

Research and Development



# Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride)

## Review Draft

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Cite or Quote)

## Part 2 of 2

### NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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DISCLAIMER

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## PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. The health assessment document was originally developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of ethylene dichloride as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

The EPA's Office of Health and Environmental Assessment (OHEA) is responsible for the preparation of this health assessment document. The OHEA Environmental Criteria and Assessment Office (ECAO-RTP) had overall responsibility for coordination and direction of the document (Dr. Robert M. Bruce, Project Manager). The chapters addressing physical and chemical properties, sampling and analysis and toxic effects were either rewritten or revised by Syracuse Research Corporation. The pharmacokinetics chapter was written by Dr. I.W.F. Davidson of the Bowman Gray School of Medicine, Wake Forest University. The air quality chapters addressing sources, emissions and ambient concentrations were originally written by Syracuse Research Corporation and revised by Radian Corporation under a contract with the Office of Air Quality Planning and Standards.

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# TABLE OF CONTENTS

|                                                          | <u>Page</u> |
|----------------------------------------------------------|-------------|
| LIST OF TABLES.....                                      | xi          |
| LIST OF FIGURES.....                                     | xvi         |
| 1. SUMMARY AND CONCLUSIONS.....                          | 1-1         |
| 2. INTRODUCTION.....                                     | 2-1         |
| 3. PHYSICAL AND CHEMICAL PROPERTIES.....                 | 3-1         |
| 3.1 NAME.....                                            | 3-1         |
| 3.2 CAS REGISTRY, RTECS, AND STORET NUMBERS.....         | 3-1         |
| 3.3 DESCRIPTION.....                                     | 3-1         |
| 3.4 STRUCTURE.....                                       | 3-1         |
| 3.5 PHYSICAL PROPERTIES OF PURE ETHYLENE DICHLORIDE..... | 3-1         |
| 4. SAMPLING AND ANALYSIS OF ETHYLENE DICHLORIDE.....     | 4-1         |
| 4.1 SAMPLING.....                                        | 4-1         |
| 4.2 ANALYSIS.....                                        | 4-1         |
| 4.2.1 Ethylene Dichloride in Air.....                    | 4-1         |
| 4.2.2 Ethylene Dichloride in Water.....                  | 4-2         |
| 4.2.3 Ethylene Dichloride in Solid Samples.....          | 4-3         |
| 4.2.4 Ethylene Dichloride in Blood.....                  | 4-3         |
| 4.2.5 Ethylene Dichloride in Urine.....                  | 4-3         |
| 4.2.6 Ethylene Dichloride in Tissue.....                 | 4-4         |
| 5. SOURCES IN THE ENVIRONMENT.....                       | 5-1         |
| 5.1 PRODUCTION PROCESSES.....                            | 5-1         |
| 5.2 ETHYLENE DICHLORIDE PRODUCERS.....                   | 5-2         |
| 5.3 ETHYLENE DICHLORIDE PRODUCTION AND TRENDS.....       | 5-2         |
| 5.4 ETHYLENE DICHLORIDE USES.....                        | 5-5         |
| 5.5 SOURCES OF EMISSIONS.....                            | 5-9         |
| 5.5.1 Production and Related Facilities.....             | 5-12        |
| 5.5.2 Dispersive Uses.....                               | 5-13        |
| 5.5.3 Conclusions.....                                   | 5-14        |
| 6. FATE AND TRANSPORT IN THE ENVIRONMENT.....            | 6-1         |
| 6.1 ATMOSPHERE.....                                      | 6-1         |
| 6.2 AQUATIC MEDIA.....                                   | 6-7         |
| 6.3 SOIL.....                                            | 6-8         |
| 6.4 SUMMARY.....                                         | 6-9         |

# TABLE OF CONTENTS (cont.)

|                                                              | <u>Page</u> |
|--------------------------------------------------------------|-------------|
| 7. ENVIRONMENTAL LEVELS AND EXPOSURE.....                    | 7-1         |
| 7.1 ENVIRONMENTAL LEVELS.....                                | 7-1         |
| 7.1.1 Atmospheric Levels.....                                | 7-1         |
| 7.1.2 Ground and Surface Water Levels.....                   | 7-9         |
| 7.1.3 Soil and Sediment Levels.....                          | 7-14        |
| 7.2 ENVIRONMENTAL EXPOSURE.....                              | 7-14        |
| 7.2.1 Exposure from Air.....                                 | 7-18        |
| 7.2.2 Exposure from Water.....                               | 7-20        |
| 7.2.3 Exposure from Food.....                                | 7-20        |
| 7.3 CONCLUSIONS.....                                         | 7-20        |
| 8. ECOLOGICAL EFFECTS.....                                   | 8-1         |
| 9. BIOLOGICAL EFFECTS IN MAN AND EXPERIMENTAL ANIMALS.....   | 9-1         |
| 9.1 PHARMACOKINETICS.....                                    | 9-1         |
| 9.1.1 Absorption and Distribution.....                       | 9-1         |
| 9.1.2 Excretion.....                                         | 9-18        |
| 9.1.3 Metabolism.....                                        | 9-32        |
| 9.1.4 Summary and Conclusions.....                           | 9-55        |
| 9.2 ACUTE, SUBCHRONIC AND CHRONIC TOXICITY.....              | 9-57        |
| 9.2.1 Effects in Humans.....                                 | 9-57        |
| 9.2.2 Effects in Animals.....                                | 9-86        |
| 9.2.3 Summary of Acute, Subchronic and Chronic Toxicity..... | 9-115       |
| 9.3 REPRODUCTIVE AND TERATOGENIC EFFECTS.....                | 9-122       |
| 9.3.1 Summary.....                                           | 9-129       |
| 9.4 MUTAGENICITY.....                                        | 9-131       |
| 9.5 CARCINOGENICITY.....                                     | 9-166       |
| 9.5.1 Animal Studies.....                                    | 9-166       |
| 9.5.2 Epidemiologic Studies.....                             | 9-205       |
| 9.5.3 Quantitative Estimates.....                            | 9-206       |
| 9.5.4 Summary.....                                           | 9-233       |
| 9.5.5 Conclusions.....                                       | 9-234       |
| 10. REFERENCES .....                                         | 10-1        |
| Appendix A                                                   |             |
| Appendix B                                                   |             |
| Appendix C                                                   |             |

# LIST OF TABLES

| <u>Table</u> |                                                                                                                                             | <u>Page</u> |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 5-1          | Major Manufacturers of Ethylene Dichloride.....                                                                                             | 5-3         |
| 5-2          | U.S. Production and Sales of Ethylene Dichloride.....                                                                                       | 5-4         |
| 5-3          | Ethylene Dichloride Uses.....                                                                                                               | 5-6         |
| 5-4          | Consumption of Ethylene Dichloride in 1979 and 1974.....                                                                                    | 5-7         |
| 5-5          | Uses of Ethylene Dichloride for Intermediate Purposes.....                                                                                  | 5-8         |
| 5-6          | Estimated Environmental Releases of Ethylene<br>Dichloride in 1979.....                                                                     | 5-11        |
| 6-1          | Rate Constants for a Few Chlorinated Ethanes at<br>Room Temperature.....                                                                    | 6-3         |
| 7-1          | Ambient Atmospheric Levels of Ethylene Dichloride.....                                                                                      | 7-2         |
| 7-2          | Ambient Concentrations of Ethylene Dichloride in<br>Urban Areas.....                                                                        | 7-8         |
| 7-3          | Reported Occurrence of Ethylene Dichloride in Groundwater<br>System.....                                                                    | 7-15        |
| 7-4          | Reported Occurrence of Ethylene Dichloride in Surface<br>Water Systems.....                                                                 | 7-16        |
| 7-5          | State Data on Ethylene Dichloride in Groundwater.....                                                                                       | 7-17        |
| 7-6          | Estimated Respiratory Intake of Ethylene Dichloride by<br>Adults and Infants.....                                                           | 7-19        |
| 7-7          | Maximum Concentration Level in the Vicinity of Various<br>Emission Sources.....                                                             | 7-21        |
| 7-8          | Total Estimated Population (in Thousands) Exposed to<br>Ethylene Dichloride in Drinking Water at the Indicated<br>Concentration Ranges..... | 7-22        |
| 7-9          | Estimated Drinking Water Intake of Ethylene Dichloride<br>by Adults and Infants.....                                                        | 7-23        |
| 9-1          | Physical Properties of Ethylene Dichloride and<br>Other Chloroethanes.....                                                                  | 9-3         |
| 9-2          | Partition Coefficients for Ethylene Dichloride.....                                                                                         | 9-4         |

LIST OF TABLES (cont.)

| <u>Table</u> |                                                                                                                                                                                                          | <u>Page</u> |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 9-3          | Fate of $^{14}\text{C}$ -EDC in Rats 48 Hours After Oral (150 mg/kg) or Inhalation (150 ppm, 6-hr) Exposure.....                                                                                         | 9-6         |
| 9-4          | Peak Blood and Tissue Levels After Single Oral Dosage of EDC in Male Rats.....                                                                                                                           | 9-8         |
| 9-5          | The Absorption Rate Constants ( $k_a$ ) and Area Under Curve (AUC) for Rats After Single Oral with Doses of EDC in Oil and in Water as Vehicle and After Intravenous Administration.....                 | 9-9         |
| 9-6          | EDC Tissue Levels After 50 ppm Inhalatory Exposure.....                                                                                                                                                  | 9-14        |
| 9-7          | EDC Tissue Levels After 250 ppm Inhalatory Exposure.....                                                                                                                                                 | 9-15        |
| 9-8          | Blood Tissue Levels of EDC in Male Rats 2 Hours After Single Oral Doses in Corn Oil.....                                                                                                                 | 9-17        |
| 9-9          | Percent Distribution of Radioactivity Excreted (48-hr) by Mice Receiving 1,2-Dichloroethane- $^{14}\text{C}$ .....                                                                                       | 9-20        |
| 9-10         | Pharmacokinetic Parameters of EDC Administered as Single Bolus Intravenous Injections in Saline to Sprague-Dawley Male Rats. Parameters Calculated from a 2-Compartment Open Model.....                  | 9-24        |
| 9-11         | Pharmacokinetic Parameters of EDC Administered as Single Oral Doses in Corn Oil and Water to Sprague-Dawley Male Rats. Parameters Calculated from a 2-Compartment Open Model.....                        | 9-26        |
| 9-12         | Pharmacokinetic Parameters of EDC Following Termination of Steady State Inhalation (5-hr Exposure) of 50 and 250 ppm to Male Sprague-Dawley Rats.....                                                    | 9-29        |
| 9-13         | Pharmacokinetic Parameters of EDC Following Termination of Steady State Inhalation Conditions; 6-Hr Exposure, 150 ppm to Male Osborne-Mendel Rats. Parameters Calculated from a 2-Compartment Model..... | 9-30        |
| 9-14         | Identified Metabolites of Ethylene Dichloride and Ethylene Bromide.....                                                                                                                                  | 9-34        |
| 9-15         | Percent Distribution of Radioactivity Excreted (48-hr) as Urinary Metabolites by Mice Receiving 1,2-Dichloroethane- $^{14}\text{C}$ or 2-Chloroacetic Acid- $^{14}\text{C}$ .....                        | 9-37        |

LIST OF TABLES (cont.)

| <u>Table</u> |                                                                                                                                                                                           | <u>Page</u> |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 9-16         | Total Macromolecular Binding and DNA Binding in Selected Tissue of Rats After Exposure to <sup>14</sup> C-EDC by Oral or Inhalation Routes.....                                           | 9-52        |
| 9-17         | Effect of Dietary Disulfiram Upon the <sup>14</sup> C Content of Liver Nuclei Isolated 24 or 48 Hours After Administration of a Single Oral Dose of 15 mg/mg [U- <sup>14</sup> C]EDB..... | 9-54        |
| 9-18         | Effects Associated with Acute Lethal Oral Doses of Ethylene Dichloride in Humans.....                                                                                                     | 9-58        |
| 9-19         | Effects of Acute Oral Ingestion of 1,2-Dichloroethane (Survey Results).....                                                                                                               | 9-65        |
| 9-20         | Effect of Ethylene Dichloride Exposure on Eye Sensitivity to Light.....                                                                                                                   | 9-72        |
| 9-21         | Morbidity and Lost Workdays of Aircraft Industry Gluers Exposed to Ethylene Dichloride.....                                                                                               | 9-78        |
| 9-22         | Concentrations of Ethylene Dichloride in Oil Refinery Mineral Oil Purification Process Air.....                                                                                           | 9-80        |
| 9-23         | Effects Observed in Polish Oil Refinery Workers.....                                                                                                                                      | 9-81        |
| 9-24         | Effects of Acute Exposure to Ethylene Dichloride.....                                                                                                                                     | 9-87        |
| 9-25         | Effect of Ethylene Dichloride on the Cornea.....                                                                                                                                          | 9-95        |
| 9-26         | Effect of Subchronic Exposure to Ethylene Dichloride.....                                                                                                                                 | 9-102       |
| 9-27         | Summary of Mutagenicity Testing of EDC: Gene Mutations in Bacteria.....                                                                                                                   | 9-132       |
| 9-28         | Summary of Mutagenicity Testing of EDC: Higher Plants.....                                                                                                                                | 9-145       |
| 9-29         | Summary of Mutagenicity Testing of EDC: Gene Mutation Tests in Insects.....                                                                                                               | 9-147       |
| 9-30         | Summary of Mutagenicity Testing of EDC: Mammalian Cells in Culture.....                                                                                                                   | 9-153       |
| 9-31         | Summary of Mutagenicity Testing of EDC: Chromosomal Aberrations Tests.....                                                                                                                | 9-155       |
| 9-32         | Summary of Mutagenicity Testing of EDC: PolA Assay.....                                                                                                                                   | 9-160       |
| 9-33         | Summary of Mutagenicity Testing of EDC: DNA Binding Studies.....                                                                                                                          | 9-163       |

# LIST OF TABLES

| <u>Table</u> |                                                                                                                       | <u>Page</u> |
|--------------|-----------------------------------------------------------------------------------------------------------------------|-------------|
| 9-34         | Design Summary for 1,2-Dichloroethane (EDC) Gavage<br>Experiment in Osborne-Mendel Rats.....                          | 9-168       |
| 9-35         | Terminal Survival of Osborne-Mendel Rats Treated With<br>1,2-Dichloroethane (EDC).....                                | 9-172       |
| 9-36         | Squamous Cell Carcinomas of the Forestomach in Osborne-<br>Mendel Rats Treated With 1,2-Dichloroethane (EDC).....     | 9-173       |
| 9-37         | Hemangiosarcomas in Osborne-Mendel Rats Treated With<br>1,2-Dichloroethane (EDC).....                                 | 9-174       |
| 9-38         | Adenocarcinomas of the Mammary Gland in Female Osborne-<br>Mendel Rats Treated With 1,2-Dichloroethane (EDC).....     | 9-175       |
| 9-39         | Design Summary for 1,2-Dichloroethane (EDC) Gavage<br>Experiment in B6C3F1 Mice.....                                  | 9-177       |
| 9-40         | Terminal Survival of B6C3F1 Mice Treated With<br>1,2-Dichloroethane (EDC).....                                        | 9-178       |
| 9-41         | Hepatocellular Carcinomas in B6C3F1 Mice Treated With<br>1,2-Dichloroethane (EDC).....                                | 9-181       |
| 9-42         | Alveolar/Bronchiolar Adenomas in B6C3F1 Mice Treated<br>With 1,2-Dichloroethane (EDC).....                            | 9-182       |
| 9-43         | Squamous Cell Carcinomas of the Forestomach in B6C3F1 Mice<br>Treated With 1,2-Dichloroethane (EDC).....              | 9-183       |
| 9-44         | Adenocarcinomas of the Mammary Gland in Female B6C3F1 Mice<br>Treated With 1,2-Dichloroethane (EDC).....              | 9-184       |
| 9-45         | Endometrial Polyp or Endometrial Stromal Sarcomas in Female<br>B6C3F1 Mice Treated With 1,2-Dichloroethane (EDC)..... | 9-184       |
| 9-46         | Characterization of 1,2-Dichloroethane (EDC) Inhalation<br>Experiment in Sprague-Dawley Rats.....                     | 9-185       |
| 9-47         | Design Summary for 1,2-Dichloroethane (EDC) Experiment<br>in Sprague-Dawley Rats.....                                 | 9-186       |
| 9-48         | Survival of Sprague-Dawley Rats Exposed to EDC at 52 and<br>104 Weeks.....                                            | 9-188       |
| 9-49         | Tumor Incidence in Sprague-Dawley Rats Exposed to EDC.....                                                            | 9-189       |
| 9-50         | Mammary Tumors in Sprague-Dawley Rats Exposed to EDC.....                                                             | 9-193       |

# LIST OF TABLES

| <u>Table</u> |                                                                                                                                                           | <u>Page</u> |
|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 9-51         | Design Summary for 1,2-Dichloroethane (EDC) Experiment<br>in Swiss Mice.....                                                                              | 9-196       |
| 9-52         | Survival of Swiss Mice Exposed to EDC at 52 and 78 Weeks.....                                                                                             | 9-197       |
| 9-53         | Tumor Incidence in Swiss Mice Exposed to EDC.....                                                                                                         | 9-198       |
| 9-54         | Pulmonary Tumor Response in Strain A/st Mice<br>Injected with EDC.....                                                                                    | 9-202       |
| 9-55         | Mouse Skin Bioassay of 1,2-Dichloroethane and<br>Chloroacetaldehyde.....                                                                                  | 9-204       |
| 9-56         | Incidence Rates of Hemangiosarcomas in the Circulatory<br>Systems of Male Osborne-Mendel Rats.....                                                        | 9-220       |
| 9-57         | Incidence Rates of Hepatocellular Carcinomas in Male<br>B6C3F1 Mice.....                                                                                  | 9-220       |
| 9-58         | Upper-Bound Estimate of Risk At 1 Mg/kg/day.....                                                                                                          | 9-223       |
| 9-59         | Relative Carcinogenic Potencies Among 53 Chemicals<br>Evaluated by the Carcinogen Assessment Group as Suspect<br>Human Carcinogens <sup>1,2,3</sup> ..... | 9-230       |

# LIST OF FIGURES

| <u>Figure</u> |                                                                                                                                                                                                | <u>Page</u> |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 9-1           | EDC levels after single oral administration in rats.....                                                                                                                                       | 9-7         |
| 9-2           | Top: Blood levels of EDC observed during and following a 6-hour inhalation exposure to 150 ppm EDC. Bottom: Semi-logarithmic plot of EDC blood levels vs. time after exposure termination..... | 9-12        |
| 9-3           | Blood levels of EDC in rats after i.v. administration.....                                                                                                                                     | 9-23        |
| 9-4           | Levels of EDC in rats after inhalatory exposure to 50 ppm (top) and 250 ppm (bottom). Levels were measured at termination of 5-hour exposure period.....                                       | 9-27        |
| 9-5           | Microsomal oxidative metabolism of 1,2-dihaloethanes.....                                                                                                                                      | 9-39        |
| 9-6           | Further metabolism of 2-chloroacetaldehyde and 1-chloro-2-chloroethane from microsomal oxidation.....                                                                                          | 9-41        |
| 9-7           | Cytosolic metabolism of ethylene dichloride.....                                                                                                                                               | 9-44        |
| 9-8           | Growth curves for male and female Osborne-Mendel rats administered 1,2-dichloroethane (EDC) by gavage.....                                                                                     | 9-170       |
| 9-9           | Survival comparisons for male and female Osborne-Mendel rats administered 1,2-dichloroethane (EDC) by gavage.....                                                                              | 9-171       |
| 9-10          | Growth curves for male and female B6C3F1 mice administered 1,2-dichloroethane (EDC) by gavage.....                                                                                             | 9-179       |
| 9-11          | Survival comparisons for male and female B6C3F1 mice administered 1,2-Dichloroethane (EDC) by gavage.....                                                                                      | 9-180       |
| 9-12          | Point and upper-bound estimates of four dose-response models over low-dose region on basis of hemangiosarcomas in rats; dose with surface correction.....                                      | 9-224       |
| 9-13          | Point and upper-bound estimates of four dose-response models over low-dose region on the basis of liver carcinomas in mice; dose with surface correction.....                                  | 9-225       |
| 9-14          | Histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the Carcinogen Assessment Group.....                                           | 9-229       |

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## APPENDIX A

### COMPARISON AMONG DIFFERENT EXTRAPOLATION MODELS

Four models used for low-dose extrapolation, assuming the independent background, are:

Multistage: 
$$P(d) = 1 - \exp [-(q_1 d + \dots + q_k d^k)]$$

where  $q_i$  are non-negative parameters;

Probit: 
$$P(d) = \int_{-\infty}^{A + B \ln(d)} f(x) dx$$

where  $f(\cdot)$  is the standard normal probability density function;

Weibull: 
$$P(d) = 1 - \exp [-bd^k]$$

where  $b$  and  $k$  are non-negative parameters; and

One-hit: 
$$P(d) = 1 - \exp [-bd]$$

where  $b$  is a non-negative parameter.

The maximum likelihood estimates (MLE) of the parameters in the multi-stage and one-hit models are calculated by means of the program GLOBAL82, which was developed by Howe and Crump (1982). The MLE estimates of the parameters in the probit and Weibull models are calculated by means of the program RISK81, which was developed by Kovar and Krewski (1981).

Table A-1 presents the MLE of parameters in each of the four models that are applicable to a data set.

TABLE A-1. MAXIMUM LIKELIHOOD ESTIMATES OF THE PARAMETERS FOR EACH OF THE FOUR  
EXTRAPOLATION MODELS BASED ON DIFFERENT DATA BASES

| Data base                                                               | Multistage                                                 | Probit                    | Weibull                                 | One-hit                   |
|-------------------------------------------------------------------------|------------------------------------------------------------|---------------------------|-----------------------------------------|---------------------------|
| Hemangiosarcomas in male rats, dose with surface correction             | $q_1 = 3.65 \times 10^{-2}$<br>$q_2 = 0$                   | $A = -1.43$<br>$B = 0.34$ | $b = 9.08 \times 10^{-2}$<br>$k = 0.52$ | $b = 3.65 \times 10^{-2}$ |
| Hemangiosarcomas in male rats, dose without surface correction          | $q_1 = 7.0 \times 10^{-3}$<br>$q_2 = 0$                    | $A = -1.99$<br>$B = 0.34$ | $b = 3.84 \times 10^{-2}$<br>$k = 0.52$ | $b = 7.03 \times 10^{-3}$ |
| Hepatocellular carcinomas in male mice, dose with surface correction    | $q_1 = 1.03 \times 10^{-2}$<br>$q_2 = 1.47 \times 10^{-3}$ | $A = -2.75$<br>$B = 0.86$ | $b = 8.07 \times 10^{-3}$<br>$k = 1.49$ | $b = 2.32 \times 10^{-2}$ |
| Heptocellular carcinomas in male mice, dose without surface corrections | $q_1 = 8.18 \times 10^{-4}$<br>$q_2 = 9.25 \times 10^{-6}$ | $A = -4.92$<br>$B = 0.86$ | $b = 1.84 \times 10^{-4}$<br>$k = 1.49$ | $b = 3.04 \times 10^{-3}$ |

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## APPENDIX B

### RISK CALCULATION BASED ON TIME-TO-EVENT DATA

Because of the high mortality rate of rats in the high-dose group of the NCI (1978) gavage study, it is more appropriate to use time-to-event data (Table B-1) to calculate the potency of EDC. The probability of cancer by time  $t$  at dose  $d$  is given by:

$$P(d,t) = 1 - \exp [-f(t) \times g(d)]$$

where  $g(d)$  is a polynomial in dose  $d$ , and  $f(t)$  is a function of time  $t$ . The maximum likelihood estimate of the parameters and the asymptotic properties of the incremental risk estimate were investigated by Daffer et al. (1980). Their approach to estimating the parameters resembles Cox's regression-life-table approach (Cox 1972), in which the time function  $f(t)$  need not be specified.

Using the data in Table B-1, the lifetime cancer risk is estimated to be

$$q_1^* = 6.9 \times 10^{-2} \text{ mg/kg/day}$$

This value is the 95% upper bound of the risk calculated at  $t = 90$  weeks. Since the model fits the data very well up to 90 weeks but poorly beyond 90 weeks (overestimates),  $P(d, 90)$  is used to approximate the lifetime risk. This seems reasonable because the median lifespan for control animals is also less than 90 weeks (approximately 70% of the control animals died before 90 weeks).

TABLE B-1. TIME-TO-DEATH IN WEEKS FROM HEMANGIOSARCOMAS  
IN MALE OSBORNE-MENDEL RATS FED EDC BY GAVAGE

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Control (vehicle and untreated):

28, 37, 50, 50, 53, 53, 53, 54, 57, 57, 57, 57, 57, 61, 61,  
69, 71, 76, 78, 80, 80, 83, 85, 86, 87, 89, 90, 101, 101,  
104, 106, 106, 106, 106, 106, 108, 110, 110, 110, 110.

Low-dose group:

30, 34, 36, 51, 52, 52, 55, 55, 59, 61, 63, 65, 69, 73(H)<sup>a</sup>,  
74(H), 75, 75, 76, 77, 77, 77(H), 77, 80, 81, 82, 82, 82, 84,  
87(H), 89(H), 89, 89, 89, 90, 92, 92, 93(H), 95(H), 96, 97,  
98, 99, 99, 102(H), 103, 103, 104, 104, 109(H), 110.

High-dose group:

3, 8, 9, 9, 10, 10, 10, 10, 10, 11, 15, 15, 16, 20, 22, 33,  
33, 33, 34, 37, 41, 48, 51, 52, 54, 57, 58, 59, 60, 61(H),  
62, 63, 63, 68(H), 68(H), 71, 72, 73, 74, 74(H), 74, 74, 76(H),  
76, 78(H), 83(H), 84, 89, 101.

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<sup>a</sup>H indicates death from hemangiosarcoma.

## APPENDIX C

### MUTAGENIC POTENCIES BY GAVAGE AND INHALATION ROUTES

calculating the potency of EDB by gavage are presented in Table 1. The data from the high-dose group are not used because the dose of the high-dose group was drastically modified during the experiment. The time-weighted dose almost identical to that of the low-dose group using a life-table approach (Kaplan and Meier 1958), the estimated potency at week 49 (the end of the study) is 0.37 with the 95% confidence limit at 0.46. Thus, the upper-bound estimate of the potency using a hit model,  $P = 1 - \exp(-bd)$ , is:

$$-\ln(1-P)/d$$

$$-\ln(1-0.46)/5.01$$

$$0.12 \text{ mg/kg/day.}$$

The potency, adjusting for the less-than-lifetime study, is

$$0.12 \times (90/49)^3 = 0.74 \text{ mg/kg/day}$$

The lifetime span that is also used in the EDC calculation when the data are used.

The potency is approximately 10 times more potent than EDC (i.e.,

The data used for calculating the potency of EDB by inhalation are presented in Table C-2. The carcinogenic potency of EDB by inhalation is calculated on the basis of nasal cavity tumors in male rats from the NCI inhalation study on EDB (NCI 1979), using the linearized multistage model. The potency of EDB by inhalation is

$$6.77 \times 10^{-5}/(\text{ug}/\text{m}^3).$$

TABLE C-1. TIME-TO-DEATH IN WEEKS FROM HEMANGIOSARCOMAS  
IN MALE OSBORNE-MENDEL RATS FED EDB BY GAVAGE  
(NCI 1978)

Low-dose group (38 mg/kg/day)<sup>a</sup>

31(H)<sup>b</sup>, 32, 34(H), 34(H), 35, 36, 37, 38(H), 39, 39, 40, 41,  
42, 43, 43, 43, 43, 43, 43, 44, 44, 44, 46, 46, 47, 47, 48(H),  
48, 48, 48, 48, 49(H), 49(H), 49(H), 49(H), 49(H), 49(H), 49,  
49, 49, 49, 49, 49, 49, 49, 49, 49, 49, 49, 49, 49.

<sup>a</sup>The animals were fed EDB 5 days per week for 47 weeks (out of 49 weeks observation period). The human equivalent dose is  $(38 \text{ mg/kg/day}) \times (5/7) \times (47/49) \times (0.5/70)^{1/3} = 5.01 \text{ mg/kg/day}$ .

<sup>b</sup>H indicates that the animals died from hemangiosarcomas. It is assumed that all animals observed with tumors at week 49 died from the tumors. This assumption seems reasonable, since the time from exposure to tumor death was very short.

TABLE C-2. INCIDENCE OF NASAL CAVITY TUMORS IN MALE  
FISCHER 344 RATS ADMINISTERED EDB BY INHALATION  
(NCI 1979)

| Human equivalent<br>dose ( $\mu\text{g}/\text{m}^3$ ) <sup>a</sup> | Animal dose<br>(ppm) | Response    |
|--------------------------------------------------------------------|----------------------|-------------|
| 0                                                                  | 0                    | 0/50 (0%)   |
| $1.39 \times 10^4$                                                 | 10                   | 39/50 (78%) |
| $5.57 \times 10^4$                                                 | 40                   | 41/50 (82%) |

<sup>a</sup>Human equivalent dose =  $d \times (5/7) \times (6/24) = 0.178 \times d$ . The dose is converted to the unit of  $\mu\text{g}/\text{m}^3$  by using  $1 \text{ ppm} = 7.83 \times 10^3 \mu\text{g}/\text{m}^3$ .