of the National Cancer Institute (NCI) Carcinogenesis Bioassay of 1,2-Dichloroethane (Ethylene Dichloride; EDC).

Technical Report No. 55 (1978)

Conducted by the audit subcommittee, ECD panel of the Chemical Manufacturers Association (CMA).

Report Prepared By:

Ross E. Jones, Ph.D.
Audit Subcommittee Member — Date

Reviewed By:

Dennis K. Newman, B.S.
Audit Subcommittee Member — Date

Janet C. Johnson, H.T. (A.S.C.P.)
Histology Consultant to CMA — Date

Zeb G. Bell, Jr., ScD.
Audit Consultant to CMA — Date

Volume I



Volume II

## 1. ABSTRACT

This audit was performed to assess the conduct of the in-life portion of the National Cancer Institute (NCI) 1,2-dichloroethane (ethylene dichloride; EDC) carcinogenesis bioassay on B6C3F1 mice and Osborne-Mendel rats and to determine if the conditions of the bioassay reasonably support the conclusions presented in the NCI Technical Report No. 55 (NCI-CG-TR-55; 1978).

This audit of the raw data covered: 1) compound preparation, analyses, and prechronic studies; 2) animal accountability, identification of animals, compound administration, antemortem observations, and environmental conditions; 3) gavage accidents and postmortem observations exclusive of histopathology; and 4) slide-block match-ups.

The findings of this audit revealed that the concentrations of the dosing solutions cannot be verified (no solution analysis records were found). Individual group identity for the animals could not be verified because neither the feet nor the ears were harvested in most cases (and when present were not coded as specified in the protocol). In addition, because of the absence of markings, the individual animal numbers could not be verified.

There is evidence of failure to histologically process and microscopically evaluate grossly identified stomach and liver lesions in rats as well as liver lesions in mice. These gross lesions were still among the residual wet tissues. Of the randomly selected male and female mice, 8.3% and 4.1%, respectively, had unprocessed liver lesions among the residual wet tissues. For the rats 4.1 and 12.5 percent of the randomly selected male and females (8 per sex per group), respectively, had gross liver lesions which had not been processed for histological examination. The male and female rats also had 20.8 and 4.1 percent, respectively, unprocessed stomach lesions.

There were no reported gavage errors (accidents) in this study which represents a remarkable laboratory performance; however, an alternate plausible explanation involves the replacement of animals into the study (substitution) for early natural deaths (found dead) and the gavage errors were not distinguishable from the natural deaths so these gavage accidents (misintubations) were also replaced.

The rats that died early in the study were noted to be in various stages of autolysis ranging from slight to advanced. This autolysis is suggestive of an inattention on the part of the animal caretakers and suggestive of a lack of physical observations being performed.

No compound mixes of 1,2-dichloroethane/corn oil were analyzed to confirm the dose concentrations in either the prechronic studies or the chronic bioassay. There were no raw data records to confirm the environmental conditions as stated in the NCI report. In addition, there were no raw data records found to verify statements of animal identification, cage rotation, or room assignments.

In conclusion, these audit findings of the 1,2-dichloroethane carcinogenesis bioassay in-life portion revealed significant data record gaps, omissions, and uncertainties which prohibits any validation of the study conduct. The National Cancer Insitiute needs to thoroughly assess and resolve the deficiencies in the bioassay before the conclusions listed in the Technical Report can be scientifically supported. The audit of the in-life protion of the 1,2-dichloroethane bioassay at this time is indeterminate in that: 1) there were omissions and voids in the data base records including numerous slides and tissue blocks which were not present for the vehicle control and treated groups, i.e., no slides, tissue blocks, or wet tissues were found for the untreated animals

even after a thorough search of the repository and upon inquiry at the contract laboratory. 2) There were 18 mice bioassays in progress at one time all of which were performed in a large room (open area or bay). While this practice is not necessarily unmanageable, one must consider the total audit findings along with the physical layout and procedures (or lack thereof) in validation of the conclusions presented in the Technical Report. The failure to individually code each animal by either ear tag, ear punch/-notch, etc., under such housing conditions must weight heavily upon the level of scientific uncertainty associated with these bioassays. 3) the random selection and examination of residual wet tissue bags revealed suspicious and unprocessed animal lesions in male and female rats and mice. These unsectioned lesions need to be processed to complete the histopathology and to establish the incidence rates for tumors. 4) There is evidence that animals were substituted into the study to replace early natural deaths; however, their source, group assignments, treatment scheme, final disposition, numbers of extra animals carried for this bioassay could not be validated from the data in the repsoitory. The replacement animals (extras) and substitutions are factors that need clarification and validation and would impact upon the handling of the statistical analyses. 5) The reported few gavage errors (misintubations/accidental deaths) could reflect excellent gavage techniques, but the substitution of extra animals into the study for early natural deaths could mask the real incidence of gavage errors. This is supported by the animals which died during the study, all of which had varying levels of autolysis and this coupled with the lack of any procedures by the testing facility to retrospectively discern misintubations, the actual gavage errors may have been also substituted. 6) There were no tissue blocks, slides, or wet tissue bags located for the untreated controls even after an extensive search of the repositiry files and contacting the testing laboratory. Further, one third of the total tissue blocks for the vehicle and treated rats could not be located in

the repository. 7) The technical report contains statements which cannot be validated by the raw data base, such as the purity of 1,2-dichloroethane; temperature and humidity of the rooms; and air changes, cage rotation and assignments. The technical report failed to include all of the information relative to the subchronic testing used in establishing the maximum tolerated dose for the 1,2-dichloroethane bioassay. 8) The physical housing of four other rat studies in one room for similar named compound (1,2-dibromoethane, 1,1-dichloroethane, etc.) to 1,2-dichloroethane, is quite disconcerting, especially under the test conditions and procedures revealed by this audit. After carefully examining the available raw data for the 1,2-dichloroethane carcinogenesis bioassay there can be no assurance the conclusions presented in the NCI Technical Report are accurate or represent the carcinogenic potential of the test compound to Osborne-Mendel rats or B6C3F1 mice. Any definitive conclusions based on this bioassay as to the carcinogenicity of 1,2-dichloroethane, must await the resolution of these audit findings.

## 2. INTRODUCTION

The National Cancer Act of 1971 provided legislative authority for the National Cancer Institute (NCI) to plan and develop a coordinated cancer research program. The major activity of the Carcinogenesis Program was the identification of carcinogens in the environment and workplace. The responsibilities of the program were to develop and maintain the cancer program[1]. The two major goals of the program were to: 1) identify chemicals that were potential carcinogens, and 2) improve the methodology for testing[2]. For these carcinogenesis bioassays guidelines were prepared to detail the methods to be employed in the conduct of the bioassay. These guidelines were for the conduct of studies using rodents with the oral administration of the test substance over a two year period[3]. Because the NCI Carcinogenesis Program had limited in-house facilities for the conduct of the bioassays, these research projects were subcontracted to various laboratories[4]. These laboratories were contracted under Tracor Jitco, Inc. the prime contractor for the NCI Carcinogenesis Testing Program[5].

The 1,2-dichloroethane (CAS No. 107-06-2; NCI No. C00511) carcinogenesis bioassay was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia. Hazleton was initially under direct contract to the NCI but was later under subcontract to Tracor Jitco, Inc.[6]; under subcontract No. 74-28-106002[7]. The effective date of the contract was not located among the records in the repository; however, the first mouse subchronic study was started on March 29, 1971 and the chronic gavage bioassay for the rats commenced on March 30, 1972[8].

Since this bioassay was performed before FDA proposed Good Laboratory practices (GLP) in the Federal Register (November 19, 1976), there were thus no FDA inspections of the laboratory during this study. Correspondence pertaining to a site visit to Hazleton by

NCI and/or Tracor-Jitco for protocol compliances was not found. However, due to the numerous NCI contracted studies ongoing at Hazleton during this period, this correspondence may be located with another study or the general files.

The NCI Technical Report was published in 1978 (NCI-CG-TR-55). The experimental design was determined by the NCI Project Officers and the principal investigators for the contract who were Dr. M. B. Powers, Dr. R. W. Voelker, Dr. W. A. Olson and Dr. W. M. Weatherholtz.

Histopathologic examinations were performed by Dr. R. H. Habermann and reviewed by Dr. R. W. Voelker at Hazleton. The histopathology findings and reports were reviewed by the Pathology Working Group (PWG)[9] and Tracor Jitco[10]. While the resolution of the lesions on the slides and the narratives were achieved, there was apparently no similar validation procedure performed as to the conduct of the in-life portion of the bioassay to assure all of the tissue lesions were processed and made available for pathological review or to the PWG.

The Chemical Manufacturers Association (CMA) was granted approval to audit the 1,2-dichloroethane carcinogenesis bioassay in-life raw data materials by the National Toxicology Program (NTP)[11].

The CMA audit team visited the NTP Repository on August 13-16, 1984, to perform the audit.

3. SCOPE OF THE AUDIT

The areas reviewed during the August 13-16, 1984, visit to the NTP repository covered the following:

A. 1,2-dichloroethane/Corn Oil Solution Preparation and Analytical Procedures (D. K. Newman)
   - Material accountability, shipment, and purity.
   - Analytical methods.
   - Solution preparation for analyses.
   - Materials review for:
     Six, 90-day subchronic studies.
     Two-year, Chronic bioassay.
   - Stability of 1,2-dichloroethane in corn oil.
   - Protocols, Standard Operating Procedures and amendments to the protocols.
   - Compound Utilization records.

B. Prechronic Studies (Dr. R. E. Jones)
   - Sequence of tests.
   - Dose level selection and gavage procedures.
   - Individual Animal Data Record sheets (IADR).
   - Accidental deaths.
   - Conclusions reported in NCI Technical Report.

C. Compound Administration, Antemortem Observations (Dr. R. E. Jones and D. K. Newman)
   - Animal accountability.
   - Shipping and receiving invoices, orders, and records.
   - Quarantine of animals.
   - Animal identification (coding).
   - Randomization of animals.
   - Cage placement and rotation procedures.
   - Clinical observations.
   - Body weights.
   - Dosing procedures.
   - Protocols, Standard Operating Procedures, and amendments.

D. Environmental Conditions (Dr. R. E. Jones)
   - Room assignment of animals.
   - Ventilation
   - Temperature and humidity records.

E. Postmortem Findings Exclusive of Histopathology (J. C. Johnson)
   - Animal accountability.
   - Animal identification verification.
   - Tissue collection and preservation.
   - Correlation of gross and microscopic findings.
   - Mortality.

F. Animal Identification-Verification (J. C. Johnson)
   - Examination of ear coding in residual wet tissues.
   - Misidentifications and/or unverifiable animals.

G. Gavage Error Verification (Dr. R. E. Jones and D. K. Newman)
   - Prechronic studies.
   - Chronic Bioassay.

H. Slide-Block Match-ups (Dr. R. E. Jones)
   - B6C3F1 mice.
   - Osborne-Mendel.

## 4. AUDIT FINDINGS

### A. 1,2-Dichloroethane/Corn Oil Solution Preparation and Analytical Procedures

#### I. Chemicals & Purity

The NCI Bioassay Report (page 5) on 1,2-dichloroethane states that technical grade chemical was purchased from Dow Chemical. There was no raw data in the form of shipping invoices, receipts or purchase orders that would substantiate this. There was no record of any lot numbers being recorded on this chemical, whether assigned by the Hazleton Laboratory or the manufacturer. Therefore, whether this chemical was shipped in one batch or whether various batches or lots of 1,2-dichloroethane were used is impossible to ascertain. There was no chemical inventory record completed detailing dispensed amounts of 1,2-dichloroethane, shipments received, storage containers, or stored conditions. When there are multiple studies in progress (as was the case herein) this information is vital for the proper determination of sample handling.

The NCI Bioassay report (page 5) indicates that Duke's corn oil was used to formulate the dose solutions. There was no raw data in the form of shipping slips, purchase orders, or invoices that would verify the source of the corn oil, the assignment of lot numbers, or the amounts used during the bioassay.

There was no raw data available at the time of this audit that would verify the three purity analyses of 1,2-dichloroethane stated in the NCI Bioassay Report (page 5). The only purity analysis report found was

conducted by Midwest Research Institute (MRI) for Hazleton June 8, 1978[12]. This analysis, presumably of the same bioassay material (lot number unknown), showed the 1,2 dichloroethane to be 99.9% pure. The technical report only states that the test material used was greater than 90%. There was no record of the corn oil being analyzed for peroxides in order to determine rancidity levels.

II. Dosage Preparation - Administration

The Daily Mixing Log (dose solution preparation) was completed regularly by Hazleton. No analytical data existed in the repository that would verify the concentrations of any of the dose solutions administered during the bioassay. No record of any kind was found that would document whether or not any dose solution analyses were even performed. The Daily Mixing log did contain mixing periods that had entries covered with opaque fluid, (5/31/73, 8/9/73). Both of these dates should not have been mixed according to the 1 week non-treatment:4 weeks treated cyclical procedure being followed at that time in the rat bioassay (page 12 NCI report). An oral intubation record of the dose volume administered to each group during the chronic bioassay was completed by Hazleton. A spot check of dose volumes administered with the solution concentrations prepared in the Daily Mixing Log indicated no calculation errors or instances of improper dosing.

The NCI Bioassay Report states that the dose solutions were prepared weekly and stored at 1°C. These solutions were considered stable for 10 days under these storage conditions (page 5). There is no record of any stability test being carried out on dose solution stored at 1°C. The only information on dose solution analysis was a memo comparing recovery of 1,2-dichloroethane in corn oil and a steriod suspension vehicle to determine the best vehicle[13]. The recovery of 1,2-dichloroethane from the corn oil solution decreased from 84% to 33% in the period of three hours. Although not specified, the assumption was made that this test was conducted at room temperature.

B. Prechronic Studies Review

The eight-week prechronic studies performed by Hazleton in connection with 1,2-dichloroethane appear in Table 1. The first three mice studies were terminated early; the first two studies (17a and 17b) employed a steroid suspending vehicle which was noted during the second study to be inadequate[14]. This steroid vehicle was also used in the first rat study 17a. Thus, because of the steroid vehicle and the fact that in the first mouse study (17a) no noticable body weight effects nor death were observed, these studies were repeated. Because of the lack of effects in the first mouse study, the doses were increased for the second study (see Table 2). With the change from the steroid vehicle to corn oil vehicle, the third study was performed at the same dose levels as the first study. However, because of numerous deaths in all but one group during week 2 presumably not related to 1,2-dichloroethane and no other effects noted, the study was terminated and repeated (17d) at the same doses as employed in 17b.

The first rat study (17a) was repeated due to the steriod vehicle which was employed. Of all the studies, only the last mouse (17d) and last rat (17b) studies were reported by Hazleton and included in the NCI Technical report. The results for the unreported studies are presented in Table 3. The mice from the second study with steroid vehicle (17b) which received the same doses as the mice in the fourth study (17d) were not as severely effected, this may be due to the vehicle which was used. The mice in the 17b study showed effects only at 631 and 1000 mg/kg/day, whereas the mice from 17d showed effects at 398 mg/kg/day and greater. One mouse (03268034f) in the 17d study during week 4 was coded 62 10 11 71 which means that the animal died (62) and was also normal (11) with

labored breathing (10) and ataxia (71)[15]. The rats in the first study did receive the steriod vehicle and in addition one animal in the high dose group died twice, during weeks six and eight[16].

Concerning possible gavage errors for the subchronic study, there is no code listed on the observation code - Intec System for gavage error death[17]. Thus, no conclusion as to deaths due to gavage errors can be made. However, in numerous other gavage studies deaths via gavage error are not uncommon.

The daily mixing record sheets for the subchronic studies appear to be calculations to be followed rather than the actual quantities mixed for the various dose levels[18], therefore, the exact concentration of 1,2-dichloroethane administered to the animals is not confirmed by the records. The data do support the recognition of the procedure for mixing but whether this was accomplished remained unverifiable.

In summary, the prechronic studies performed on 1,2-dichloroethane were inconsistently performed (changing vehicles and sporatic mortality in all groups) and produced confounding results. The Technical Report only refers to one mouse and one rat study when six studies were performed to establish the maximum tolerated dose (MTD) for the chronic bioassay. These studies reflect the confounding factors and uncertainties encountered in the process to establish an appropriate MTD.

TABLE 1

1,2-DICHLOROETHANE 8-WEEK DURATION
PRECHRONIC STUDIES PERFORMED AT HAZLETON

| Species | Test No. | Dates | | |
|---|---|---|---|---|
| | | Start | End | Scheduled Termination |
| Mice | 17a | 3/29/71 | 5/5/71* | 5/24/71 |
| Mice | 17b | 5/10/71 | 6/23/71* | 7/5/71 |
| Mice | 17c | 8/2/71 | 8/31/71* | 9/27/71 |
| Mice | 17d | 9/20/71 | 11/15/71 | 11/15/71 |
| Rats | 17a | 4/5/71 | 5/31/71 | 5/31/71 |
| Rats | 17b | 7/26/71 | 9/20/71 | 9/20/71 |

* Study terminated early

TABLE 2

1,2-DICHLOROETHANE 8-WEEK DURATION
PRECHRONIC STUDIES PERFORMED AT HAZLETON

Dose Levels Employed (mg/kg/day)

| Species | Test Number | | | |
|---|---|---|---|---|
| | 17a | 17b | 17c | 17d |
| Mice | 0 | 0 | 0 | 0 |
| | 40 | 159 | 40 | 159 |
| | 63 | 251 | 63 | 251 |
| | 100 | 398 | 100 | 398 |
| | 159 | 631 | 159 | 631 |
| | 251 | 1000 | 251 | 1000 |
| Rats | 0 | 0 | | |
| | 40 | 40 | | |
| | 63 | 63 | | |
| | 100 | 100 | | |
| | 159 | 159 | | |
| | 251 | 251 | | |

TABLE 3

1,2-DICHLOROETHANE 8 WEEK DURATION
PRECHRONIC STUDIES PERFORMED AT
HAZLETON RESULTS OF EARLY TERMINATED STUDIES

Study 17a mice - sterile steriod suspending vehicle used

| Group | Dose Level mg/kg/day | Mortality Week 0 | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|---|---|
| 1* | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| 2* | 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3* | 63 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4* | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5* | 159 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6* | 251 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

*No significant body weight effects

TABLE 3 (Continued)

Study 17b mice - sterile steriod suspending vehicle used weeks 3, 4 and 5; corn oil used all other weeks.

| Group | Dose Level mg/kg/day | Mortality Week 0 | 1 | 2 | 3 | 4 | 5 | 6 | Total |
|---|---|---|---|---|---|---|---|---|---|
| 1* | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2* | 159 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3* | 251 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| 4* | 398 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5[a] | 631 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| 6[b] | 1000 | 0 | 6 | 0 | 1 | 1 | 1 | 1 | 10 |

*No significant body weight effects.

[a]Body weights were slightly depressed for weeks 5 and 6.

[b]Body weights were depressed for weeks 1, 2, 3, 4, 5, and 6.

TABLE 3 (Continued)

Study 17c mice - corn oil used

| Group | Dose Level mg/kg/day | Mortality Week 0 | 1 | 2 | 3 | 4 | Total |
|---|---|---|---|---|---|---|---|
| 1* | 0 | 0 | 0 | 2 | 0 | 0 | 2 |
| 2* | 40 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3* | 63 | 0 | 0 | 2 | 0 | 0 | 2 |
| 4* | 100 | 0 | 0 | 2 | 1 | 0 | 3 |
| 5* | 159 | 0 | 0 | 1 | 0 | 0 | 1 |
| 6* | 251 | 0 | 0 | 2 | 0 | 0 | 2 |

*No significant body weight effects

TABLE 3 (Continued)

Study 17a rats - corn oil used

| Group | Dose Level mg/kg/day | Mortality Week 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| 1* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2* | 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3* | 63 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4* | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5* | 159 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| 6* | 251 | 4 | 1 | 2 | 0 | 0 | 1[a] | 0 | 0[a] | 8 |

*No significant body weight effects

[a]Animal 92221 which died week 6 was listed as dying again during Week 8.

C. Compound Administration and Antemortem Observations

Animals

There were no shipping invoices for either the rats or mice located among the raw data files in the repository. Secondary information was found to indicate that the animals were received from Charles River Breeding Laboratories, Inc., of Wilmington, Massachusetts[19]. However, the untreated control rats were apparently from Battelle Memorial Institute[20]. Thus, a complicating factor was introduced into the rat bioassay if they were to be compared to the treated rats[21]. In addition, the untreated animals were apparently shared with other studies[22]. The exact numbers of rats and mice received could not be validated and the source, treatment, or identification of known substitutions into the study are factors that need clarification and impact significantly upon a correct interpretation of the bioassay.

The NCI report notes (page 6) that the animals were quarantined for at least 10 days; this is consistent with the information relating to rats, however, the mice may have been quarantined for only 5 days[23]. The NCI report indicates (page 6) that the animals were observed for visible signs of disease or parasites, however, no records could be found to indicate how or whether these observations were performed. These statements were more reflective of what was suppose to be done rather than what was actually accomplished and can be validated.

The NCI report (Table 1 page 10) lists four treatment groups of rats of 50 animals per sex and a vehicle and untreated control group of only 20 rats/sex/group. The treated and vehicle control rats were listed as being approximately 9 weeks old at initiation which is consistent with the records.

The untreated rats were not housed in the same room with the vehicle and treated rats[24]. The untreated rats were listed in the NCI report as being of a different age and were on test for different periods which also is consistent with the records. Thus, there were no appropriate untreated control animals to compare with the treated animals.

The NCI report (Table 2 page 11) lists four treatment groups of mice of 50 animals per sex and a vehicle and untreated control group of only 20 mice/sex/group. The treated and vehicle control mice were listed as being approximately 5 weeks old at initiation which is consistant with the records. The untreated mice were noted in the NCI report to be of a different age and were on test for different periods which also is consistant with the records. Exact room assignment(s) for the mice could not be determined from the available records and notes suggesting room changes during the study progress need clarification.

The vehicle control and treated animals for both rats and mice were apparently randomized into their respective groups[25,26], however, the NCI report does not mention this. How the untreated animals (rats and mice) were selected or distributed is unknown.

The animals were individually housed but the method of identification is unknown. A memo from Tracor Jitco[27] states that the animals should be identified by ear clips. However, the NCI report does not mention the method of identification and the general protocols from Hazleton do not specify what method is to be employed (General Protocols: Project No. 976-500, 976-400, 976-205 or Hazleton's Animal Care Procedures for Bioassay Program[28]). The identification via ear clips was not

accomplished, as will be discussed later in this audit report, as the ears were generally not found in the residual wet tissues (nor were the feet present to examine for toe clip; another acceptable method of identification) and those that were found bore no identification.

Compound Administration

There were records of the volumes of 1,2-dichloroethane/corn oil administered to each group but not for each test animal. The Tracor Jitco "Data and Information Needed" notes that the amount of test material/vehicle prepared at each mixing is required[29], whereas the Hazleton protocol is vague on this point[28]. Moreover, the general Hazleton protocol was not always followed as noted on the first page of the general protocol[28].

D. Environmental Conditions

The data in the repository were reviewed to ascertain whether the temperatures (20° to 24°C) and relative humidities (45 to 55 percent) experienced by the test animals were as specified in the NCI report (page 6). The only records available were from a general description from Hazleton[30] which was apparently used also for other studies. No daily or individual room records of any kind were available to ascertain the exact temperature and humidity of the room. Therefore, no documentation was available to validate the NCI report.

The animal rooms were noted in the NCI technical report to have been ventilated at 12 to 15 air changes per hour (page 6) and in the Hazleton Environmental Data Records[30]. However, there was no raw data in the repository to verify that these levels of ventilation were achieved or maintained over the bioassay period (no ventilation surveys).

In addition to the temperature, humidity and air changes, there are other non-verifiable aspects of the 1,2-dichloroethane bioassay such as, animal cage assignments and performance of cage rotations as specified, or the positioning of cages in racks as specified[30].

The exact room assignment for the rats could not be verified. The rats were assigned to room number 350, however, they were assigned room number 374 previous to that[31]. The date of this room change as noted on the room assignment sheet was 11-19-75[31] over one year after the study ended. The negative control rats (untreated) were in room number 576 and again the room assignment sheet dated November 11, 1975 states that the vehicle and treated rats were in room number 374[32]. No room assignments for the mice were found in the data at the repository.

As noted in the NCI technical report (page 7) the rats treated with 1,2-dichloroethane were housed with rats being treated with four other compounds. The lack of identification of animals as to their treatment group and individual number and the voids in knowledge as to how the animals were treated and where needs to be addressed in light of the fact that the mice treated with 1,2-dichloroethane were housed with mice being treated with 17 other compounds.

In summary, the environmental conditions of the animal rooms cannot be verified as specified in the Hazleton Environmental Data Record, or the NCI Technical Report. The statements pertaining to cage rotation, ventilation rates, room assignments, among others cannot be verified based upon the raw data reviewed at the NTP repository.

E. Postmortem Findings Exclusive of Histopathology

Procedure

Animal numbers were selected at random from IAPT's using the following criteria:

1) age at death was 65 weeks or greater
2) no tumors present in target organs
3) no malignant lymphoma present
4) no advanced autolysis on Table II

Tissue bags were removed from the storage box and the label information was checked for accuracy. Tissues were removed from the bag. A check was made for ears and comments recorded if they were found.

All remaining sections of liver, lung, and uterus (females) were located in the mice wet tissue and examined carefully for any notable lesions. Liver and stomach were examined in the rat wet tissues. Gross observations were recorded if present, otherwise NOL (no observable lesion) was recorded. All tissues were placed back in bags provided and sealed. Recording of observations and comments and the sealing of bags was performed by a member of the repository staff.

Animal Accountability

According to Project Sheet 976-400[33] (applicable to all chronic carcinogenic Bioassay studies in mice) - "Although the animals will be weighed separately, they will not receive individual identity until such time that they are individually housed (see below)." The protocol continues "Any animal that

develops a palpable tissue mass or appears moribund will be identified, individually housed and subject to necropsy should the condition of the animal not improve."

According to Project Sheet 976-500[28] (applicable to all chronic carcinogenic Bioassay studies in rats) - "Animals will be individually housed in hanging wire cages." No mention is made of an animal identification system.

A "Single Animal Autopsy Sheet" (SAAS) (Hazleton Lab Form #382) was apparently completed at necropsy with information recorded as to what tissues were taken, gross lesions present, and other comments. The Individual Animal Data Records (IADR's) (NIH-1624-8) were completed at a later time from information obtained from the SAAS. In some cases a photocopy of the gross comment area of the SAAS has been cut up and pasted onto the IADR for that animal. In addition, the IADRs were not signed by the prosector.

Tissue Collection and Preservation

Tissues which were collected are listed in the general project sheets but no specific tissues were called for in the Tracor Jitco information needed[34]. The only tissues checked during the audit were: for mice - lung (there were no lung remains found in any bag), liver, and uterus (females); for rats - liver and stomach.

The carcasses were present for some but not all animals. A project sheet[35] noted that the laboratory was no longer to keep carcasses, thus after February 28, 1974 no carcasses were preserved. In addition, skin was severed at the neck so no ears were found attached to the carcasses.

The untreated control wet tissue could not be located by members of the repository staff during this audit, thus the animals selected for review could not be examined.

Raw Data Observations

1) There was no documentation found of when and by whom histology procedures were performed. There is no record of number of blocks or number of slides produced.

2) Red ink was used on bag labels and in many cases the writing is illegible. These labels may cause confusion in the proper identification of the animals, especially since the animals are not individually identified.

3) There are many write overs and changes on the IADR's, SAAS's, and bag labels. These facts also may contribute to misidentification of animals.

Correlation of Audit Gross Findings to Findings Listed on IADR's

After comparing the gross comments from the audit to the comments on the SAAS and the IADR, the following animals gross lesions were missed at necropsy based upon the random sampling, and therefore, these were not histologically examined. Those lesions include the following:

MICE

Vehicle Control Male

#19: Liver - .5 cm dia. raised area on the surface of an unknown lobe

High Dose Male

#1: Liver - .7 cm dia. raised area on the edge of what appears to be the left lateral lobe.

High Dose Females

#26: Liver - 4 mm x 3 mm nodule near margin of an unknown lobe

RATS

Vehicle Control Male

#13: Stomach - 4 mm x 2.5 mm raised area at junction of the fundic and cardiac regions

Low Dose Male

#18: Stomach - Cardiac region contains pinpoint to 4 mm raised areas on mucosal surface

High Dose Male

#6: Stomach - 2 mm dia. raised area on serosal surface of the cardiac region

#20: Liver - 3.5 mm dia. raised nodule near the margin of the papillary process

Stomach - 4 mm x 2.5 firm ulcer - like area in the cardiac region

#45: Stomach - 5 mm dia. polyp - like nodular lesion on the serosal surface of the cardiac stomach

Vehicle Control Female

#4: Liver - several 2 cm dia. slightly raised circular areas on unknown lobes

#10: Liver - multiple 2 mm dia. slightly raised circular areas on unknown lobes

#16: Liver - 1.5 x 2 mm dia. dark nodule on surface of unknown lobe

High Dose Female

#21: Stomach - 7 mm x 5 mm mass on serosal surface of the cardiac region

TABLE 4

NUMBERS OF MISSED LESIONS IN MICE AND RATS FROM THE NCI BIOASSAY ON 1,2-DICHLOROETHANE

| Animal | Group | Sex | Number of animals[1] with missed lesions: Liver | (%) | Stomach | (%) |
|---|---|---|---|---|---|---|
| Mice | Vehicle | M | 1/8 | 12.5 | - | |
| | | F | 0/8 | 0 | - | |
| | Low | M | 0/8 | 0 | - | |
| | | F | 0/8 | 0 | - | |
| | High | M | 1/8 | 12.5 | - | |
| | | F | 1/8 | 12.5 | - | |
| Rat | Vehicle | M | 0/8 | 0 | 1/8 | 12.5 |
| | | F | 3/8 | 37.5 | 0/8 | 0 |
| | Low | M | 0/8 | 0 | 1/8 | 12.5 |
| | | F | 0/8 | 0 | 0/8 | 0 |
| | High | M | 1/8 | 12.5 | 3/8 | 37.5 |
| | | F | 0/8 | 0 | 1/8 | 12.5 |

[1]Number of animals with missed lesions/number of randomly selected animals.

F. Animal Identification Verification

At the time the wet tissue was examined, an attempt was made to verify the identification of each animal by examining the ears (see Section E).

No protocol or evidence was found in any of the data examined as to what method of animal identification was employed.

The "Data and Information Needed for Each Test Chemical for Technical Report[27]" issued Traco-Jitco, Section C -- Animals and Environment, #6 Method of Identification, specifies that an animal numbering scheme such as ear clips will be used. The raw data and residual wet tissues confirms that the animals themselves were not individually coded by either ear clips (notches), ear tags, or toe clip. Upon examination of the wet tissues, no ears, feet, or tags could be found to verify the animal's correct identification. Where some few ears or feet were present to be examined, there were no markings (clips, notches) on these animals. For example, only one ear was present among the residual wet tissues for high dose female mouse number 15. To be properly identified, both ears would have to be coded and although one ear was missing, the remaining ear required a code of 10 or 5 which was not evident upon examination. Both ears were present for vehicle control female rat number 12 but neither were coded by punch or notch. Vehicle control male rat number 6 also had both ears present but without a code in either of the ears. It is understood the laboratory may have used cage cards to identify animals in the study. Such systems only identify where the particular animal belongs and not what animal number it really is. The multiple grouping of test animals and the different number of studies in progress in the same room required some more positive method of animal identifications rather than cage codes. Further, no cage codes could be found among the records in the repository.

The only identifications found for animals were on the wet tissue bags which were apparently generated at necropsy based upon the cage cards. There were wet tissue bags opened which contained tags with the histology number for that animal. Why such tags were present is unknown.

The audit team attempted an alternate evaluation to validate the proper animal identification in the absence of the ears, feet, tags, etc. A spot check for the consistent input of data on the Individual Animal Data Records (IADR's) and the weights recorded on the wet tissue bag were performed. There were the following discrepancies noted which raises doubt as to the animal's proper identification. Vehicle control male mouse number 16 had a wet tissue bag label "date of death" as 11/28/73, whereas the IADR shows the "date of death" as 11/8/73. While this may be a transposed error, this does not adequately explain the wet tissue bag weight for that mouse as 35.5 grams and the IADR shows it as 25 grams.

Male mouse number 17 wet tissue bag label lists the "date of death" as 11/21/73 while the IADR shows 11/27/73. The wet tissue bag recorded weight is inconsistent with the weights shown on the IADR (23.8 grams versus 35 grams for the wet tissue bag and IADR, respectively).

More disconcerting is the apparent failure to harvest ears and feet to validate any animal codes. When the brain is to be removed, the ears are often cut off, however, this does not adequately explain why ears were removed <u>even</u> when the entire carcass was preserved and the brains were not removed from the skull.

There is evidence that some rats were replaced; either at the time of death of the "original" or before the study started. These replacements are noted in the observation records and coded 05 (replacement)[38]. However, the observation code system notes that a death code is not used if the animal is replaced[39], yet this was done[38] (code 62).

C. Gavage Accidents (Errors) Review

There were no significant numbers of accidential deaths via gavage among rats or mice in both the reported prechronic studies and the chronic bioassays.

The rats in the chronic bioassay which died early were all noted to be autolyzed as noted on the animal data sheets for the low dose[36] and high dose[37] groups. The NCI report (pages A-3, B-3, C-3, and D-3) states that partially autolyzed animals were excluded from histopathological examination; however, all the animals were examined. The NCI report does not list these rats as being in various stages of autolysis, from slight to very advanced. The NCI Technical Report is therefore inconsistent and inaccurate with reference to excluding autolyzed animals from histopathological examination and statistical calculations.

The fact that all of these early deaths were in some state of autolysis is suggestive of inattention on the part of the animal caretakers and therefore suggestive of a lack of physical observations. In addition, this inattentiveness may be reflective in the area of necropsy and thus have impacted upon the identification (or lack thereof) of small tumors and other lesions.

H. Slide-Block Comparison

Mice

Numerous blocks were missing in the animals which were checked. Of 22 low and high dosed mice, 17 animals had 1 block missing. Most (19 of 22) of the slides and blocks only contained the histology number, there was no animal number nor individual slide or block numbers. In one case, there was one block with no slide and one questionable match.

Rats

Of the 3 boxes of blocks that were supposed to be in the repository, only 2 were present - box 1 of 3 and box 3 of 3 - box 2 was missing which contained histology numbers 89-440 through 89-509. In addition, in box 3 the blocks for the last 2 animals 89-599 and 89-600 were missing.

There were 2 blocks found which were apparently from another study - histology numbers did not match any from this study. In some cases the tissues included target organs and tissue masses. The labeling of the blocks and slides was similar to the mice in that most of the slides and blocks were not labeled properly. Many of the blocks for the rat tissue were not sealed properly and the tissues have dried out; thus, recuts are impossible.

The other concern was that there were numerous slides missing (blocks were present) for animals where diagnoses had been previously made. Therefore, the pathology reported for these animals would be harder to validate in that the blocks would have to be recut (new slides made); however, there are animals where both the slide and corresponding block are missing.

## 5. LIST OF DISCREPANCIES AND DEFICIENCIES

The audit findings are listed in order of their likely impact upon the scientific interpretation of the 1,2-dichloroethane carcinogenesis bioassay and the NCI Technical Report. Some of the deficiencies and inadequacies are recognized to be retrospectively correctable, however, a large number are deemed uncorrectable. The purpose of this audit was to assess the conduct of the study and not necessarily to resolve the discrepancies found by the audit.

All of the findings are supported by documentation (or the lack of) and these appear in Volume II.

1. There were omissions and voids in the data base records including numerous slides and tissue blocks which were not present for the rats. These missing records, slides, and blocks make many of the deficiencies of this study uncorrectable until they are located. Some of the records for this study were "placed" in a seperate file from the files for this bioassay before this audit was performed. These records may contain information that would explain some items noted in this report.

2. There were 18 mice bioassays and 5 rat bioassays in progress at one time. The fact that the animals were not coded and that the results reported in this bioassay were similar to results reported in the corresponding bioassays run in the same room must be considered with the total audit findings.

3. Of the randomly selected male and female mice 8.3% and 4.1%, respectively, had unprocessed liver lesions among the residual wet tissue.

4. Of the randomly selected male and female rats 4.1% and 12.5%, respectively, had unprocessed liver lesions. In addition, 20.8% and 4.1% of the male and female rats, respectively, had unprocessed stomach lesions. With the knowledge that many of the blocks from the vehicle and treated rats are missing, this deficiency is not correctable until these blocks are located.

5. There is evidence that animals were used as "replacements" in the study for some early deaths. The source, assignments, treatment scheme, disposition or numbers of these animals could not be validated.

6. The reported few misintubations and accidential deaths may be inaccurate in light of the "replacement" animals and the apparent lack of frequent physical observations and numerous autolyzed animals.

7. There were no tissue blocks, slides, or wet tissue bags located for the untreated control rats and mice. The data from these animals is questionable until these items are located. In addition, the untreated controls were of a different age, from a different source, and were on study at a different time period than the vehicle and treated animals.

8. The technical report contains statements concerning environmental conditions, animal and cage handling, and room assignments which cannot be validated by the raw data.

9. The rats were housed with rats being treated with 4 other compounds while the mice were housed with mice being treated with 17 other compounds. Some of these compounds are similar to 1,2-dichloroethane.

## 6. DISCUSSION

The audit findings presented in Section 4 of this audit report have highlighted the uncertainties in the study conduct and the inadequate attention devoted to accurately reporting of tissue lesions by the contract laboratory and the incorporation of these into the NCI Technical Report.

The level of scientific confidence placed upon the conclusions reached in a chronic bioassay depends to a large degree upon knowledge of the conduct of the research performed, the uncertainties in the raw data base, and the accurate inclusion of these in the NCI Technical Report.

The omissions and voids of data, the lack of any identification of any animal and inability to verify group assignments, the unprocessed gross liver lesions, the vagueness of daily gavage records, animal accountability unknowns, the conduct and interpretations of the prechronic studies, unverified environmental conditions, among other factors, placed a significant burden upon those scientists who are to determine whether the facts concerning the study conduct reasonably support the conclusions that appear in the NCI Technical Report.

There can be no doubt that the NCI Technical Report did not include information and data that could influence the interpretation of the bioassay.

After careful examination and in-depth review of the raw data, there can be no assurance that the conclusions presented are accurate or represent the carcinogenic potential of 1,2-dichloroethane in the bioassay conducted by Hazleton Laboratories. Any interpretation of this bioassay has been confounded by its poor conduct, omissions, and uncertainties as revealed and documented by this audit report.

## 7. CONCLUSIONS

The conduct of the 1,2-dichloroethane carcinogenesis bioassay was evaluated based upon the data available in the NTP repository to determine if the study findings reasonably support the conclusions presented in the NCI Technical Report. When all of the discrepancies and deficiencies presented herein are thoroughly considered, any conclusions as to the outcome of the study, must await the resolution of these audit findings. The conclusion is reached that the studies were inadequately administered by the primary contractor, poorly executed by the contract laboratory, inaccurately presented in the Technical Report and are incomplete. The improper execution of the study as demonstrated by the presence of unprocessed gross lesions, significant omissions and voids in the data base, substitution of animals, the numerous autolyzed animals, absence of daily dosing records, retrospective changes in the data base, animals not identified and thus a lack of group verification, and other inconsistencies prohibit any reasonable or scientific interpretation of the 1,2-dichloroethane carcinogenesis bioassay performed by Hazleton Laboratories. The study conduct is deemed seriously flawed and the conclusions presented in the NCI Technical Report could be misleading and inaccurate.

## 8. SUPPORTING LIST OF REFERENCES


1. Guidelines for Carcinogen Bioassay in Small Rodents. National Cancer Institute, Tech. Report Series No. 1. NCI-CG-TR-1, February, 1976. (Preface)

2. Carcinogenesis Bioassay of Trichloroethylene. National Cancer Institute, Tech. Report Series No. 2. NCI-CG-TR-2, February, 1976.

3. Ref 1, Page 1 Introduction.

4. Ref 2, Page i Foreword.

5. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. National Cancer Institute, Tech. Report Series No. 55, NCI-CG-TR-55, 1978 p. iii.

6. Ibid p. iii

7. Letter to Tracor Jitco, Inc. from M. B. Powers dated January 18, 1977.

8. Memo to Dr. C. Wessel from Dr. J. F. Roben dated November 11, 1975.

9. Letter to Dr. W. McDonald (Tracor Jitco, Inc.) from DHEW dated February 15, 1977.

10. Letter to Dr. R. Voelker (Hazleton) from Tracor Jitco, Inc. dated January 21, 1976.

11. Telephone conversations of Dr. H. Shah (CMA) with Dr. E. McConnell (NTP) and Dr. Hildabrant (Repository).

12. MRI - Analysis of Ethylene Dichloride

13. Memo to Minner from Quality Control - NCI program, dated June 23, 1971.

14. Memo to Minner from Fink, dated June 23, 1971.

15. Data sheet for subchronic mouse study 17d, week 4.

16. Data sheets for subchronic rat study 17a, weeks 6 and 8.

17. Observation code-Intec System.

18. Daily Mixing Record (Project 976-206).

19. Memorandum to Dr. J. F. Robens from W. D. Reichardt, dated November 10, 1976.

20. Page of handwritten notes, dated 10/28.

21. Memorandum to Dr. C. Wessel from Dr. M. Davis, dated November 14, 1975.

22. Data sheet for rats and mice.

23. Data sheet for mice - randomization sheet.

24. Room assignments for rats, dated November 11, 1975.

25. Randomization sheet, rats.

26. Randomization sheet, mice.

27. Tracor Jitco - Data and Information Needed, Section C.

28. Hazleton Protocol - Project No. 976-500

29. Tracor Jitco - Data and Information Needed, Section B.

30. Environmental Data Record for contracts 702209, 723278 (noted dated).

31. Room assignments, Hazleton, dated 10/22/75.

32. Tracor Jitco, room assignments, dated 11/11/75.

33. Hazleton Project Sheet No. 976-400.

34. Data and Information Needed for Each Test Chemical for Technical Report - Tracor Jitco, Section E.

35. Project Sheet No. 7 - Hazleton, dated February 28, 1974.

36. Animal data sheets, rats Group 4.

37. Ibid, Group 3.

38. Group observation record, date 60773, interval 62 colony 1, Group 3.

39. Observation code - Intec System - last line.

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Vincent

TATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
102 Q STREET
.O. BOX 2815
ACRAMENTO, CA 95812

April 8, 1985

Geraldine V. Cox, Ph.D.
Vice President
Chemical Manufacturers' Association
2501 M Street, N.W.
Washington, D.C. 20037

Dear Dr. Cox:

Subject: Your Comments on Ethylene Dichloride

Thank you for your comments on Part A of Report on Ethylene Dichloride to the Scientific Review Panel. The Department of Health Services will prepare responses to your comments on Part B. Those responses and this letter will appear in Part C of the revised report, which CMA will receive as it is sent to the Scientific Review Panel.

Our responses to your comments on part A follow:

Comment on EDC as a precursor to methyl chloroform.

We have removed methyl chloroform as a reaction product of EDC.

Comment on the minor emissions from pesticides (p. 2)

The emissions of 2.7 tons of EDC per year were included for completeness of the inventory without a contention that they are significant in themselves. However, the Department of Food and Agriculture (DFA) has informed us that their figure of 2.7 tons is wrong; the correct weight is 65 tons for 1983. We are investigating the issue of EDC's future use as a grain fumigant with DFA.

Comment on the signficance of possible emissions from sewage treatment plants (p. 2)

We discuss sewage treatment plants as potential sources of EDC for the sake of completeness because some readers may know that very large EDC emissions have been attributed to plants outside California. As we state in the report, there is no way to reliably estimate EDC emissions from sewage plants in this state; however, emissions are probably much smaller than those from sewage

plants elsewhere. We do not intend to imply that sewage treatment plants emit considerable EDC in California. We will investigate this issue further in the risk management phase if EDC is identified as a toxic air contaminant.

Comment on the signficance of emissions from landfills (p. 2)

You are correct that the known rate of use of EDC in California today would not likely lead to high emission rates from landfills. However, there is no question that large quantities of EDC were placed in landfills in the past and that high concentrations of EDC, as tabulated in the report, were recorded near landfills in 1980 and 1982. Such wastes may still be significant emission sources. Note that we have carefully qualified our estimate of 100 tons per year in the South Coast Air Basin as uncertain and possibly out-of-date and that we do not include it in the total inventory for the basin. Again, we plan to investigate this issue further in the risk management phase.

Comment on projecting EDC emissions due to solvent use (p. 3)

The base year for the projection is 1980. The amount of EDC used as a solvent in that year was taken from reference 5 (not 6 as indicated in Table I-1). In Figure I-1, the projected growth rate of EDC use, when normalized by the 1980 amount, is that for the total output of solvents by SIC category 2800, Chemicals and Allied Products. The future growth rate of the total output of solvents was extrapolated from historical growth. We would appreciate receiving any projections you have for EDC use in California.

Comment on EDC's persistence in the atmopshere (p. 3)

With a half-life of 42 days in the atmosphere, EDC from any source in an air basin is very likely to be distributed widely over the basin before its mass is appreciably attenuated. This is our meaning of "persistent."

Comments on the statistics derived from ambient monitoring (pp. 3,4)

Thirteen percent of all samples collected in 1983 were quantifiable according to the Haagen-Smit Laboratory's criterion of producing a detector signal at least ten times the detector's "noise." Additional samples produced detected-but-not-reported signals between three and ten times the noise. The Lab's policy is to not report the concentrations or even the number of such results. However, there is no doubt from the results that EDC is often detectable in the atmosphere.

You are quite correct that the assignment of one-half the reporting limit to samples analyzed below that limit (our standard practice) yields an unreliable mean in the case of EDC. That is why we note on page III-1 that the mean of 68 ppt carries an uncertainty of $\pm$50 ppt. This is equivalent to stating that EDC is present at a year-round average concentration greater than zero but probably less than 100 ppt.

Applying the maximum likelihood risk estimate of 53 deaths per million per ppb to the lower end of the confidence interval, 18 ppt, rather than to the mean of 68 ppt, yields a lifetime risk of one excess cancer per million people. Applying the upper limit of risk, 88 excess cancers per million per ppb to 68 ppt yields six excess cancers per million people. The Air Resources Board must consider this range of risk in any risk management action it takes.

Comment on the need to monitor for EDC

The expanded air monitoring network monitors the ambient concentrations of 19 substances that have been or may be proposed as toxic air contaminants. Because EDC is measured with the same GC detector as several other compounds, compiling data on it entails very little added cost.

EDC is not unmeasurable as you contend. Rather, the analytical technique used to generate the data reported in Part A is insufficiently sensitive to meet the Haagen-Smit Lab's reporting criteria on most samples. Greater sensitivity could be achieved if better knowledge of EDC concentrations becomes necessary in the future.

Please contact me at (916) 322-6023, if you have any questions regarding our responses.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: P. Venturini
R. Neutra, DHS

April 8, 1985

Edward J. Faeder, PhD
Manager of Environmental Operations
Southern California Edison Co.
P.O. Box 800
Rosemead, CA 91770

Dear Dr. Faeder:

Subject: Your Comments on Ethylene Dichloride

Your letter of March 22, 1985, concerning Report on Ethylene Dichloride to the Scientific Review Panel; Part B has been forwarded to the Department of Health Services. They will prepare responses to your comments, which we will include along with your letter in Part C of the revised report. Southern California Edison will receive the revised report when it is submitted to the Scientific Review Panel.

Thank you for your comments.

Sincerely,

Original Signed By

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: P. Venturini, ARB
R. Neutra, DHS

bcc: R. Bode
J. Munson

R. Vincent:sonja

Vincent

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

April 8, 1985

Mr. Bryant C. Fischback
Manager, Environemtnal Services
Dow Chemical USA
P. O. Box 1398
Pittsburg, CA 94565

Dear Mr. Fischback:

Subject: Your March 25, 1985 Letter Regarding Review of Ethylene Dichloride

Thank you for your review of Report on Ethylene Dichloride to the Scientific Review Panel, Parts A and B. Your letter comments on certain errors in Appendix C of Part A, and it incorporates draft comments by the Chemical Manufacturers' Association (CMA) on Parts A and B.

Regarding your comments on Appendix C, we will correct the errors. None of the calculations are affected by the errors, all of which occur in the narrative rather than in the equations.

We have received CMA's final version of the draft comments sent by you. Because the final and draft comments are substantially the same, we have enclosed our responses to CMA regarding Part A.

The Department of Health Services will prepare responses to CMA's comments on Part B. They and your letter will appear in Part C of the revised report, which you will receive as it is sent to the Scientific Review Panel.

Please call me at (916) 322-6023 if you have any questions regarding our responses.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

Attachment

cc: Peter D. Venturini
R. Neutra

## DHS Response to Comments on EDC

Comment: While it is recognized that IARC has designated EDC as an animal carcinogen and as a probable human carcinogen, the NCI gavage bioassay was severely flawed in regard to exceeding the maximum tolerated dose in the rat study. The rat portion of the EDC bioassay was compromised and is unsatisfactory for the evaluation of carcinogenic effect.

As a result of our concern about the conduct of the NCI bioassay, the EDC Panel (of the CMA) conducted an audit of the in-life phase of the bioassay. A copy of this audit is enclosed with these comments. (Commentor - Chemical Manufacturers Association, CMA)

DHS Response: The staff of DHS appreciates the CMA sharing their EDC panel's audit of the NCI bioassay. We would likewise appreciate receiving a copy of their audit of the Maltoni study (since this study was sponsored by CMA). The audit of the Maltoni bioassay could resolve many of the problems that DHS has with the study.

The NCI gavage bioassay of EDC was reviewed and approved by an independent scientific review panel. IARC independently reviewed the data. Following this review, the IARC panel concluded that the gavage assay met scientific criteria and that EDC should be designated as an animal carcinogen. The staff of DHS believe that these unbiased, independent reviews, by the some of the world's most eminent scientists, have sufficently addressed the issue of the adequacy of the NTP study and the high dose rat portion of the study.

The staff of DHS agree that there were significant dosage problems (as specifically stated in the EDC document) with the NCI bioassay (as well as with the Maltoni et al. bioassay). However, we do not

believe that these problems invalidate the NCI rat study. A decreased dosage time, 78 weeks instead of a full lifetime, and early mortality could reduce the observed carcinogenic risk. This early mortality could cause an underestimation of the carcinogenic potential of EDC.

Comment: The Maltoni study contributes significantly toward the understanding of the toxicological effects of EDC. We disagree with the position of the DHS staff that the Maltoni studies are of little consequence. (Commentor - CMA)

DHS Response: The commentors did not make clear how the Maltoni study contributes to the understanding of the toxicological effects of EDC. In contrast to the NCI bioassay, the Maltoni et al. study was published in a nonpeer reviewed format. As pointed out in the response to the previous comment, severe mortality in a bioassay may compromise the study. The Maltoni study also suffered from severe mortality. In this case, because of the lack of a carcinogenic response, the staff of DHS believe that the high mortality rate in the Maltoni bioassay did compromise the study, and that this study is unsatisfactory for evalation of carcinogenic effect (as was demonstrated in the EDC document).

Comment: The DHS staff failed to recognize that in a cancer bioassay, not all dose levels need elicit a carcinogenic response. The two lower dose levels in the Maltoni et al. study could be considered as an attempt to identify an no-observed-effect-level (NOEL). (Commentor - CMA)

DHS Response: Since the authors of the Maltoni study did not provide any rationale for the use of the lower dose levels, the latter may have been intended as the commentor suggests. In commenting on the lower dose levels, the staff of DHS was pointing out that even at the worst case (100% absorption and no metabolic differences between inhalation and gavage), the lower two dose levels could not result

in an observable carcinogenic response based on the potency in the NCI study. Since the dosage was insufficient to induce an observable carcinogenic response, the lack of a response at the lowest two doses is not evidence for a NOEL. Comparison between the NCI and the Maltoni studies reduces to one of a study (NCI) with two dose levels providing a carcinogenic response and a single dose level study (Maltoni et al.), potentially capable of providing a response, with no carcinogenic response.

Comment: DHS stated as fact an assumption ... that the Sprague-Dawley (rat) strain is less sensitive than the Osborne-Mendel strain in responding to carcinogenic agents. The Sprague-Dawley rat was used by Maltoni in his studies of vinyl chloride and a very definite carcinogenic response was observed. (Commentor - CMA)

DHS Response: The Staff of DHS did not state as fact that the Sprague-Dawley strain is less sensitive than the Osborne-Mendel. The staff was stating that relatively small differences in strain sensitivity could account for the negative response in the high dose Maltoni study.

The commentors are correct in noting that the Sprague-Dawley strain provided evidence of vinyl chloride carcinogenicity. Vinyl chloride (VC) is an excellent example, since the carcinogenic potency of VC and EDC are very similiar. In Maltoni's VC studies six exposure levels were used. These ranged from 50 ppm to 10,000 ppm. A carcinogenic response was observed in all but the lowest exposure group (50 ppm).

If Maltoni had used the concentrations employed in the EDC study in his VC bioassay, only one dose level would have resulted in a carcinogenic response. It is not a question of whether this strain can demonstrate a carcinogenic response, but rather the choice of dose levels for EDC and whether the rat strain employed is less sensitive than the Osborne-Mendel stain.

The commentors make a valid point in suggesting a comparison of the vinyl chloride inhalation data. This will be been done in a revision of the EDC document. It is possible to compare the sensitivity of three strains of rats: Sprague-Dawley, Wistar (Maltoni, 1980) and the CD rat (Charles River) (Lee et al., 1978) to vinyl chloride by inhalation. This comparison demonstrated that the TD50 (dose to induce tumors in 50% of the animals) is as follows:

| | |
|---|---|
| CD (Charles River) strain | 56 mg/kg-day |
| Sprague-Dawley strain | 746 mg/kg-day |
| Wistar strain | 111,000 mg/kg-day |

The CD (Charles River) strain of rat has a more than ten-fold greater sensitivity to liver cancer than does the Sprague-Dawley strain. This estimate is not corrected for the fact that the CD strain were only observed for 1 year (concurrent with exposure) and were immediately sacrificed. Whereas the other two stains, also exposed for one year, were observed until death (138 weeks). The assumption that the Sprague-Dawley rats may be two-fold less sensitive than the Osborne-Mendel is highly conservative. The staff of DHS will continue to research the question and any continued assistance from CMA is appreciated.

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Lee, C.C., et al. (1977) Inhalation toxicology of vinyl chloride and vinylidene chloride. Environ. Health Perspect. 21:25.

Maltoni, C. (1980) Carcinogenesis bioassay of vinyl chloride monomer with paricular reference to multiple sites and dosage review. Presented at the conference to re-evaluate toxicity of vinyl chloride, polyvinyl chloride - structural analogues. March 20-21, NIH, Besthesda, Maryland.