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Environmental Protection
Agency

Office of
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January 1979

EPA

Toxic Substances

Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency

THIRD REPORT

OF THE

TSCA INTERAGENCY TESTING COMMITTEE

TO THE

ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

October 1978

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TOXIC SUBSTANCES CONTROL ACT

INTERAGENCY TESTING COMMITTEE

722 Jackson Place, N.W.
Washington, D.C. 20006

October 2, 1978

Honorable Douglas M. Costle
Administrator
Environmental Protection Agency
Room W1200 (A-100)
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Costle:

On behalf of the TSCA Interagency Testing Committee I am transmitting to you our latest revisions to the Section 4(e) Priority List. These revisions and the Committee's reasons for recommending them are presented in the enclosed document entitled, "Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency." The representatives of the statutory member agencies are in consensus on these revisions.

We will be continuing our review of those chemical substances and mixtures which have not yet been designated to the Priority List and shall report to you on our recommendations in accordance with the provisions of the Act.

Sincerely yours,

Marvin E. Stephenson

Marvin E. Stephenson, Ph.D.
Chairman

Enclosure

TSCA INTERAGENCY TESTING COMMITTEE

Statutory Member Agencies

COUNCIL ON ENVIRONMENTAL QUALITY

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Nathan J. Karch, Alternate

DEPARTMENT OF COMMERCE

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DEPARTMENT OF THE INTERIOR

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FOOD AND DRUG ADMINISTRATION

Allen H. Heim

Winston deMonsabert

COMMITTEE STAFF

Executive Secretary: Carol A. Mapes

Secretary: Madye B. Cole

ACKNOWLEDGMENTS

The Committee members acknowledge the support and invaluable contributions of the many individuals and groups who have significantly aided us in our work. These include:

-- the Federal agencies who have cooperated by providing support through the liaison members;

-- Clement Associates, Inc., technical support contractor;

-- the U.S. Environmental Protection Agency (EPA) for funding the technical support contract and the National Institute for Occupational Safety and Health, the Council on Environmental Quality, and the National Cancer Institute for assisting in the funding;

-- former liaison member Robert Hehir, Consumer Product Safety Commission;

-- former EPA staff member Donald G. Barnes, Office of Toxic Substances;

-- EPA staff members who assisted the Committee in a variety of activities, in particular:

    John W. Lyon, Office of General Counsel,
    Ralph C. Northrop, Jr., Office of Toxic Substances, and
    Amy Rispin, Office of Toxic Substances;

-- the numerous experts who prepared presentations and material for the Committee;

-- the industries that responded to the Contractor's request for information on specific chemical substances and categories; and

-- the many individuals and organizations who responded to the Committee's previous reports.

SUMMARY

A major section (Sec. 4) of the Toxic Substances Control Act of 1976 (TSCA, Pub. L. 94-469) provides for the testing of chemicals in commerce which may pose an unreasonable risk to human health or the environment. This section of the Act also provides for establishment of a Committee, composed of representatives from eight designated Federal agencies, to recommend chemical substances or mixtures to which the Administrator of the U.S. Environmental Protection Agency (EPA) should give priority consideration for the promulgation of testing rules. The Committee makes such revisions in the Section 4(e) Priority List as it determines to be necessary and transmits them to the Administrator, at least every six months.

As a result of its deliberations during the past six months, the Committee is revising the TSCA Section 4(e) Priority List by the addition of one individual substance and two categories of substances. Each of these new recommendations is being designated by the Committee for action by EPA within twelve months. The Committee considers these additions to be of the same priority as the previous entries. The chemical substance and categories being added to the Priority List are presented alphabetically, together with the types of studies recommended, as follows:

Substance or Category	Recommended Studies
Chlorinated Benzenes, Tri-, Tetra- and Penta-	Carcinogenicity, mutagenicity, teratogenicity, other toxic effects, environmental effects, and epidemiology
1,2-Dichloropropane	Carcinogenicity, mutagenicity, teratogenicity, other toxic effects, environmental effects, and epidemiology
Glycidol and Its Derivatives	Carcinogenicity, mutagenicity, teratogenicity, other toxic effects, and epidemiology

Information dossiers on these new entries will be forwarded to the EPA Administrator at the earliest practicable date.

THIRD REPORT

OF THE

TSCA INTERAGENCY TESTING COMMITTEE

TO THE

ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

OCTOBER 1978

CHAPTER 1. INTRODUCTION

1.1 Background

The Interagency Testing Committee (Committee) was established under Section 4(e) of the Toxic Substances Control Act of 1976 (TSCA, Pub. L. 94-469). The specific mandate of the Committee is to identify and recommend to the Administrator of the U.S. Environmental Protection Agency (EPA) chemical substances or mixtures in commerce which should be tested to determine their potential hazard to human health and/or the environment. The Act specifies that the Committee's recommendations to the Administrator will be in the form of a list !Section 4(e) Priority List1 to be published in the Federal Register. The Committee also is directed to make such revisions in the list as it determines to be necessary and transmit them to the Administrator, at least every six months after submission of its initial list.

The Committee has eight statutory members appointed by the Federal agencies identified for membership in Section 4(e)(2)(A) of the Act as well as a number of alternate members as permitted by Section 4(e)(2)(B)(i). In addition, the Committee has invited several other Federal agencies with programs related to the control of toxic substances to designate liaison representatives to participate in its meetings. The current Committee members, alternates, and liaison representatives are identified in the front of this report.

1.2 Previous Reports

In July 1977, the Committee published a Preliminary List of 330 chemical substances and categories which it had identified for further consideration (Reference No. 1). Using previously described techniques (Reference No. 2), the Committee ultimately identified approximately eighty chemical substances and categories

for detailed review and requested its technical contractor to prepare dossiers on selected chemicals and categories. The review of these dossiers, combined with the knowledge and professional judgment of the Committee members, formed the basis for the Committee's initial recommendations to the EPA Administrator (Reference No. 2) and subsequent additions to the Section 4(e) Priority List (Reference No. 3).

1.3 Committee Activities During This Reporting Period

During the past six months, the Committee completed a detailed review of all chemicals and categories selected for dossier preparation as well as the review of a number of additional chemicals, with the following exceptions: a) those chemical substances and categories for which dossiers are being prepared and will be reviewed prior to the Committee's April, 1979, report; and b) those chemicals whose further consideration has been deferred pending receipt of additional information.

1.4 Future Committee Activities

The Committee is currently updating its Master File of chemicals. This effort will be followed by a selection of chemicals and scoring procedures similar to those described in previous Committee reports (Reference Nos. 2 & 3). These procedures will provide one method for identifying additional chemicals for detailed review and, simultaneously, will enable a periodic re-evaluation of those chemicals which have been reviewed, but not selected for inclusion in the Section 4(e) Priority List.

CHAPTER 2. AVAILABILITY OF TESTING FACILITIES AND PERSONNEL

The Committee again emphasizes its concerns about the National capability for conducting long-term tests of biological effects, as expressed in its second report to the EPA Administrator (Reference No. 3). As previously stated, the Committee's paramount concern is for the availability of adequately trained personnel. The Committee, therefore, reiterates its belief that the Civil Service Commission could do much to stimulate interest in professions such as toxicology, pathology, epidemiology, and related environmental and occupational health specialties by creating series and registers for these professions.

- The Committee supports current efforts by the Environmental Protection Agency to initiate the establishment of a Civil Service Commission series for toxicologists.

- The Committee again recommends a National survey to assess the future availability of personnel and testing facilities.

- The Committee again recommends that this survey also determine the adequacy of the supply of test organisms for assessing specific health and environmental effects.

To determine whether the number of personnel and facilities are adequate to meet the predicted needs of TSCA/EPA, there also must be some assessment of the TSCA testing requirements in relation to those of other Federal agencies and the private sector.

- The predicted competition for these facilities by users from the Federal and private sectors might be partially alleviated if some short-term, national-testing-priority scheme were developed to enable the most crucial needs to be met as additional personnel and facilities are developed.

CHAPTER 3. RECOMMENDATIONS OF THE COMMITTEE

3.1 Chemical Substances and Categories Recommended for Testing

The Interagency Testing Committee is revising the TSCA Section 4(e) Priority List by the addition of one individual substance and two categories of substances for which testing is recommended. These chemicals were selected after consideration of the factors identified in TSCA Section 4(e)(1)(A), other relevant factors identified by the Committee, and the knowledge and professional judgment of Committee members. The recommended studies deemed appropriate for determining the potential hazard(s) of each new entry and the reasons for such recommendations are described in Section 3.3 of this report. As in the case of the Committee's previous recommendations, each chemical substance and category is being designated by the Committee for action by EPA within twelve months.

Table 1 presents the complete Section 4(e) Priority List including the date by which the EPA Administrator must take action on each entry. As in previous Committee reports (Reference Nos. 2 & 3), the entries are listed alphabetically. The Committee considers each of its new entries to the List to be of equal importance. Therefore, each of these new entries should be given the same priority for purposes of initiating action as required under TSCA Section 4(e). Unless stated otherwise, the chemical substance recommended for testing is the product to which the population is exposed.

3.2 Designated Substances on Which Studies are Planned or Ongoing

The Committee is aware that it has added to the Section 4(e) Priority List certain chemical substances which are either currently under study or have been selected for study by other groups. Such studies may concern one or more of the effects for which the Committee has recommended testing. Set forth below is the Committee's reasoning for its past and future designation of such substances.

The Committee generally does not regard knowledge that studies are planned or ongoing as a sufficient basis to defer consideration of a substance for designation for the effect under investigation or for any other effect. The Committee's judgment as to whether a substance has been adequately tested for health and environmental effects must rest with the data that are presently available. Such data do not exist for planned studies and may be in various stages of generation for ongoing studies. In addition, the Committee is unable to predict if an ongoing study would be successfully concluded (i.e., disease, toxicity, or other unforeseen events may cause a study to be aborted). Whenever they have been identified, planned and ongoing studies are noted in the dossiers on designated substances.

Table 1. The TSCA Section 4(e) Priority List, Arranged Alphabetically

Chemical Substance or Category	Designated for Action By
Acrylamide	April 1979
Alkyl epoxides	October 1978
Alkyl phthalates	October 1978
Aryl phosphates	April 1979
Chlorinated benzenes, mono- and di-	October 1978
Chlorinated benzenes, tri-, tetra- and penta-	October 1979
Chlorinated naphthalenes	April 1979
Chlorinated paraffins	October 1978
Chloromethane	October 1978
Cresols	October 1978
Dichloromethane	April 1979
1,2-Dichloropropane	October 1979
Glycidol and its derivatives	October 1979
Halogenated alkyl epoxides	April 1979
Hexachloro-1,3-butadiene	October 1978
Nitrobenzene	October 1978
Polychlorinated terphenyls	April 1979
Pyridine	April 1979
Toluene	October 1978
1,1,1-Trichloroethane	April 1979
Xylenes	October 1978

The above statement does not mean that the Committee's consideration of substances will never include planned or ongoing studies. If the details of a study are known and its conclusions imminent, the Committee may delay considering the substance until the results become available. When the Committee considers that a chemical substance is under sufficient assessment by other groups, it may defer consideration of the substance. Because the Committee recognizes that each case must be judged individually, it has not establish formal criteria regarding the impact that planned or ongoing studies may have on its recommendations.

3.3 Reasons for Recommending Testing of the Additional Substances and Categories

Table 2 summarizes the studies recommended for each additional entry on the Section 4(e) Priority List. As directed by TSCA Section 4(e)(1)(B) the Committee also is presenting its reasons for recommending specific types of studies. In addition to the rationales presented herein, supporting dossiers of information are being finalized and will be transmitted to the Administrator, EPA, at the earliest practicable date.

3.3.A CHLORINATED BENZENES, TRI-, TETRA- AND PENTA-

RECOMMENDED STUDIES

Carcinogenicity
Mutagenicity
Teratogenicity
Other Toxic Effects
Environmental Effects
Epidemiology

CATEGORY IDENTIFICATION: This category consists of: 1,2,3-trichlorobenzene (CAS No. 87-61-6); 1,2,4-trichlorobenzene (CAS No. 120-82-1); 1,3,5-trichlorobenzene (CAS No. 108-70-3); 1,2,3,4-tetrachlorobenzene (CAS No. 634-66-2); 1,2,3,5-tetrachlorobenzene (CAS No. 634-90-2); 1,2,4,5-tetrachlorobenzene (CAS No. 95-94-3); and pentachlorobenzene (CAS No. 608-93-5).

REASONS FOR RECOMMENDATIONS:

Production, Release and Exposure: Although the Committee was not able to obtain accurate production, environmental release, and worker exposure figures, one source suggests that over 1 million

Table 2. Summary of Recommended Studies

Substance or Category	Carcino-genicity	Muta-genicity	Terato-genicity	Other* Toxic Effects	Environ-mental Effects	Epidemiology
1. Chlorinated Benzenes, Tri-, Tetra- and Penta-	X	X	X	X[a]	X	X
2. 1,2-Dichloropropane	X	X	X	X[b]	X	X
3. Glycidol and Its Derivatives	X	X	X	X[c]		X

*The systems of particular concern are as follows: a) neurological and hematopoietic; b) reproductive and neurological; and c) reproductive.

workers are exposed to trichlorobenzenes. The Committee also judges that a variety of sources are responsible for the observed contamination of air, water, soil and food chains by chlorinated benzenes. Possible sources of contamination include the use of chlorobenzenes as chemical intermediates and solvents in the manufacture of dyes, lubricants and pesticides as well as other uses such as transformer oils. Recent decreases in the use of polychlorinated biphenyls may result in an increased usage of trichlorobenzenes as transformer oils. Chlorinated benzenes are also present as contaminants in and degradation products of pesticides and occur in chlorinated municipal, agricultural and industrial effluents. The predicted partition coefficients of chlorobenzenes suggest that they may accumulate in biological systems. The high probability for exposure to the human population and environment of these relatively persistent and toxic substances is emphasized in the following recommendations.

Carcinogenicity: No carcinogenicity studies on tri-, tetra- and pentachlorobenzenes were found in the searched literature, although hexachlorobenzene is a demonstrated animal carcinogen. The Committee, therefore, recommends that tests be conducted to assess the carcinogenic potential of these chemicals.

Mutagenicity: Although a single mutagenicity study for 1,2,4-trichlorobenzene was negative, additional testing is needed to assess the mutagenic potential of the chlorobenzenes.

Teratogenicity: Pentachlorobenzene administered to pregnant rats reduced the mean number of live fetuses per litter and increased the incidence of sternal defects and extra ribs. Studies are recommended to assess the teratogenic potential of the chlorobenzenes.

Other Toxic Effects: Degeneration of liver cells and hepatic porphyria have been observed in rodents exposed to chlorobenzenes. Dose-related increases in liver to body weight ratios in highly porphyric rats were accompanied by the induction of hepatic microsomal enzymes. Monkeys given high doses of 1,2,4-trichlorobenzene showed severe weight loss and fine tremors. Guinea pigs given high doses of chlorobenzenes have been reported to convulse and die. The Committee recommends testing, with emphasis on the neurological and hematopoietic systems, to further assess the toxic effects of the chlorobenzenes.

Environmental Effects: There is a paucity of information on the acute and chronic effects of tri-, tetra- and pentachlorobenzenes on wild and domestic birds and mammals, fish, amphibians, reptiles, invertebrates, plants and algae. Since residues have been detected in aquatic situations, particular emphasis should be placed on long-term environmental studies in freshwater and marine environments with concern for the biological significance of residues and effects on reproduction, behavior and survival of fish, fish-eating birds and mammals, and food chain organisms.

Epidemiology: Since the nature of human exposure to chlorobenzenes is extremely broad, the Committee believes that epidemiological studies may be important in assessing the effects of long-term exposure to chlorobenzenes.

3.3.B 1,2-DICHLOROPROPANE

RECOMMENDED STUDIES

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Toxic Effects
- Environmental Effects
- Epidemiology

SUBSTANCE IDENTIFICATION: CAS No. 78-87-5

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: 1,2-Dichloropropane is produced in large quantities with a production rate in 1976 of 71 million pounds. Because of its widespread use as a solvent, as well as a multiplicity of other uses, 1,2-dichloropropane has a potentially high occupational exposure (over 1 million workers). Its potential use in many consumer products also may lead to wide general exposure. Little is known about the release rate of 1,2-dichloropropane into the environment.

Carcinogenicity: The testing carried out thus far on the carcinogenicity of 1,2-dichloropropane is insufficient to allow an appropriate appraisal of its carcinogenicity. The Committee, therefore, recommends that additional carcinogenicity studies be conducted.

Mutagenicity: Although positive mutagenicity tests have been reported in Salmonella typhimurium and in Aspergillus nedulans for dichloropropane, the isomer was not specified. The Committee recommends that mutagenicity testing be done specifically on 1,2-dichloropropane.

Teratogenicity: Because no information on the teratogenicity of 1,2-dichloropropane was found in the searched literature, the Committee recommends that teratogenicity tests be conducted.

Other Toxic Effects: Fatty degeneration of the liver and kidney and necrosis of the adrenals have been observed in experimental animals following acute, high-level exposures to 1,2-dichloropropane. Although one low-level exposure study has been reported, it is considered to be inadequate to assess the chronic effects of 1,2-dichloropropane. Since this compound is structurally similar to 1,2-dibromo-3-chloropropane, the Committee recommends that particular emphasis be placed on the reproductive and neurological effects of this chemical.

Environmental Effects: In view of its volatility and high specific gravity, the ecological impact of 1,2-dichloropropane may be localized to those environments receiving continuous exposure associated with this chemical's use and disposal. The potential for bioaccumulation suggests the need for further testing to determine the biological significance of exposure to wild and domestic birds, mammals, fish, and invertebrates. Specific areas of environmental concern include: chronic toxicity to fish and invertebrates; effects on avian and mammalian reproduction and behavior; and effects on soil invertebrates and terrestrial insects.

Epidemiology: There is no information available on chronic effects in humans exposed to 1,2-dichloropropane over an extended period of time. Because of the potentially widespread exposure, epidemiological studies may be particularly important in assessing the human health effects of 1,2-dichloropropane.

3.3.C GLYCIDOL and ITS DERIVATIVES

RECOMMENDED STUDIES

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Toxic Effects
- Epidemiology

CATEGORY IDENTIFICATION: This category consists of glycidol (CAS No. 556-52-5) and several glycidyl ethers and esters. Example chemicals in this category are glycidyl acrylate (CAS No. 106-90-1), glycidyl methacrylate (CAS No. 106-91-2), allyl glycidyl ether (CAS No. 106-92-3), n-butyl glycidyl ether (CAS No. 2426-08-6), para-cresyl glycidyl ether (CAS No. 2186-24-5), phenyl glycidyl ether (CAS No. 122-60-1), and the diglycidyl ether of bisphenol A (CAS No. 1675-54-3).

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: Most of these commercially significant chemicals have annual production volumes in excess of 1,000 pounds (1976). Although exposure estimates are not available for all the chemicals in this category, NIOSH estimates that 105,000, 118,000 and 105,000 workers are exposed to glycidol, glycidyl ethers, and glycidyl methacrylate, respectively.

Carcinogenicity: Although glycidol and glycidyl methacrylate have been tested for carcinogenicity, neither meets current testing standards. In view of the potential alkylating properties of these compounds, and the demonstrated carcinogenicity of triethylene glycol diglycidyl ether and the structurally related glycidal, the Committee recommends carcinogenicity studies.

Mutagenicity: Since glycidol, allyl glycidyl ether, n-butyl glycidyl ether, and phenyl glycidyl ether have been reported to be mutagenic in several assay systems, the mutagenic potential of other category members should be determined.

Teratogenicity: With the exception of negative test results on phenyl glycidyl ether, the teratogenic potentials of these compounds have not been evaluated. The Committee, therefore, recommends studies to evaluate the teratogenic potential of other Compounds in this category.

Other Toxic Effects: Most of these chemicals are skin and eye irritants, while some induce sensitization and cross-sensitization reactions in exposed workers. A diversity of toxic effects also has been observed in experimental animals following administration of these compounds. The most frequently observed effects are CNS depression, incoordination and ataxia, although some of these compounds reportedly induce testicular atrophy and temporary sterility in rats. Adverse effects on the kidneys, liver, pancreas, and adrenals also have been observed in experimental animals. The Committee, therefore, recommends studies to evaluate the toxicity of these chemicals. The reproductive system is of particular interest.

Epidemiology: Epidemiology studies should be conducted to assess the extent of human health effects.

REFERENCES

1. Preliminary List of Chemical Substances for Further Evaluation, Toxic Substances Control Act Interagency Testing Committee, July 1977.

2. Initial Report to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, October 1, 1977. Published in the FEDERAL REGISTER, Vol. 42, No. 197, Wednesday, October 12, 1977, pp. 55026-55080. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560-10-78/001, January 1978.

3. Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, April 1978. Published in the FEDERAL REGISTER Vol. 43, No. 76, Wednesday, April 19, 1978, pp. 16684-16688. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560-10-78/002, July 1978.

Member Agencies

Council on Environmental Quality
Department of Commerce
Environmental Protection Agency
National Cancer Institute
National Institute of Environmental Health Sciences
National Institute for Occupational Safety and Health
National Science Foundation
Occupational Safety and Health Administration

Liaison Agencies

Consumer Product Safety Commission
Department of Defense
Department of the Interior
Food and Drug Administration

TOXIC SUBSTANCES CONTROL ACT

INTERAGENCY TESTING COMMITTEE

722 Jackson Place, N.W.
Washington, D.C. 20006

January 8, 1979

Honorable Douglas M. Costle
Administrator
Environmental Protection Agency
Room W1200 (A-100)
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Costle:

On behalf of the Interagency Testing Committee, I am pleased to transmit with this letter the supporting dossiers of information on the chemical and categories which the ITC recommended to you for priority consideration under Section 4 of the Toxic Substances Control Act in October 1978. In a draft version, these dossiers were used as the primary, though not sole, source of information for the Committee's recommendations. In preparing this document in its final form, some new information came to our attention. None of the new data would cause the Committee to revise its recommendations at this date; however, for the sake of completeness, an addendum of these data has been added.

I would also like to correct an example cited in the rationale for the category entitled "Glycidol and its Derivatives" and clarify this category's identification. On page 11 of the Committee's Third Report, under the heading "Carcinogenicity" the second sentence is changed to read:

> In view of the potential alkylating properties of these compounds, and the demonstrated carcinogenicity of triethylene glycol diglycidyl ether and the structurally related glycidal, the Committee recommends carcinogenicity studies.

I am enclosing a copy of the October report with a corrected page eleven. You may wish to note this correction in the Federal Register.

The Committee staff has had considerable discussion with representatives of industrial concerns who manufacture glycidyl ethers concerning the name of this category. The Committee recognizes that the glycidyl ethers and esters are not commercially synthesized from glycidol. However, for simplicity in naming the category, the term "derivatives" is used to mean esters and ethers, which are, regardless of synthetic route, considered to be derivatives of the alcohol glycidol.

Sincerely yours,

Carter Schuth

Carter Schuth (Mrs.)
Chairperson, TSCA/ITS

INFORMATION DOSSIERS ON SUBSTANCES

DESIGNATED BY

TSCA INTERAGENCY TESTING COMMITTEE

(October 1978)

Prepared by

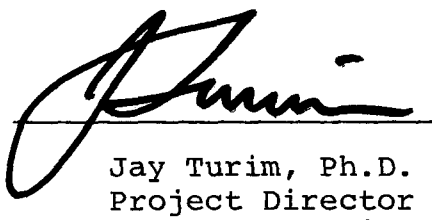
Clement Associates, Inc.
1010 Wisconsin Avenue, NW
Washington, DC 20007

December 1978

Contract No. EQ8AC013

Prepared for

TSCA Interagency Testing Committee
Washington, DC

Approved by 

Jay Turim, Ph.D.
Project Director
Clement Associates, Inc.

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FOREWORD

This document has been prepared for the Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC) by its technical contractor, Clement Associates, Inc. The Committee is charged with making recommendations to the Administrator of the Environmental Protection Agency (EPA) with respect to which chemicals should be tested to determine their hazards to human health or the environment.

The dossiers in this document were originally drafted by Clement and were reviewed in detail by the Committee, which in certain instances added information. Conclusions made by Clement scientists about specific studies were also reviewed by the Committee. Comments by Clement scientists are denoted in the text with the word "comment." The information in the dossiers reflects the collective knowledge and judgment of the Committee and its technical contractor. These dossiers have been used by the Committee as the primary basis for recommending the chemicals for priority testing.

The dossiers were designed to provide the Committee with sufficient information on the chemicals' physical and chemical properties, exposure characteristics, and biological and environmental effects to support an informed judgment on whether they should be given priority for testing.

The dossiers contain information from selected computerized data bases (see Appendix A). Standard secondary sources (see

Appendix B), monographs, criteria documents, reviews, abstracts of papers presented at scientific meetings, and reports available from government agency files and trade association libraries were also consulted. Material received in response to the Committee's request in the Federal Register in July 1977 for information on certain substances was also reviewed. Relevant data obtained from manufacturers in response to a written request for information are included. Clement scientists and Committee members also relied upon their own knowledge of the literature to supplement the data derived from these sources. Except when indicated otherwise, the information cited in these dossiers was derived from the primary sources.

During the revision of these dossiers, some information that had not been available to the ITC when it prepared the October 1978 report to the EPA Administrator was found. That information is given in the Addendum.

Preparation of the dossiers was directed by Dr. Jay Turim, Project Director, Dr. Mary R. Kornreich, Deputy Project Director and Dr. Mukund Shah, Team Leader. Others participating in the dossier preparation were Dr. Morton Beroza, Lorraine Cameron, Robert Fensterheim, Nan Gray, John Guy, John Joseph, Dr. Yugal Luthra, Fred Pinkney, Karin Rosenblatt, Dave Smith, and Barbara Turnham. Technical editors were Lorna T. Ryan, Dr. Matthew Hale, Jr., and Amy Turim.

CHLOROBENZENES

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CHLOROBENZENES

OVERVIEW

The chlorobenzenes discussed in this dossier are 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, 1,3,5-trichlorobenzene, 1,2,3,4-tetrachlorobenzene, 1,2,4,5-tetrachlorobenzene, and pentachlorobenzene. Most are white crystals or flakes, but 1,3,5-trichlorobenzene is a colorless stable liquid. They are generally insoluble in water, slightly soluble in alcohol, and very soluble in organic substances such as ether, benzene, and carbon disulfide.

In 1972, 15.6 million pounds of 1,2,4-trichlorobenzene were produced in the United States. No other production figures for the chlorobenzenes in this dossier were found in the sources searched. It was estimated in the National Occupational Hazard Survey that 5,000 workers in the United States are exposed to 1,2,4-trichlorobenzene and 3,000 workers to 1,3,5-trichlorobenzene. It is reported in the survey that 1,081,000 workers are exposed to "trichlorobenzene," but no indication is given of which isomer or isomers are represented by this figure. No production or exposure figures for the other chlorobenzenes discussed were found in the sources searched. The chlorobenzenes are used as chemical intermediates and solvents and in the manufacturing of dyes, lubricants, and insecticides. They are present as metabolites and contaminants in such pesticides as lindane and hexachlorobenzene.

Industrial effluents and pesticides are reported to release

chlorobenzenes into the air, soil, and water, where these chemicals are likely to persist and accumulate in the food chain. They have been observed in municipal, industrial, and agricultural discharge and in sea and river waters. 1,2,3-Trichlorobenzene has been found in U.S. drinking water in concentrations of up to 0.001 mg/liter. All the chlorobenzenes have been found in solid wastes and fish and other aquatic organisms. Pentachlorobenzene has been identified in wheat products, animal feed, and chicken and pork fat. 1,2,3,4-Tetrachlorobenzene and pentachlorobenzene were found in human adipose tissue in Japan. The chlorinated benzenes are likely to persist in the environment for long periods and bioaccumulate to a great degree. 1,2,3,4-Tetrachlorobenzene accumulated by a factor of about 100 times the daily dose in rats fed the compound at 2 mg/kg/day for 12 weeks. In general, the more chlorinated the benzene the more it resists degradation.

No information on the toxicity to humans of the chlorobenzenes in this dossier was found in the sources searched. In animals, rates of absorption and transformation of these compounds decline as the extent of chlorination increases. The less chlorinated benzenes may be metabolized to phenolic derivatives or dechlorinated. Pentachlorobenzene is reported to be relatively inert metabolically. All the chlorobenzenes, being lipophilic, tend to be deposited and stored in body fat. In metabolic studies with animals, the parent chlorobenzene and metabolites have been detected in expired air, urine, feces, gut contents, and numerous tissues.

Dose-related increases in liver to body weight ratios in rats were accompanied by the induction of microsomal enzymes. Degeneration of liver cells and hepatic porphyria have also been observed in rats exposed to chlorinated benzenes. Highly porphyric rats exposed to chlorinated benzenes showed extreme weakness, ataxia, clonic contraction, and enlarged livers.

The most highly chlorinated benzene, hexachlorobenzene, which is not discussed in this dossier, has been found to be carcinogenic in Syrian golden hamsters. However, no reports of carcinogenicity studies on the incompletely chlorinated benzenes were found in the sources searched. A single mutagenicity study for 1,2,4-trichlorobenzene was negative but experimental details could not be evaluated from the information given in the source. Pentachlorobenzene administered to pregnant rats reduced the mean number of live fetuses per litter and increased the incidence of sternal defects and extra ribs. No other teratogenicity studies were found.

Chlorinated benzenes have been found to retard the growth of fungi, beetles, termites, and snails. Shrimp exposed continuously to 1,3,5-trichlorobenzene at 10 ppm died within a week without producing young.

CHLOROBENZENES

1,2,3-TRICHLOROBENZENE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 87-61-6

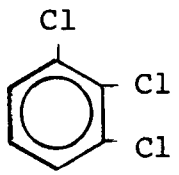
2. NIOSH No.:

3. Synonyms and Trade Names

No information was found in the sources searched.

B. Formulas and Molecular Weight

1. Structural Formula



(HCP 1976)

2. Empirical Formula

$C_6H_3Cl_3$ (HCP 1976)

3. Molecular Weight

181.45 (HCP 1976)

C. Physical Properties

1. Description

White crystals (CCD 1977)

2. Boiling Point

218-219°C (HCP 1976)

3. Melting Point

53-54°C (HCP 1976)

4. Vapor Pressure

1 mm at 40.0°C (HCP 1976)

5. Solubility

Insoluble in water; slightly soluble in alcohol; very soluble in ether, benzene, and carbon disulfide

(HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

No information was found in the sources searched.

D. Composition of the Commercial Product

No information was found in the sources searched.

1,2,3-TRICHLOROBENZENE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

No information was found in the sources searched.

2. Manufacturers

No information was found in the sources searched.

3. Use

As an organic intermediate, in the dyeing industry (CCD 1977, Hites 1973)

4. Occupational Exposure

No information was found in the sources searched.

5. Release

According to Verschueren (1977), 1,2,3-trichlorobenzene is released into water and air as a result of agricultural runoff, termite control operations, the use of transformer oil, and its general use in laboratories.

1,2,3-Trichlorobenzene has been identified as a metabolite of the pesticide lindane in pheasant egg yolks (Saha and Burrage 1976), in a culture of mold grown spontaneously on grated carrots (Engst et al. 1977), and in houseflies (Reed and Forgash 1970).

B. Environmental Fate

1. Occurrence

The U.S. Environmental Protection Agency (USEPA 1977) reported that 1,2,3-trichlorobenzene was measured at 0.021-0.046 mg/liter in municipal discharge entering the Catawba Creek, in North Carolina. According to Lunde (1976), the compound was found in plaice, eel, sprat, whiting, and cod taken off Norway.

Unspecified trichlorobenzenes have been found in the Merrimack River in New England at 0.1-0.5 ppb (Hites 1973). These contaminants are believed to originate from local dye industries. Unspecified trichlorobenzenes have also been identified in longnose suckers (Catostomus catostomus) taken near a Canadian mill effluent (Kaiser 1977) and in sprat (Clupea sprattus) (Lunde and Baumann 1976). They have been found at concentrations ranging from 0.1 to 1.6 mg/liter in water from the Coosa River in Georgia near the cities of Dalton, Calhoun, and Rome.

The U.S. EPA (1977) has reported that unspecified trichlorobenzenes have been measured at concentrations of up to 0.001 mg/liter in U.S. drinking water, at 0.005 mg/liter in the Coosa River, Georgia, and at 0.019-0.46 mg/liter in the Catawba Creek, North Carolina. Young et al. (1976 as reported by USEPA 1977) detected trichlorobenzenes in waste waters from several major municipal areas and in the air of Southern California. Fish from Lake Superior and Lake Huron have been found to contain very small amounts of trichlorobenzene (USEPA 1977).

MacKenzie (1971) reported slight residues of Polystream, which

gradually disappeared, in oysters and clams. Polystream is a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, and is used to reduce snail attack on oysters.

2. Transformation

Pseudomonas bacteria degrade 1,2,3-trichlorobenzene at 200 mg/liter at 30°C with a ring disruption of 87% in 5 days (Verschueren 1977). A mutant strain of the bacteria degrades the compound under the same conditions with a ring disruption of 100% in 43 hours.

Comment: 1,2,3-Trichlorobenzene is a chemically stable solid that is insoluble in water but soluble in fat solvents. It has a boiling point of 218-219°C and a vapor pressure of 1 mm at 40°C. It can react with chemical oxidizing agents (Sax 1975). The compound, if released, could enter the water by transport with soil/sediment and organic detritus systems. Some of the compound may also enter the atmosphere because, like 1,2,4-trichlorobenzene, it may co-distill with water, particularly if it is aerated. As a chlorinated aromatic, it is susceptible to attack by hydroxyl radicals with an estimated half-life (by extrapolation from studies of benzene and chlorinated benzenes) of several days. In view of its chemical properties, however, the compound will probably degrade slowly in the environment and may therefore persist if released in large amounts.

3. Bioaccumulation

According to Jondorf et al. (1955), 62% of 1,2,3-trichlorobenzene administered to rabbits was conjugated and excreted

in the urine during a period of 5 days after dosing. None of the compound was found in the feces. For experimental details, see 1,2,3-Trichlorobenzene, Section III.B.1. De Bruin (1976) suggested that rates of absorption and transformation of the polychlorinated benzenes decline as halogen substitution increases.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, accumulated in the tissues of oysters and clams in small amounts when it was applied to oyster beds at 1.9 hectaliters/hectare. These residues disappeared within 119 days. See 1,2,3-Trichlorobenzene, Section IV.A.4., for a description of experimental details.

Comment: 1,2,3-Trichlorobenzene is chemically stable, insoluble in water, and lipophilic, and it is somewhat volatile. These properties as well as the data on metabolism suggest that the compound is likely to bioaccumulate, but not to as great an extent as the more highly chlorinated benzenes. The findings of low levels of 1,2,3-trichlorobenzene in fish (see 1,2,3-Trichlorobenzenes, Section II.B.1) seem to support this judgment.

1,2,3-TRICHLOROBENZENE

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources seached.

B. Tests on Laboratory Organisms

1. Metabolism

In a study of the metabolism of several polychlorinated benzenes, Kohli et al. (1976) gave intraperitoneal injections of 300 mg of 1,2,3-trichlorobenzene dissolved in 10-15 ml of vegetable oil to an unspecified number of male rabbits, each weighing 4-5 kg. The authors reported that in urine collected for 10 days 11% of the dose was excreted as the metabolite 2,3,4-trichlorophenol, 2% as 3,4,5-trichlorophenyl acetate, and 1% as 2,3,6-trichlorophenol. The authors suggested that these metabolites may have been formed from arene oxides.

Jondorf et al. (1955) reported that 1,2,3-trichlorobenzene was slowly metabolized by rabbits to a major metabolite--2,3,4-trichlorophenol--and to several minor metabolites--3,4,5-trichlorophenol, 3,4,5-trichlorocatechol, and 2,3,4-trichlorophenylmercapturic acid. The authors gave 4.5 g of the compound to three rabbits by stomach tube as a 25% (wt/vol) solution in arachis oil. In the 5 days after dosing, 62% of the dose appeared in the urine as conjugates of glucuronic acid (50%) and sulfuric acid (12%).

Safe et al. (1976) investigated the metabolism of chlorinated aromatic compounds by the frog (Rana pipiens). They dissolved 80 mg of 1,2,3-trichlorobenzene in 4-5 ml of vegetable oil and administered it intraperitoneally in equal quantities to four animals. They reported that approximately 1% of the dose was excreted in the course of 8 days as 2,3,4-trichlorophenol. No other urinary metabolites were detected.

2. Toxic Effects

a. Acute Toxicity

No information was found in the sources searched.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the source searched.

e. Other Toxicity

Ariyoshi et al. (1975a) investigated the effects of 1,2,3-trichlorobenzene on rats. They gave six female Wistar rats oral doses of 250 mg/kg of the substance in 2% tragacanth gum solution once a day for 3 days. The rats were sacrificed 24 hours after the last dose was administered and their livers removed. The authors reported statistically significant increases in the concentrations of cytochrome P-450, micro-

somal phosphorus, and microsomal protein in the liver. They found no effects on liver weight or on glycogen and triglyceride levels.

Rimington and Ziegler (1963) administered chlorinated benzenes to rats to induce experimental hepatic porphyria. They gave three male albino rats 1,2,3-trichlorobenzene at 785 mg/kg by gastric intubation daily for 7 days and measured porphyrins and porphyrin precursors in 24-hour urine samples. The levels of coproporphyrin, uroporphyrin, porphobilinogen, and delta-aminolevulic acid were higher in the exposed rats than in a control group of five male albino rats. The exposed rats lost weight and showed loss of appetite. Highly porphyric rats commonly showed extreme weakness, ataxia, clonic contractions, and enlarged livers. Histologic examination revealed degenerated liver cells but no actual necrosis.

IV. ENVIRONMENTAL EFFECTS

A. ECOLOGICAL EFFECTS

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Safe et al. (1976) reported that approximately 1% of an intraperitoneally administered dose of 1,2,3-trichlorobenzene was converted to metabolites by the frog (Rana pipiens). Comment: The experimental design and mode of exposure in this study were not appropriate for the determination of toxic effects. For experimental details, see 1,2,3-Trichlorobenzene, Section III.B.1.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, was toxic to pipefish (Syngnathus fuscus) and mummichogs (Fundulus heteroclitus) when applied to oyster beds at 1.9 hectaliters/hectare. See 1,2,3-Trichlorobenzene, Section IV.A.4, for further details.

4. Invertebrates

Loosanoff et al. (1960a and 1960b as reported by MacKenzie 1971) reported that trichlorinated benzenes are

toxic to several species of marine gastropods, including the thick-lipped drill (Eupleura caudata) and the Atlantic oyster drill (Urosalpinx cinerea). MacKenzie did not provide further details.

MacKenzie (1971) studied the efficacy of chlorinated benzenes in killing oyster drills (snails that prey on oysters). Polystream, a mixture of polychlorinated benzenes containing a minimum of 95% active trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene was used. Polystream was mixed with dry sand or a granular clay that carried it to the bottom and dispersed it. The rate of application was 1.9 hectaliters/hectare of oyster bed. When water current velocities were low, all oyster drills were killed. At water current velocities between 0.9 and 2.7 km/hr, 66-85% of the drills died. When the current was strong, the Polystream was dispersed and therefore no deaths were observed. At low water velocity, significant numbers of small clams and other invertebrates were killed. The growth of oysters appeared normal in the treated beds.

Davis and Hidu (1969) studied the effect of an unspecified trichlorobenzene or mixture of trichlorobenzenes on the embryonic development of the hard clam (Mercenaria mercenaria) and the American oyster (Crassostrea virginica) and on the survival and growth of the hard clam at the larval stage. Acetone was used as the solvent. According to the authors, the percentage of eggs that developed normally in clams exposed at 1 and 10 ppm was 72 and 58%, respectively, of the per-

centage that developed normally in controls. The survival rate of clam larvae exposed at the two concentrations was 108 and 69%, respectively, of the survival rate of controls. There was no significant effect on the mean length of clam larvae at either concentration. The percentage of eggs that developed normally in oysters exposed at 1 and 10 ppm was 59 and 21%, respectively, of the percentage that developed normally in controls.

According to Verschueren (1977), 1,2,3-trichlorobenzene is used to control termites. Gibson (1957 as reported by USEPA 1977) reported that an unspecified trichlorobenzene mixed in a 1-5 ratio with diesel oil was 100% lethal to the Douglas Fir beetle (Dendroctonus pseudotsugae).

5. Plants and Algae

Richardson (1968 as reported by USEPA 1977) reported that an unspecified trichlorobenzene retarded the radial growth of the fungi Pythium ultimum, Rhizoctonia solani, and Trichoderma viride. No experimental details were given.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

1,2,4-TRICHLOROBENZENE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 120-82-1

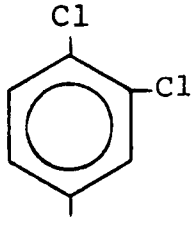
2. NIOSH No.: DC21000

3. Synonyms and Trade Names

unsym-Trichlorobenzene (NIOSH 1977)

B. Formulas and Molecular Weight

1. Structural Formula



(HCP 1976)

2. Empirical Formula

$C_6H_3Cl_3$ (HCP 1976)

3. Molecular Weight

181.45 (HCP 1976)

C. Physical Properties

1. Description

Colorless, stable liquid (CCD 1977)

2. Boiling Point

213.5°C (HCP 1976)

3. Melting Point

16.95°C (HCP 1976)

4. Vapor Pressure

1 mm at 38.4°C (HCP 1976)

5. Solubility

Insoluble in water; slightly soluble in alcohol; very soluble in ether (HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.4542^{20}_{4} (HCP 1976)

D. Composition of the Commercial Product

No information was found in the sources searched.

1,2,4,-TRICHLOROBENZENE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

15.6 million lb (1972) (USITC 1972)

Listed by the USITC under the section "Cyclic Intermediates," but no production data given (USITC 1976)

2. Manufacturers

Dow Chemical Co. (USITC 1976)

3. Use

As a solvent in chemical manufacturing; in dyes and intermediates; as a dielectric fluid; in synthetic transformer oils; in lubricants; as a heat-transfer medium; in insecticides

(CCD 1976)

4. Occupational Exposure

Rank: 1657

Estimated number of persons exposed: 5,000*

*rough estimate

(NOHS 1976)

5. Release

1,2,4-Trichlorobenzene has been identified as a metabolite of the pesticide lindane in pheasant egg yolks and chicks (Saha and Burrage 1976), in houseflies (Reed and Forgash 1970), and in a cul-

ture of mold grown spontaneously on grated carrots (Engst et al. 1977).

1,2,4-Trichlorobenzene has been identified in textile waste effluents (see 1,2,4-Trichlorobenzene, Section II.B.1) (Erisman and Gordon 1975 as reported by USEPA 1977).

B. Environmental Fate

1. Occurrence

Erisman and Gordon (1975 as reported by USEPA 1977) detected 1,2,4-trichlorobenzene in textile waste effluents. The compound has also been measured in monitorings of industrial discharges into the Catawba River, North Carolina (0.012 mg/liter) and the Chattanooga Creek, Tennessee (0.5 mg/liter), in waste waters from several major municipal areas (<0.01-275 µg/liter), in river water after surface runoff (0.007 mg/liter), and in the atmosphere (USEPA 1977).

Traces of three trichlorobenzenes, mostly 1,2,4-trichlorobenzene, were detected in bread and breakfast cereals (Westoo et al. 1971). The chemicals were reported to be residues formed from the pesticide lindane during baking.

For information on the occurrence of unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section II.B.1.

2. Transformation

Simmons et al. (1976) reported that 1,2,4-trichlorobenzene is biodegradable in waste-water treatment plants. The extent of biodegradation of the chlorinated benzenes, like that of many

other organic compounds, is dependent on its residence time as well as the concentration of effective microorganisms in the system. Prior exposure to 1,2,4-trichlorobenzene led to an increase in the population of effective microorganisms and thus an increased biodegradation rate. The authors also showed that more than 65% of 1,2,4-trichlorobenzene in the waste water of a textile finishing plant was removed in a well-aerated basin with a 5-day retention. Removal from another industrial waste-water treatment plant was found to be about 75% in activated sludge with a 6-hour retention.

Garrison and Hill (1972 as reported by USEPA 1977) reported that 1,2,4-trichlorobenzene at 100 g/liter volatilized from aerated water in less than 4 hours.

Pseudomonas bacteria degrade 1,2,4-trichlorobenzene at 200 mg/liter at 30°C with a ring disruption of 92% in 5 days. A mutant strain degrades the compound under the same conditions with a ring disruption of 100% in 46 hours (Verschueren 1977). BOD_{20} values for 1,2,4-trichlorobenzene were reported to be 78, 100, and 50% of the theoretical value, depending on the source of the microorganisms used for biodegradation (USEPA 1977).

1,2,4-Trichlorobenzene is susceptible in air to attack by hydroxyl radicals and its half-life in the atmosphere has been estimated by extrapolation from studies of benzene and chlorobenzenes to be from one to several days (Simmons et al. 1976).

Comment: Some of these data as well as the chemical and physical properties of 1,2,4-trichlorobenzene indicate that, if released, it may enter the atmosphere as well as water (by trans-

port with soil/sediment and organic detritus systems). It is likely to degrade slowly in the environment and therefore may persist if released in large amounts.

3. Bioaccumulation

According to Jondorf et al. (1955), 38% of a dose of 1,2,4-trichlorobenzene administered to rabbits was conjugated and excreted in the urine during a period of 5 days after dosing. None of the compound was found in the feces. For experimental details, see 1,2,4-Trichlorobenzene, Section III.B.1. De Bruin (1976) suggested that rates of absorption and transformation of the polychlorinated benzenes decline as halogen substitution increases.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, accumulated in the tissues of oysters and clams when it was applied to oyster beds at 1.9 hectaliters/hectare. The residues disappeared within 119 days. See 1,2,3-Trichlorobenzene, Section IV.A.4, for a description of experimental details.

Comment: 1,2,4-Trichlorobenzene is chemically stable, insoluble in water, and lipophilic, and it is somewhat volatile. These properties as well as the data on metabolism given above suggest that the compound is likely to bioaccumulate, but not to as great an extent as the more highly chlorinated benzenes. The findings of low levels of trichlorobenzenes in fish (see 1,2,3-Trichlorobenzene, Section II.B.1) seem to support this judgment.

1,2,4-TRICHLOROBENZENE

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Organisms

1. Metabolism

In a study of the metabolism of several polychlorinated benzenes, Kohli et al. (1976) gave intraperitoneal injections of 300 mg of 1,2,4-trichlorobenzene dissolved in 10-15 ml of vegetable oil to an unspecified number of male rabbits, each weighing 4-5 kg. The authors reported that in urine collected for 10 days 6% of the dose was excreted as the metabolite 2,3,5-trichlorophenol and 5% as 2,4,5-trichlorophenol. The authors suggested that these metabolites may have been formed from arene oxides.

Jondorf et al. (1955) reported that 1,2,4-trichlorobenzene was slowly metabolized by rabbits to two major metabolites--2,4,5- and 2,3,5-trichlorophenol--and to several minor metabolites--3,4,6-trichlorocatechol, 2,3,5-trichlorophenylmercapturic acid, and 2,4,5-trichlorophenylmercapturic acid. The authors gave 6 g of the compound to three rabbits by stomach tube as a 25% (wt/vol) solution in arachis oil. In the 5 days after dosing, 38% of the dose appeared in the urine as oxygen conjugates.

Safe et al. (1976) investigated the metabolism of chlorinated aromatic compounds by the frog (Rana pipiens). They dis-

solved 80 mg of 1,2,4-trichlorobenzene in 4-5 ml of vegetable oil and administered it intraperitoneally in equal quantities to four animals. The only excretory metabolite identified in the course of 8 days was 2,4,5-trichlorophenol, which accounted for approximately 0.7% of the original dose.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of 1,2,4-trichlorobenzene, as reported by the NIOSH RTECS data base (1978) and by Brown et al. (1969), is given in Table III-1:

TABLE III-1

ACUTE TOXICITY OF 1,2,4-TRICHLOROBENZENE

Parameter	Dosage	Animal	Route
LD50[1,2]	756 mg/kg	Rat	Oral
LD50[1,2]	766 mg/kg	Mouse	Oral
LD50[2]	6,139 mg/kg	Rat	Percutaneous
LDLo[1]	500 mg/kg	Mouse	Intraperitoneal

[1]NIOSH (1978)
[2]Brown et al. (1969)

Yang and Peterson (1977) reported that male Holtzman rats injected intraperitoneally with 1,2,4-trichlorobenzene (5 mmoles/kg) exhibited greater bile duct pancreatic fluid flow and lower pancreatic fluid protein concentration than did control rats.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

Smith et al. (1978) detected no evidence of mutagenic activity by 1,2,4-trichlorobenzene or its metabolites. The abstract of the study did not provide any experimental details.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Coate et al. (1977) exposed groups of 30 male Sprague-Dawley albino rats, 16 male New Zealand white rabbits, and 9 male cynomolgus monkeys to 1,2,4-trichlorobenzene by inhalation at concentrations of 25, 50, and 100 ppm. The exposures were for 7 hours/day, 5 days/week, for 26 weeks. A control group was exposed to air. Five rats from each group were sacrificed after 13 weeks. All surviving animals were sacrificed after 26 weeks. The authors reported that the exposures caused no changes in hematological and serum biochemical test results or in body weights and survival. They found no effects of exposure on pulmonary function and operant behavior tests in monkeys and in ophthalmoscopic examinations in rabbits and monkeys. No exposure-related abnormalities or other effects were apparent in the tissues from animals exposed for 26 weeks, although microscopic examination showed changes in the livers and kidneys of rats killed after 4

and 13 weeks of exposure. These included enlarged hepatocytes in rats exposed at 50 and 100 ppm. Other changes, which were reported not to be dose-related, included slightly increased vacuolation of hepatocytes, granuloma formation, and increased biliary hyperplasia in livers and hyaline degeneration in the inner zone of the kidney cortex.

Carlson and Tardiff (1976) administered oral doses of 1,2,4-trichlorobenzene, once a day, for 14 days to groups of six male albino rats. The dosages were 0, 150, 300, and 600 mg/kg/day. The compound was not lethal during the 14 days of dose administration, but one rat exposed at 600 mg/kg/day died during the 2 weeks of observation after the last dose. At all the dose levels, the compound was not considered hepatotoxic, as judged by serum isocitrate dehydrogenase activity. Liver glucose-6-phosphatase activity was decreased in rats given 300 mg/kg/day or higher doses. Induced metabolism of xenobiotics was indicated by significantly decreased hexobarbital sleeping time after 14 days of dosage at 600 mg/kg/day. 1,2,4-Trichlorobenzene was a potent microsomal enzyme inducing agent in rats given oral doses of 10-40 mg/kg/day for 14 days. The authors also reported dose-related increases in glucuronyltransferase and azoreductase activities and oxy-ethyl oxy-para-nitrophenyl phenylphosphonothioate (EPN) detoxification. A dose-related increase in liver to body-weight ratio substantiated these biochemical findings.

Ariyoshi et al. (1975a) also investigated the effects of 1,2,4-trichlorobenzene on rats. They gave six female Wistar rats oral doses of 250 mg/kg of the substance in 2% tragacanth gum

solution once a day for 3 days. The rats were sacrificed 24 hours after the last dose was administered and their livers were removed for biochemical analyses. The authors reported increased activities of drug-metabolizing enzymes and statistically significant increases in the concentrations of cytochrome P-450, microsomal phosphorus, and microsomal protein in the liver. The rats' liver weights increased markedly, although the concentrations of glycogen and triglyceride were not affected.

Rimington and Ziegler (1963) administered chlorinated benzenes to rats to induce experimental hepatic porphyria. They gave three male albino rats 1,2,4-trichlorobenzene at 730 mg/kg by gastric intubation daily for 15 days and measured porphyrins and porphyrin precursors in 24-hour urine samples. The levels of coproporphyrin, uroporphyrin, porphobilinogen, and delta-aminolevulic acid were higher in the exposed rats than in a control group of five male albino rats. The rats lost weight and showed loss of appetite. Highly porphyric rats commonly showed extreme weakness, ataxia, clonic contractions, and enlarged livers. Histologic examination revealed degenerated liver cells but no actual necrosis.

Carlson (1977) found that porphyria did not develop in rats administered 1,2,4-trichlorobenzene in corn oil orally at concentrations of 50, 100, and 200 mg/kg. Groups of five female rats were given the substance for 30, 60, 90, or 120 days. Liver weights increased, but there were only minor increases in liver porphyrins. Urinary excretion of delta-aminolevulic acid and porphobilinogen did not differ from that in control animals.

Smith et al. (1978) gave rhesus monkeys single daily oral doses of 1,2,4-trichlorobenzene at 1-173.6 mg/kg. (The abstract did not specify the duration of the exposure period.) The authors reported that the substance was apparently nontoxic at 25 mg/kg or lower but was toxic at 90 mg/kg or higher. When given 173.6 mg/kg, monkeys showed severe weight loss and fine tremors and died within 20-30 days. Monkeys that received the higher doses showed evidence of hepatic induction, including a shift in the pattern of urinary chlorguanide metabolites and increased clearance of labeled 1,2,4-trichlorobenzene administered intravenously.

Brown et al. (1969) reported that 1,2,4-trichlorobenzene was unlikely to produce dermatitis in rabbits or guinea pigs unless contact was repetitive or prolonged. For 3 consecutive days, they placed 1 ml of the substance on the back of each of four male and four female rabbits. For 5 days/week for 3 weeks, they placed 1 ml on the back of a male rabbit, 1 ml on a female rabbit, and 0.5 ml on each of five male and five female guinea pigs. The authors observed fissuring, which they considered a typical result of degreasing. In histopathological examinations, the skin from the rabbits exposed for 3 weeks showed spongiosis, acanthosis, parakeratosis, and inflammation of the superficial dermis. Some of the exposed guinea pigs had convulsions and died. Their livers contained necrotic foci.

Powers et al. (1975) applied 0.2 ml of 1,2,4-trichlorobenzene on the inner surfaces of rabbits' ears. Three groups of 12 rabbits received applications of 5, 25, and 100% 1,2,4-

trichlorobenzene, three times a week, for 13 weeks. The authors reported that the repeated applications caused no systemic effects or visceral lesions. Rats exposed to the substance at 25 and 100% showed no evidence of acneform dermatitis but did have moderate to severe skin irritation characterized by erythema, scaling, desquamation, encrustation, slight enlargement of follicles, and some hair loss and scarring. Skin biopsy samples showed dermal irritation with slight to moderate acanthosis and hyperkeratosis.

1,2,4-TRICHLOROBENZENE

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

NIOSH (1977) reported that the Aquatic Toxicity Rating (96-hr TLm, species unspecified) of 1,2,4-trichlorobenzene is 10-1 ppm.

Safe et al. (1976) reported that approximately 0.7% of an intraperitoneally administered dose of 1,2,4-trichlorobenzene was converted to metabolites by the frog (Rana pipiens). Comment: The experimental design and mode of exposure in this study were not appropriate for the determination of toxic effects. For experimental details, see Section III.B.1.

For data on unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section IV.A.3.

4. Invertebrates

For data on unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section IV.A.4.

5. Plants and Algae

For data on unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section IV.A.5.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

N. Ito of the First Department of Pathology, Nagoya City University Medical School, Nagoya, Japan, has completed a study of the effects on ICR mice of exposure to 1,2,4-trichlorobenzene by intragastric injection (WHO 1978). The results of the study have not yet been published.

1,3,5-TRICHLOROBENZENE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 108-70-3

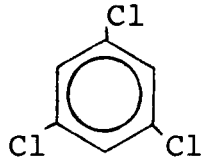
2. NIOSH No.:

3. Synonyms and Trade Names

No information was found in the sources searched.

B. Formulas and Molecular Weight

1. Structural Formula



(HCP 1976)

2. Empirical Formula

$C_6H_3Cl_3$ (HCP 1976)

3. Molecular Weight

181.45 (HCP 1976)

C. Physical Properties

1. Description

Crystals (Merck 1976)

2. Boiling Point

208°C (HCP 1976)

3. Melting Point

63-64°C (HCP 1976)

4. Vapor Pressure

10 mm at 78°C (HCP 1976)

5. Solubility

Slightly soluble in alcohol; insoluble in water; very soluble in ether, benzene, carbon disulfide, and ligroin

(HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

No information was found in the sources searched.

D. Composition of the Commercial Product

No information was found in the sources searched.

1,3,5-TRICHLOROBENZENE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

No information was found in the sources searched.

2. Manufacturers

No information was found in the sources searched.

3. Use

No information was found in the sources searched.

4. Occupational Exposure

Rate: 3713

Estimated number of persons exposed: 3,000*

*rough estimate (NOHS 1976)

5. Release

1,3,5-Trichlorobenzene has been identified as a metabolite of the pesticide lindane in pheasant egg yolks (Saha and Burrage 1976) and in a culture of mold grown spontaneously on grated carrots (Engst et al. 1977).

The compound has been identified in industrial discharge (see 1,3,5-Trichlorobenzene, Section II.B.1.)

B. Environmental Fate

1. Occurrence

The U.S. EPA (1977) reported that 1,3,5-trichlorobenzene was found at 0.026 mg/liter in industrial waste discharged into the Holston River, Tennessee. Trace amounts at concentrations of up to 0.9 mg/liter have been detected by Young et al. (1976 as reported by USEPA 1977) in waste waters from several major municipal areas and in the air of southern California. The chemical was found in extracts of plaice, eel, sprat, whiting, and cod taken off Norway (Lunde 1976). It has also been identified as a harmful substance in Rhine water (Jacobs et al. 1974).

For information on the occurrence of unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section II.B.1.

2. Transformation

Pseudomonas bacteria degrade 1,3,5-trichlorobenzene at 200 mg/liter at 30°C with a ring disruption of 78% in 120 hours (Verschueren 1977). A mutant strain of the bacteria degrades the compound under the same conditions with a ring disruption of 100% in 43 hours.

Comment: 1,3,5-Trichlorobenzene is a chemically stable solid that is insoluble in water but soluble in fat solvents. It has a boiling point of 208°C and a vapor pressure of 10 mm at 78°C. The compound, if released, could enter the water by transport with soil/sediment and organic detritus systems. Some of the compound may also enter the atmosphere because, like 1,2,4-trichlorobenzene, it may codistill with water, particularly if it is aerated. As a

chlorinated aromatic, it is susceptible to attack by hydroxyl radicals with an estimated half-life (by extrapolation from studies of benzene and chlorinated benzenes) of several days. In view of its chemical properties, however, the compound will probably degrade slowly in the environment and may therefore persist if released in large amounts.

3. Bioaccumulation

According to Jondorf et al. (1955), 23% of 1,3,5-trichlorobenzene administered to rabbits was conjugated and excreted in the urine during a period of 5 days after dosing. For experimental details, see 1,3,5-Trichlorobenzene, Section III.B.1. De Bruin (1976) suggested that rates of absorption and transformation of the polychlorinated benzenes decline as halogen substitution increases.

Jacobs et al. (1974), reported that 1,3,5-trichlorobenzene given orally to rats at 2 mg/kg/day accumulated more in the fat than in the liver, kidney, heart, or blood.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, accumulated in the tissues of oysters and clams in small amounts when it was applied to oyster beds at 1.9 hectaliters/hectare. These residues disappeared within 119 days. See 1,2,3-Trichlorobenzene, Section IV.A.4, for a description of experimental details.

Comment: 1,3,5-Trichlorobenzene is chemically stable, insoluble in water, and lipophilic, and it is somewhat volatile.

These properties as well as the data on metabolism given above suggest that the compound is likely to bioaccumulate, but not to as great an extent as the more highly chlorinated benzenes. The findings of low levels of 1,3,5-trichlorobenzene in fish (see 1,3,5-Trichlorobenzene Section II.B.1) seem to support this judgment.

1,3,5-TRICHLOROBENZENE

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Organisms

1. Metabolism

In a study of the metabolism of several polychlorinated benzenes, Kohli et al. (1976) gave intraperitoneal injections of 300 mg of 1,3,5-trichlorobenzene dissolved in 10-15 ml of vegetable oil to an unspecified number of male rabbits, each weighing 4-5 kg. The authors reported that in urine collected for 10 days 1.4% of the dose was excreted as the metabolite 2,3,5-trichlorophenol and 3% as 2,4,6-trichlorophenol. The authors suggested that these metabolites may have been formed from arene oxide intermediates.

In an earlier study, Parke and Williams (1960) administered 1,3,5-trichlorobenzene orally at 0.5 g/kg to female rabbits. They reported that the compound was oxidized to a small extent to 2,4,6-trichlorophenol and excreted in the urine. They also obtained chromatographic evidence that 4-chlorophenol and 4-chlorocatechol were minor urinary metabolites. They suggested that the formation of phenols indicated that the compound was in part dechlorinated to chlorobenzene, possible by gut bacteria. They identified monochlorobenzene in exhaled air 3-4 days after treatment and they found evidence of chlorobenzene in the tissues. In the two animals, 13 and 1.5% of the administered dose was eliminated un-

changed in the feces and 12 and 8.5% in expired air. According to the authors, the main bulk of the 1,3,5-trichlorobenzene was found unchanged in the gut contents (19 and 18%) and the tissues (5% in the pelt, 5 and 4.5% in depot fat, 22 and 20% in the rest of the body).

Jondorf et al. (1955) reported that 1,3,5-trichlorobenzene was very slowly metabolized by rabbits to 2,4,6-trichlorophenol, a major metabolite. The authors gave 1.5 g of the compound to six rabbits by stomach tube as a 25% (wt/vol) solution in arachis oil. In the 5 days after dosing, 23% of the dose appeared in the urine as oxygen conjugates. Unchanged 1,3,5-trichlorobenzene was found in the feces.

Jacobs et al. (1974) reported that 1,3,5-trichlorobenzene given orally to rats at 2 mg/kg/day accumulated more in the fat than in the liver, kidney, heart, or blood.

Safe et al. (1976) investigated the metabolism of chlorinated aromatic compounds by the frog (Rana pipiens). They dissolved 80 mg of 1,3,5-trichlorobenzene in 4-5 ml of vegetable oil and administered it equally by intraperitoneal injection to four animals. They reported that approximately 0.7% of the dose was excreted in the course of 8 days as 2,4,6-trichlorophenol. No other metabolites were detected.

2. Toxic Effects

a. Acute Toxicity

No information was found in the sources searched.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Ariyoshi et al. (1975a) investigated the effects of 1,3,5-trichlorobenzene on rats. They gave six female Wistar rats oral doses of 250 mg/kg of the substance in 2% tragacanth gum solution once a day for 3 days. The rats were killed 24 hours after the last dose and their livers were removed. The authors reported statistically significant increases in aminopyrine demethylase activity and in the concentrations of microsomal phosphorus and protein in the liver. They found no effects on liver weight or on glycogen and triglyceride levels.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Safe et al. (1976) reported that approximately 0.7% of an intraperitoneally administered dose of 1,3,5-trichlorobenzene was converted to metabolites by the frog (Rana pipiens). Comment: The experimental design and mode of exposure in this study were not appropriate for the determination of toxic effects. For experimental details, see 1,3,5-Trichlorobenzene, Section III.B.1.

4. Invertebrates

Grosch (1973) exposed groups of 10 pairs of male and female shrimp (Artemia salina) to 1,3,5-trichlorobenzene at 10 ppm in water for 24 hours. He reported a statistically significant decrease in the life span of the females, a delay of more than a week in the appearance of the first broods, and significant decreases in the average number of broods per pair and the average number of zygotes produced. All shrimp in several populations of 80 each exposed continuously at 10 ppm died within a week without producing young.

Grosch and Hoffman (1973) exposed two groups of virgin female wasps (Bracon hebetor) to 1,3,5-trichlorobenzene. The first group received injections into the abdomen of 0.5 µl of a 10 ppm solution of the compound in acetone. The second group was left overnight in a shell vial whose interior walls had been coated with the compound. In both groups the authors reported a marked increase in death of embryos in eggs deposited from the 4th to the 12th day after treatment. The average life spans of the wasps decreased somewhat. Associated with poor hatching was an increase in the proportion of embryos dying during cleavage. Grosch and Hoffman suggested that 1,3,5-trichlorobenzene induced defects in the mitotic apparatus of the wasps.

For data on unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section IV.A.4.

5. Plants and Algae

For data on unspecified trichlorobenzenes, see 1,2,3-Trichlorobenzene, Section IV.A.5.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

TRICHLOROBENZENE

NIH/EPA (1978) reports a CAS No. of 12002-48-1 for an unspecified trichlorobenzene. It lists Pyranol 1478 as a synonym.

In the National Occupational Hazard Survey (1976), it is estimated that 1,081,000 workers are exposed to trichlorobenzene, which gives it a rank of 191. No indication is given of which isomer or isomers are represented by these figures, but there are separate entries in the survey for the 1,2,4 and the 1,3,5 isomers.

According to the USITC (1976), PPG Industries produces a mixture of 1,2,3- and 1,2,4-trichlorobenzene.

Unspecified trichlorobenzenes have been identified in longnose suckers (Catostomus catostomus) (Kaiser 1977) and sprat (Clupea sprattus) (Lunde and Baumann 1976).

See 1,2,3-Trichlorobenzene, Sections II.B.3, IV.A.3, and IV.A.4, for information on the effects of Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene. 1,2,3-Trichlorobenzene, Section IV.A.4, also contains information on the effects of unspecified isomers of trichlorobenzene on invertebrates.

Information on specific isomers can be found in the respective sections of this dossier.

1,2,3,4-TETRACHLOROBENZENE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

CAS No.: 634-66-22

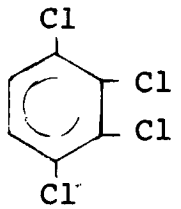
NIOSH No.:

Synonyms and Trade Names

No information was found in the sources searched.

B. Formulas and Molecular Weight

Structural Formula



(HCP 1976)

Empirical formula

$C_6H_2Cl_4$ (HCP 1976)

Molecular Weight

215.90 (HCP 1976)

C. Physical Properties

Description

White crystals (CCD 1977)

2. Boiling Point

254°C (HCP 1976)

3. Melting Point

47.5°C (HCP 1976)

4. Vapor Pressure

1 mm at 68.5°C (HCP 1976)

5. Solubility

Insoluble in water; slightly soluble in cold alcohol; soluble in hot alcohol; very soluble in ether, acetic acid, carbon disulfide, and ligroin (HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

No information was found in the sources searched.

D. Composition of the Commercial Product

No information was found in the sources searched.

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

No information was found in the sources searched.

2. Manufacturers

No information was found in the sources searched.

3. Use

As a component of dielectric fluids; in synthesis (CCD 1977)

An unspecified tetrachlorobenzene used in the pesticide Polystream (MacKenzie 1971)

4. Occupational Exposure

No information was found in the sources searched.

5. Release

1,2,3,4-Tetrachlorobenzene has been identified as a metabolite of the pesticide lindane in pheasant eggs and chicks (Saha and Burrage 1976), in flies (Reed and Forgash 1970), and in a culture of mold grown spontaneously on grated carrots (Engst et al. 1977). An unspecified tetrachlorobenzene may be released as a result of its use in the pesticide Polystream (see 1,2,3,4-Tetrachlorobenzene, Section II.B.1).

Plimmer and Klingebiel (1976) reported that photolysis of

hexachlorobenzene in methanol at wavelengths greater than 260 nm or in hexane at wavelengths greater than 220 nm produced tetrachlorobenzene.

B. Environmental Fate

1. Occurrence

1,2,3,4-Tetrachlorobenzene has been found in plaice, eel, sprat, whiting, and cod taken off Norway (Lunde 1976). Unspecified tetrachlorobenzene isomers have been identified in longnose suckers (Catostomus catostomus) taken near a Canadian mill effluent (Kaiser 1977) and in sprat (Lunde and Baumann 1976).

MacKenzie (1971) reported slight residues of Polystream, which gradually disappeared, in oysters and clams. Polystream is a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, and is used to reduce snail attack on oysters.

2. Transformation

Pseudomonas bacteria degrade 1,2,3,4-tetrachlorobenzene at 200 mg/liter at 30°C with a ring disruption of 33% in 5 days (Verschueren 1977). A mutant strain of the bacteria degrades the compound under the same conditions with a ring disruption of 74%.

Comment: 1,2,3,4-Tetrachlorobenzene is a solid that is insoluble in water and soluble in fat solvents. Its vapor pressure at 68.5°C is 1 mm and, like the other chlorinated benzenes, it can react with oxidizing agents. These properties

as well as the transformation data given above indicate that the compound, if released, could enter the water by transport with soil/sediment and organic detritus. Degradation is likely to be slow and the compound could become a pollutant if released in large amounts. Because it is less volatile, more stable, and less biodegradable than the trichlorobenzenes, it is likely to be more persistent.

3. Bioaccumulation

According to Jondorf (1958), about 43% of 1,2,3,4-tetrachlorobenzene administered to rabbits was oxidized to 2,3,4,5-tetrachlorophenol and excreted in the urine. During a period of 6 days after dosing, 10% of the dose was found in the tissues, 5% in the feces, and 8% in the expired air. See also 1,2,3,4-Tetrachlorobenzene, Section IV.B.1. De Bruin (1976) suggested that rates of absorption and transformation of the polychlorinated benzenes decline as halogen substitution increases.

Jacobs et al. (1974) reported that 1,2,3,4-tetrachlorobenzene accumulated by a factor of about 100 times the daily dose in the fat of rats fed the compound at 2 mg/kg body weight/day for 12 weeks.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, accumulated in the tissues of oysters and clams in small amounts when it was applied to oyster beds at 1.9 hectaliters/hectare. These residues disappeared within 119 days. See 1,2,3-Trichloro-

benzene, Section IV.A.4., for a description of experimental details.

Comment: 1,2,3,4-Tetrachlorobenzene is stable, insoluble in water, and highly lipophilic, and it has only slight volatility. These properties as well as the data on metabolism and bioaccumulation given above indicate that it has a definite potential for bioaccumulation. In general, the tetrachlorobenzenes bioaccumulate more than the trichlorobenzenes.

1,2,3,4-TETRACHLOROBENZENE

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Test on Laboratory Organisms

1. Metabolism

In a study of the metabolism of several polychlorinated benzenes, Kohli et al. (1976) gave intraperitoneal injections of 300 mg of 1,2,3,4-tetrachlorobenzene dissolved in 10-15 ml of vegetable oil to an unspecified number of male rabbits, each weighing 4-5 kg. The authors reported that in urine collected for 10 days 20% of the dose was excreted as the metabolite 2,3,4,5-tetrachlorophenol and 2% as 2,3,4,6-tetrachlorophenol. The authors suggested that these metabolites may have been formed from arene oxides.

In an earlier study, Jondorf et al. (1958) administered 1,2,3,4-tetrachlorobenzene at 0.5 g/kg orally to female rabbits. They reported that the compound was slowly metabolized. Approximately 43% was oxidized to 2,3,4,5-tetrachlorophenol in 6 days and excreted in the urine, partly in free form and partly conjugated. In the same period, 8% of the administered dose was expired unchanged and 5% was eliminated unchanged in the feces. Analyses of tissues after 6 days revealed 0.1% of the dose in the liver, 2% in the skin, 5% in the depot fat, 0.5% in gut contents, and 2% in the rest of the body. The

compound was not detected in the brain. The authors suggested that some dechlorination (2%) took place in the gut.

According to Jacobs et al. (1974), 1,2,3,4-tetrachlorobenzene administered orally to rats at 5 mg/kg/day in a mixture of several environmental pollutants accumulated in the fat and to a lesser extent the liver, kidney, heart, and blood.

Safe et al. (1976) investigated the metabolism of chlorinated aromatic compounds by the frog (Rana pipiens). They dissolved 80 mg of 1,2,3,4-tetrachlorobenzene in 4-5 ml of vegetable oil and administered it intraperitoneally in equal parts to four animals. They reported that less than 1% of the dose was excreted in the course of 8 days as 2,3,4,6-tetrachlorophenol. No other metabolites were detected.

2. Toxic Effects

a. Acute Toxicity

No information was found in the sources searched.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Ariyoshi et al. (1975a) investigated the effects of 1,2,3,4-tetrachlorobenzene on rats. They gave six female Wistar rats oral doses of 250 mg/kg of the substance in 2% tragacanth gum solution once a day for 3 days. The rats were sacrificed 24 hours after the last dose was administered and their livers were removed. The authors reported statistically significant increases in the concentrations of cytochrome P-450 and microsomal protein in the liver. They found significantly increased delta-aminolevulic acid synthetase activity, which they suggested was related to changes in cytochrome P-450, and increased aminopyrine demethylase activity. Mean liver weight was significantly increased, although glycogen content was decreased.

Rimington and Ziegler (1963) administered chlorinated benzenes to rats to induce experimental hepatic porphyria. They gave three male albino rats 1,2,3,4-tetrachlorobenzene at 660 mg/kg by gastric intubation daily for 10 days and measured porphyrins and porphyrin precursors in 24-hour urine samples. The levels of coproporphyrin, uroporphyrin, porphobilinogen, and delta-aminolevulic acid were higher in the exposed rats than in a control group of five male albino rats. The rats lost weight and showed loss of appetite. Highly porphyric rats commonly showed extreme weakness, ataxia, clonic contractions, and enlarged livers. Histologic examination revealed degenerated liver cells but no actual necrosis.

1,2,3,4-TETRACHLOROBENZENE

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Safe et al. (1976) reported that less than 1% of an administered dose of 1,2,3,4-tetrachlorobenzene was converted to metabolites by the frog (Rana pipiens). Comment: The experimental design and mode of exposure in this study were not appropriate for the determination of toxic effects. For experimental details, see 1,2,3,4-Tetrachlorobenzene, Section III.B.1.

For the effects of Polystream, which contains an unspecified tetrachlorobenzene, see 1,2,3-Trichlorobenzene, Section IV.A.3.

4. Invertebrates

Loosanoff et al. (1960a and 1960b as reported by MacKenzie 1971) reported that tetrachlorinated benzenes are toxic to several species of marine gastropods, including the thick-lipped drill (Eupleura caudata) and the Atlantic oyster drill (Urosalpinx cinerea). MacKenzie did not provide further details.

For the effects of Polystream, which contains an unspecified tetrachlorobenzene, see 1,2,3-Trichlorobenzene, Section IV.A.4.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

1,2,4,5-TETRACHLOROBENZENE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 95-94-3

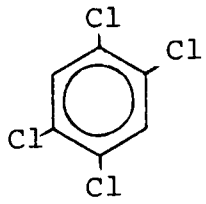
2. NIOSH No.: DB9450

3. Synonyms and Trade Names

No information was found in the sources searched.

B. Formulas and Molecular Weight

1. Structural Formula



(HCP 1976)

2. Empirical Formula

$C_6H_2Cl_4$ (HCP 1976)

3. Molecular Weight

215.90 (HCP 1976)

C. Physical Properties

1. Description

White flakes (CCD 1977)

2. Boiling Point

243-246°C (HCP 1976)

3. Melting Point

139.5-140.5°C (HCP 1976)

4. Vapor Pressure

40 mm at 146°C (HCP 1976)

5. Solubility

Insoluble in water, slightly soluble in hot alcohol; soluble in ether, benzene, chloroform, and carbon disulfide (HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.858^{22} (HCP 1976)

D. Composition of the Commercial Product

No information was found in the sources searched.

1,2,4,5-TETRACHLOROBENZENE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

Listed by the USITC under the section "Cyclic Intermediates," but no production data given (USITC 1976)

2. Manufacturers

Dow Chemical Co. (USITC 1976)

3. Use

As an intermediate for herbicides and defoliants; as an insecticide; as an impregnant for moisture resistance; in electrical insulation; as temporary protection in packing (CCD 1977)

4. Occupational Exposure

No information was found in the sources searched.

5. Release

1,2,4,5-Tetrachlorobenzene has been identified as a metabolite of the pesticide lindane in pheasant eggs and chicks (Saha and Burrage 1976), in flies (Reed and Forgash 1970), and in a culture of mold grown spontaneously on grated carrots (Engst et al. 1977). An unspecified tetrachlorobenzene may be released as a result of its use in the pesticide Polystream (see 1,2,3,4-Tetrachlorobenzene, Section II.B.1).

B. Environmental Fate

1. Occurrence

1,2,4,5-Tetrachlorobenzene has been found in plaice, eel, sprat, whiting, and cod taken off Norway (Lunde 1976). On the occurrence of unspecified tetrachlorobenzenes, see 1,2,3,4-Tetrachlorobenzene, Section II.B.1.

2. Transformation

Pseudomonas bacteria degrade 1,2,4,5-tetrachlorobenzene at 200 mg/liter at 30°C with a ring disruption of 30% in 5 days (Verschueren 1977). A mutant strain of the bacteria degrades the compound under the same conditions with a ring disruption of 80%.

Comment: 1,2,4,5-Tetrachlorobenzene is a solid that is insoluble in water and soluble in fat solvents. Its vapor pressure is 1 mm at 68.5°C, and it can react vigorously with oxidizing agents (Sax 1975). These properties as well as the transformation data given above indicate that the compound, if released, may enter the soil and water systems. Degradation is likely to be slow and the compound could become a pollutant if released in large amounts. Because it is less volatile, more stable, and less biodegradable than the trichlorobenzenes, it is likely to be more persistent.

3. Bioaccumulation

According to Jondorf et al. (1958), 2% of 1,2,4,5-tetrachlorobenzene administered orally to rabbits was metabolized to 2,3,5,6-tetrachlorophenol and was excreted in the

urine. During a period of 6 days after dosing, 48% of the dose was found in the tissues, 16% in the feces, and 2% in the expired air. De Bruin (1976) suggested that rates of absorption and transformation of the polychlorinated benzenes decline as halogen substitution increases.

According to Jacobs et al. (1974), 1,2,4,5-tetrachlorobenzene administered orally to rats at 5 mg/kg/day in a mixture of several environmental pollutants accumulated in the fat and to a lesser extent the liver, kidney, heart, and blood.

An abstract of a study by Bauer (1972) reported that 1,2,4,5-tetrachlorobenzene was adsorbed by the algae Cladophera. At 70 µg/liter of water, the bioaccumulation factor was 254. The adsorption rate was highest in the first 24 hours.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, accumulated in the tissues of oysters and clams when it was applied to oyster beds at 1.9 hectaliters/hectare. The residues disappeared within 119 days. See 1,2,3-Trichlorobenzene, Section IV.A.4, for a description of experimental details.

Comment: 1,2,4,5-Tetrachlorobenzene is stable, insoluble in water, and highly lipophilic; it is only slightly volatile. These properties as well as the data on metabolism given above indicate that the compound has a potential for bioaccumulation. In general, the tetrachlorobenzenes bioaccumulate more than the trichlorobenzenes.

1,2,4,5-TETRACHLOROBENZENE

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Organisms

1. Metabolism

In a study of the metabolism of several polychlorinated benzenes, Kohli et al. (1976) gave intraperitoneal injections of 300 mg of 1,2,4,5-tetrachlorobenzene dissolved in 10-15 ml of vegetable oil to an unspecified number of male rabbits, each weighing 4-5 kg. The authors reported that in urine collected for 10 days 2% of the dose was excreted as the metabolite 2,3,5,6-tetrachlorophenol. The authors suggested that this metabolite may have been formed from arene oxides.

In an earlier study, Jondorf et al. (1958) administered 1,2,4,5-tetrachlorobenzene at 0.5 g/kg orally to female rabbits. They reported that the compound was metabolized less readily than 1,2,3,4-tetrachlorobenzene. In 6 days, only about 2% was converted to 2,3,5,6-tetrachlorobenzene and excreted in the urine. Less predominant urinary metabolites were 2,5-dichlorophenol and 2,3,5-trichlorophenol. Of the original dose, 48% was found unchanged in the tissues (25% was in depot fat), 16% in the feces, and 2% in the expired air. The authors suggested that somewhat more than 10-15% of the dose may have been dechlorinated in the gut to dichlorophenols and trichlorophenols.

According to Jacobs et al. (1974), 1,2,4,5-tetrachlorobenzene administered orally at 5 mg/kg/day in a mixture of several environmental pollutants accumulated in the fat and to a lesser extent the liver, kidney, heart, and blood of rats.

Safe et al. (1976) investigated the metabolism of chlorinated aromatic compounds by the frog (Rana pipiens). They dissolved 80 mg of 1,2,4,5-tetrachlorobenzene in 4-5 ml of vegetable oil and administered it in equal parts by intraperitoneal injection to four animals. They reported that less than 1% of the dose was excreted in the course of 8 days as 2,4,5-tetrachlorophenol. No other metabolites were detected.

2. Toxic Effects

a. Acute Toxicity

The NIOSH RTECS data base (1978) reported that the oral LD50 of 1,2,4,5-tetrachlorobenzene was 1,500 mg/kg in the rat and 1,035 mg/kg in the mouse.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity in Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Ariyoshi et al. (1975a) investigated the effects of 1,2,4,5-tetrachlorobenzene on rats. They gave six female Wistar rats oral doses of 250 mg/kg of the substance in 2% tragacanth gum solution once a day for 3 days. The rats were sacrificed 24 hours after the last dose was administered. The authors reported a statistically significant increase in aminopyrine demethylase activity and in the concentrations of cytochrome P-450 and microsomal protein in the liver. Mean liver weight was significantly increased, although the concentrations of glycogen and triglyceride in the liver were decreased.

Rimington and Ziegler (1963) administered chlorinated benzenes to rats to induce experimental hepatic porphyria. They gave six male albino rats 1,2,4,5-tetrachlorobenzene at 905 mg/kg by gastric intubation daily for 5 days and measured porphyrins and porphyrin precursors in 24-hour urine samples. They reported that the compound had no effect on urinary porphyrin excretion. The rats lost weight and showed loss of appetite.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Safe et al. (1976) reported that less than 1% of an administered dose of 1,2,4,5-tetrachlorobenzene was converted to metabolites by the frog (Rana pipiens). Comment: The experimental design and mode of exposure in this study were not appropriate for the determination of toxic effects. For experimental details, see 1,2,4,5-Tetrachlorobenzene, Section III.B.1.

For the effects of Polystream, which contains an unspecified tetrachlorobenzene, see 1,2,3-Trichlorobenzene, Section IV.A.3.

4. Invertebrates

Loosanoff et al. (1960a and 1960b as reported by MacKenzie 1971) reported that tetrachlorinated benzenes are toxic to several species of marine gastropods, including the thick-lipped drill (Eupleura caudata) and the Atlantic oyster drill (Urosalpinx cinerea). MacKenzie did not provide further details.

For the effects of Polystream, which contains an unspecified tetrachlorobenzene, see 1,2,3-Trichlorobenzene, Section IV.A.4.

5. Plants and Algae

Ameen et al. (1960 as reported by USEPA 1977) reported that 1,2,4,5-tetrachlorobenzene at an unspecified concentration decreased the seedling vigor and germination percentage of barley, oats, and wheat in pretreated sand, loam, clay loam, and clay soils. In sand, where the damage was most severe, barley and oats did not germinate when planted 1 day after treatment; 100% germination for barley and 95% for oats occurred when they were planted 25 days after treatment. The height of the seedlings, according to the report, increased with the time between treatment and planting.

Richardson (1968 as reported by USEPA 1977) observed that 1,2,4,5-tetrachlorobenzene retarded the radial growth of the fungus Pythium ultimum but that its effect was less than trichlorobenzene's. No other experimental details were given.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

PENTACHLOROBENZENE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 608-93-5

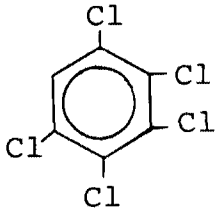
2. NIOSH No.: DA66400

3. Synonyms and Trade Names

QCB (NIOSH 1977)

B. Formulas and Molecular Weight

1. Structural Formula



(HCP 1976)

2. Empirical Formula

C_6HCl_5 (HCP 1976)

3. Molecular Weight

250.34 (HCP 1976)

C. Physical Properties

1. Description

No information was found in the sources searched.

2. Boiling Point

277°C (HCP 1976)

3. Melting Point

86°C (HCP 1976)

4. Vapor Pressure

1 mm at 98.6°C (HCP 1976)

5. Solubility

Insoluble in water and alcohol; slightly soluble in ether, benzene, carbon disulfide, and chloroform; soluble in hot alcohol (HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

$1.8342^{16.5}$ (HCP 1976)

D. Composition of the Commercial Product

No information was found in the sources searched.

PENTACHLOROBENZENE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Source

1. Production and Trends

No information was found in the sources searched.

2. Manufacturers

No information was found in the sources searched.

3. Use

In pesticide used to combat oyster drills (MacKenzie 1971)

4. Occupational Exposure

No information was found in the sources searched.

5. Release

Greve (1973) suggested that pentachlorobenzene is a contaminant of hexachlorobenzene and that it enters the food chain as a result of the use of hexachlorobenzene as a fungicide. Villaneuve et al. (1974) reported that samples of hexachlorobenzene used as a fungicide to control bunt of wheat contained 200-81,000 ppm pentachlorobenzene as a contaminant. Pentachlorobenzene is both a metabolite of and an impurity in the soil fungicide quintozene, which is used on lettuce, potatoes, and other crops (Dejonckheere et al. 1975, Beck and Hansen 1974), and it is an active ingredient in the pesticide Polystream (MacKenzie 1971). Pentachlorobenzene has been identified as a metabolite of the pesticide lindane in susceptible and resistant strains of houseflies (Reed and Forgash 1970), in

pheasant eggs and chicks (Saha and Burrage 1976), and in a culture of mold grown spontaneously on grated carrots (Engst et al. 1977).

Plimmer and Klingebiel (1976) obtained pentachlorobenzene by irradiating hexachlorobenzene with short-wave light.

B. Environmental Fate

1. Occurrence

Pentachlorobenzene has been found in sprat (Clupea sprattus) (Lunde and Baumann 1976), in plaice, eel, sprat, whiting, and cod taken off Norway (Lunde 1976), and in trout (Salmo gairdneri) exposed to water from the Rhine River for 9 months. Koeman et al. (1969) found pentachlorobenzene in roaches in the area of the Rhine in the Netherlands. Pentachlorobenzene at low concentrations has also been found in wheat products, animal feed, chicken fat, and pork fat (Greve 1973, Stijve 1971). Beck and Hansen (1974) identified the compound in soil from a potato field treated with quintozene in Denmark, and de Vos et al. (1974) identified it in greenhouse soil treated with quintozene in the Netherlands. Beck and Hansen (1974) reported that pentachlorobenzene has been found in market samples of potatoes and carrots.

MacKenzie (1971) reported low residues of Polystream, which gradually disappeared, in oysters and clams. Polystream is a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, and is used to reduce snail attack on oysters.

Morita et al. (1975 as reported by Morita 1977) found pentachlorobenzene at 0.009 ppm in samples of human adipose tissue in Japan.

2. Transformation

Beck and Hansen (1975) confirmed the persistence of the fungicide quintozene and several of its metabolites and impurities, including pentachlorobenzene, in soil under controlled laboratory conditions. They also identified these chemicals in 22 samples of soil from potato fields that had been treated with quintozene during the previous 11 years. They concluded that appreciable amounts of pentachlorobenzene will enter the soil as the result of the use of quintozene and will persist in the ground for 2-3 years.

Gäb et al. (1977) reported that pentachlorobenzene is resistant to photodegradation. They suggested that the compound could be mineralized in the atmosphere only when exposed to short-wave ultraviolet light.

Comment: These findings are consistent with pentachlorobenzene's chemical and physical properties. It is a chemically stable compound that is insoluble in water and soluble in fat solvents. Its vapor pressure (1 mm at 98.6°C) is very low. Therefore, when present in pesticides, it enters the soil and water systems, where it degrades very slowly. Its presence in fish, animal fat, food, and elsewhere in the food chain supports this judgment.

3. Bioaccumulation

De Bruin (1976) suggested that rates of absorption of the polychlorinated benzenes decline as halogen substitution increases and he reported that pentachlorobenzene is characterized by metabolic

inertness. Safe et al. (1976) reported that the halogenated aromatic compounds are known to accumulate in higher trophic levels of the food chain.

Safe et al. (1976) studied the metabolism of chlorinated aromatic pollutants by the frog (Rana pipiens). They found no pentachlorobenzene metabolites in the excretion of frogs given the compound by intraperitoneal injection. They suggested that the pentachlorobenzene was stored in fatty tissue and only slowly metabolized after release from the tissue. Kohli et al. (1976) obtained similar results in rabbits. For experimental details, see Pentachlorobenzene, Section III.B.1.

MacKenzie (1971) found that Polystream, a mixture of trichlorobenzene, tetrachlorobenzene, and pentachlorobenzene, accumulated in the tissues of oysters and clams in small amounts when it was applied to oyster beds at 1.9 hectaliters/hectare. These residues disappeared within 119 days. See 1,2,3-Trichlorobenzene, Section IV.A.4, for further details.

Comment: These findings are consistent with pentachlorobenzene's chemical and physical properties described in Section II.B.2, Transformation. Its presence in fish, animal fat, food, and elsewhere in the food chain (see Section II.B.1) confirms its marked tendency to bioaccumulate.

PENTACHLOROBENZENE

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Organisms

1. Metabolism

In a study of the metabolism of several polychlorinated benzenes, Kohli et al. (1976) gave intraperitoneal injections of 300 mg of pentachlorobenzene dissolved in 10-15 ml of vegetable oil to an unspecified number of male rabbits, each weighing 4-5 kg. The authors reported that in urine collected for 10 days 1% of the dose was excreted as the metabolite 2,3,4,5-tetrachlorophenol and 1% as pentachlorophenol. The authors suggested that these metabolites may have been formed from arene oxide intermediates.

In an earlier study, Parke and Williams (1960) administered pentachlorobenzene orally and intraperitoneally at 0.5 g/kg to two rabbits. The authors reported that the major portion (31-45%) of the oral dose was found unchanged in the gut contents after 3-4 days. In addition, 20% was found in the tissues generally and about 5% in the feces. Most of the injected dose was found after 10 days in tissues near the site of injection, with 47% in the pelt and 22% in the depot fat. About 10-20% of the oral dose was eliminated in expired air, as a mixture of less chlorinated benzenes. Not more than 1% of the dose was found as metabolites in the urine. The main urinary metabolites were parachlorophenol and

4-chlorocatechol. In two of four experiments, pentachlorophenol was identified in the urine.

Safe et al. (1976) investigated the metabolism of chlorinated aromatic compounds by the frog (Rana pipiens). They dissolved 80 mg of pentachlorobenzene in 4-5 ml of vegetable oil and administered it equally by intraperitoneal injection to four animals. They reported that the compound did not yield any metabolic products.

De Bruin (1976) reported that pentachlorobenzene is characterized by metabolic inertness.

2. Toxic Effects

a. Acute Toxicity

No information was found in the sources searched.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

Khera and Villeneuve (1975) administered pentachlorobenzene at 50, 100, and 200 mg/kg to three groups of 20 pregnant Wistar rats on days 6-15 of gestation. The mean number of live fetuses per litter and the mean fetal weight were reduced in the dams given 200 mg/kg but not in those receiving lower doses. The ratio of fetal deaths to total implants for the exposed rats was not

significantly different from the ratio for the control group of 20 rats. The authors reported that administration of pentachlorobenzene at each of the doses increased the incidence of extra ribs in fetuses. They also recorded an increased incidence of sternal defects in fetuses from dams receiving 200 mg/kg.

e. Other Toxicity

Ariyoshi et al. (1975b) investigated the effects of pentachlorobenzene on rats. They gave six female Wistar rats oral doses of 250 mg/kg of the substance in 2% tragacanth gum solution once a day for 3 days. The rats were sacrificed 24 hours after the last dose. The authors reported a statistically significant increase in the concentrations of cytochrome P-450 and triglyceride in the liver and in microsomal protein, phosphorus of phospholipids, and fatty acid of phospholipids. They found significantly increased aniline hydroxylase, aminopyrine demethylase, and delta-aminolevulinic acid synthetase activities. Liver weights were significantly increased.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Safe et al. (1976) measured no pentachlorobenzene metabolites in frogs (Rana pipiens) given the compound by intraperitoneal injection. Comment: The experimental design and mode of exposure in this study were not appropriate for the determination of toxic effects. For experimental details, see Pentachlorobenzene, Section III.B.1.

For the effects on fish of Polystream, which contains an unspecified pentachlorobenzene, see 1,2,3-Trichlorobenzene, Section IV.A.3.

4. Invertebrates

For the effects on invertebrates of Polystream, which contains an unspecified pentachlorobenzene, see 1,2,3-Trichlorobenzene, Section IV.A.4.

5. Plants and Algae

Richardson (1968 as reported by USEPA 1977) reported that pentachlorobenzene retarded the radial growth of the fungus

Trichoderma viride but that its effect was less than trichlorobenzene's. No other experimental details were given.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

SUMMARY TABLE

CHARACTERISTICS OF CHLOROBENZENES

Name	Solubility	Log P_{oct}	Estimated Environmental Release	Production	Estimated No. of Persons Exposed (Occupationally)	Use
1,2,3-Trichlorobenzene	i in H_2O; ss in alc; vs in eth, bz, and CS_2	*	*	*	*	As a chemical intermediate
1,2,4-Trichlorobenzene	i in H_2O; ss in alc; vs in eth	*	*	15.6 million lb (1972)	5,000	As a solvent in chemical manufacturing; as a dielectric fluid; in dyes, oils, lubricants, and insecticides; as a heat transfer medium
1,3,5-Trichlorobenzene	ss in alc; i in H_2O; vs in eth, bz, Cs_2, and ligroin	*	*	*	3,000	*
Trichlorobenzene	*	*	*	*	1,081,000	In pesticides

SUMMARY TABLE (continued)

Name	Solubility	Log P_{oct}	Estimated Environmental Release	Production	Estimated No. of Persons Exposed (Occupationally)	Use
1,2,3,4-Tetrachlorobenzene	i in H_2O; ss in cold alc; s in hot alc; vs in eth, acetic acid, CS_2, and ligroin	*	*	*	*	In dielectric fluids; in organic synthesis
1,2,4,5-Tetrachlorobenzene	i in H_2O; ss in hot alc; s in eth, bz, chl, and CS_2	*	*	*	*	As a herbicide and defoliant, insecticide, moisture resistent impregnant; in electric insulation; in packing materials
Pentachlorobenzene	i in H_2O and alc; ss in eth, bz, CS_2, and chl; s in hot alc	*	*	*	*	*

*No information was found in the sources searched.

Key to abbreviations:

s--soluble
ss--slightly soluble
vs--very soluble
i--insoluble
alc--alcohol
eth--ethane
bz--benzene
chl--chloroform

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1,2-DICHLOROPROPANE

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1,2-DICHLOROPROPANE

OVERVIEW

1,2-Dichloropropane is a volatile colorless liquid that is soluble in most organic solvents but only slightly soluble in water. It is used primarily as a solvent and degreasing agent, as a chemical intermediate, as a lead scavenger, and as a soil fumigant for nematodes. In the United States, 71 million pounds of the compound were produced in 1976 and 145 million pounds in 1974. An estimated 1 million workers are exposed to 1,2-dichloropropane.

Although no specific information on the environmental fate or effects of 1,2-dichloropropane was found in the sources searched, the chemical and physical properties of the compound indicate that it is not likely to persist or bioaccumulate.

Liver appears to be a primary target organ of 1,2-dichloropropane toxicity. In experimental animals, exposure to 1,2-dichloropropane has resulted in fatty degeneration, hyperplasia, and hypertrophy of the liver and changes in the activity of liver enzymes. In a single human case study, degeneration of liver cells and changes in mitochondria, endoplasmic reticulum, and Golgi apparatus were reported. Studies on laboratory animals also indicated degeneration of kidney cells, hemosiderosis of the spleen, and necrosis of adrenals.

An unspecified isomer of dichloropropane has been shown to cause mutations in Salmonella typhimurium and Aspergillus

nidulans. No adequate tests on the carcinogenicity of 1,2-dichloropropane were reported in the sources searched and no information on teratogenicity was found. 1,2-Dichloropropane has been tentatively selected for carcinogenicity testing by the National Cancer Institute.

1,2-DICHLOROPROPANE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No: 78-87-5

2. NIOSH No.: TX96250

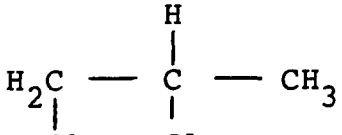
3. Synonyms and Trade Names

ENT 15,406
Propylene dichloride
alpha,beta-Dichloropropane
Propylene chloride
alpha,beta-Propylene dichloride

(NIOSH 1977)

B. Formulas and Molecular Weight

1. Structural Formula



(HCP 1976)

2. Empirical Formula

$C_3H_6Cl_2$ (HCP 1976)

3. Molecular Weight

112.99 (HCP 1976)

C. Physical Properties

1. Description

Colorless liquid; chloroformlike odor (CCD 1977)

2. Boiling Point

96.37° (HCP 1976)

3. Melting Point

-100.44°C (HCP 1976)

4. Vapor Pressure

40 mm at 19.4°C (HCP 1976)

5. Solubility

Slightly soluble in water; soluble in alcohol, ether, benzene, and chloroform (HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.5201^{20} (HCP 1976)

D. Composition of the Commercial Product

No information was found in the sources searched.

1,2-DICHLOROPROPANE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

71.0 million lb (1976)	(USITC 1976)
145.1 million lb (1974)	(USITC 1974)
40.7 million lb (1972 sales)	(USITC 1972)

2. Manufacturers

BASF Wyandotte Corp.
Dow Chemical Co.
Jefferson Chemical Co.
Olin Corp.

(USITC 1976)

3. Use

As a chemical intermediate for perchloroethylene and carbon tetrachloride; in the synthesis of amines and rubber-processing chemicals; as an inert reaction medium in chlorination and sulfonation operations; as a lead scavenger for antiknock fluids; as a solvent for fats, oils, waxes, gums, and resins; in solvent mixtures for cellulose esters and ethers; in scouring compounds; in spotting agents; in metal degreasing agents; in dry-cleaning fluids; in paint and varnish removers; as a soil fumigant for nematodes (CCD 1977,Olin 1978)

4. Occupational Exposure

NOHS Rank: 196

Estimated number of persons exposed: 1,094,000

(NOHS 1976)

ACGIH TLV-TWA: 75 ppm (350 mg/m^3) (ACGIH 1978)

5. Release

1,2-Dichloropropane has been found in effluents from a sewage treatment plant and a textile mill (Shackelford and Keith 1976).

B. Environmental Fate

1. Occurrence

1,2-Dichloropropane has been found in river water, in the ocean, and in drinking water (Shackelford and Keith 1976).

2. Transformation

Roberts and Stoydin (1976) reported that, because of volatilization, less than 1% of a dose of ^{14}C-radiolabeled 1,2-dichloropropane applied to soil in an open glass container exposed outdoors remained after 10 days. They also reported that the compound degraded only slightly (4% or less) in 5 months when applied to a loam soil and stored in sealed containers.

Comment: As a saturated chlorinated hydrocarbon, 1,2-dichloropropane is chemically stable, a property that is consistent with the data given above. It has a low water solubility (2.6 g/liter at 20°C (CCD 1977)) and a high vapor pressure (40 mm at 19.4°C (HCP 1976)), and it can react readily with oxidizing agents (Sax 1975). 1,2-Dichloropropane is biodegradable (several indigenous soil bacteria were able to use it as an energy source (Altman 1969)). These properties indicate

that, if released, most of the chemical will enter the atmosphere but some will enter the water systems. It will, for the most part, be dispersed and will not persist in the environment.

3. Bioaccumulation

No specific data on the bioaccumulation of 1,2-dichloropropane were found in the sources searched.

Comment: 1,2-Dichloropropane is a lipophilic solvent and is low in water solubility and relatively stable chemically (see Section II.B.2). These data indicate that it has a tendency to bioaccumulate, but this tendency may be offset in part by the substance's high vapor pressure (see Section II.B.2), which allows excretion through the lungs. If released in water for prolonged periods, however, it is likely to bioaccumulate in fish and aquatic invertebrates, which will be exposed to it on a continuous basis. 1,2-Dichloropropane can also be expected to biodegrade, although the chlorine substituents will slow this process. Its properties indicate that 1,2-dichloropropane will not bioaccumulate in mammals, a conclusion consistent with a recent study in rats (Hutson et al. 1971, see Section III.B.1).

III. BIOLOGICAL INFORMATION

A. Effects on Humans

Chiappino and Secchi (1968) described a case in which a 59-year-old man accidentally ingested a solvent whose toxic component was reported to be 1,2-dichloropropane (the exact dose could not be determined). Immediate symptoms included vomiting and a burning sensation in the esophagus and the stomach. By the 4th day, nausea, anorexia, vomiting, and jaundice were observed. Electron microscopy and histological studies revealed degeneration of liver cells and ultrastructural changes in mitochondria, endoplasmic reticulum, and Golgi apparatus.

Nater and Gooskens (1976) described three cases of dermatitis in workers exposed to D-D, a soil fumigant containing 27.1% 1,2-dichloropropane, 53% 1,3-dichloropropene, 6.5% 3,3-dichloropropene-1, 6.5% 2,3-dichloropropene-1, 0.4% 1,2-dichloropropene, 6.5% other chlorinated hydrocarbons, and 1% epichlorohydrin. Exposure to the fumigant at unknown concentrations produced erythematous, itching eruptions on the face and arms. The authors stated that, according to the Netherlands Ministry of Social Affairs, seven other cases of skin reactions to D-D were reported from 1966 to 1971. Almost all the cases were reported to result from D-D dripping into the shoes of farmers during spraying. The authors applied pure D-D and 10% D-D in acetone to the skin of volunteers, which resulted in dermatitis in all cases. They also performed patch tests with 1%

D-D in acetone on three subjects to determine if dermatitis occurred as a result of irritation or allergic reaction. An allergic reaction occurred in one subject. Patch tests with 97% pure 1,2-dichloropropane did not produce an allergic reaction in any of the patients.

B. Tests on Laboratory Organisms

1. Metabolism

Hutson et al. (1971) conducted two experiments on the metabolism of 1,2-dichloropropane in rats. In one experiment, six rats of each sex were given 0.88 mg of ^{14}C-labeled dichloropropane as a solution in 0.5 ml arachis oil by stomach tube. Radioactivity was measured in the urine and feces, and, after the animals were killed on day 4, in the skin, gut, and carcass. The authors reported that a mean of 48.5% of the radioactivity was excreted in the urine of male rats during the first 24 hours and a mean total of 51.1% after 4 days. In the feces, the respective figures were 5.0 and 6.9%. After 4 days, 0.5% of the administered dose was recovered in the gut, 1.7% in the skin, and 4.1% in the carcass. In females, the means were 51.9% in the urine and 3.8% in the feces during the first 24 hours. After 4 days, the mean totals were 54.4% in the urine and 4.9% in the feces; 0.5% was found in the gut, 1.4% in the skin, and 3.2% in the carcass.

In the other experiment, five female rats were given oral doses of 1.07 mg of ^{14}C-labeled dichloropropane, and the exhaled radioactivity was measured. Because 19.3% of the administered

radioactivity was exhaled as CO_2, the authors concluded that extensive metabolism of the compound occurred.

Van Dyke and Wineman (1971) studied the in vitro enzymatic dechlorination of 1,2-dichloropropane in rat liver microsomes. Of 1,2-dichloropropane added to an incubation medium (consisting of the microsomal suspension, NADP, glucose 6-phosphate, glucose 6-phosphate dehydrogenase, and a cell supernatant fraction), 5.8% was enzymatically dechlorinated.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of 1,2-dichloropropane as reported by the NIOSH RTECS data base (1978) is given in Table III-1.

TABLE III-1

ACUTE TOXICITY OF 1,2-DICHLOROPROPANE

Parameter	Dosage	Animal	Route
LD50	1,900 mg/kg	Rat	Oral
LD50	860 mg/kg	Mouse	Oral
LD50	2,000 mg/kg	Guinea pig	Oral
LD50	8,750 mg/kg	Rabbit	Skin
LDLo	5,000 mg/kg	Dog	Oral
LCLo	2,000 ppm for 4 hr	Rat	Inhalation

b. Carcinogenicity

To determine the likelihood of 1,2-dichloropropane producing hepatomas, Heppel et al. (1948) exposed 80 C3H mice (sex unspecified) to the compound by inhalation at 400 ppm. The mice received 37 exposures lasting from 4 to 7 hours. Only three mice survived a 7-month observation period. Multiple hepatomas were observed in the survivors. No controls were used in this experiment.

Comment: This study cannot be considered an adequate test for carcinogenicity because the spontaneous incidence of hepatomas in C3H mice is high and because no controls were used.

c. Mutagenicity and Cell Transformation

According to an abstract of a presentation by Bignami et al. (1977), dichloropropane (isomer unspecified) induced base substitution in the Salmonella typhimurium strains TA1538 and TA100. The authors considered the compound to be a "definite mutagen" in these strains. They also reported that the compound induced point mutations in Aspergillus nidulans by significantly increasing the frequency of mutants resistant to 8-azaguanine.

d. Teratogenicity

No information was found in the sources searched.

e. Other Toxicity

Heppel et al. (1946) exposed guinea pigs, mice, rats, and rabbits to 1,2-dichloropropane vapor at 1,000-2,200 ppm for 7 hours/day, 5 days/week, for up to 128 exposures. Histological studies were performed on the animals after autopsy. Guinea

pigs exposed at 2,200 ppm for repeated 7-hour periods developed conjunctival swelling to such a degree that they lost blinking ability. By the fifth exposure, 11 of 16 guinea pigs had died. Histological examination revealed marked fatty degeneration of the liver and kidney and necrosis of the adrenals. Ten of eleven mice died before the end of one 7-hour inhalation exposure at 2,200 ppm. The deaths followed the development of gross incoordination and prostration. Histological examination revealed fatty degeneration of the liver and kidney. Five of twenty rats died by the fifth exposure at 2,200 ppm. Histological examination showed splenic hemosiderosis and fatty degeneration of the liver. Two of four rabbits died after the second exposure at 2,200 ppm. The histological findings were similar to those for the rats.

Heppel et al. (1948) exposed rats and guinea pigs (of both sexes) and female dogs to 1,2-dichloropropane vapor at 400 ppm for 7 hours/day, 5 days/week, for up to 140 exposures. Control groups were exposed to air. Of 49 rats, 3 died after at least 108 exposures, but the authors stated that it was unlikely that the deaths resulted from the exposures. They attributed the deaths of 7 of 32 exposed guinea pigs and 12 of 42 controls to an infectious disease characterized by enlarged lymph glands. No deaths were reported in 5 dogs. According to the authors, the only ill effect caused by the exposures was decreased weight gain in rats. Histological examination showed no changes attributable to 1,2-dichloropropane. The authors also exposed 80 mice to 1,2-dichloropropane at 400 ppm on the same schedule for a total of 37 exposures. Most mice died during the course of the

exposures. Mice that died after 14-28 exposures showed congestion, fatty degeneration, and necrosis of the liver and degeneration of the kidney.

Sidorenko et al. (1976) exposed an unspecified number of white male rats to 1,2-dichloropropane by continuous inhalation at 1 and 2 mg/liter for 7 days. Changes in blood catalase and cholinesterase activity were observed 4 hours after inhalation of dichloropropane at 2 mg/ml. Histological and histochemical analysis of centrilobular sections of the liver showed damage to small blood vessels, with signs of protein-fat dystrophy; suppression of enzymic activity, and reduction in the content of ribonucleoproteins. Changes in the peripheral sections of liver lobules, including hyperplasia and hypertrophy, were also reported. In the kidneys, histostructural changes were accompanied by suppression of oxidation enzymes and phosphomonoesterases.

According to an abstract of a Russian article, Kurysheva and Ekshtat (1975) observed that daily oral administration of 14.4 and 360 mg/kg of 1,2-dichloropropane to rats raised the concentration of serum cholesterol beta-lipoproteins and gamma-globulin by day 10. By day 20, serum pseudocholinesterase was inhibited and fructose 1-monophosphate aldolase, alanine transaminase, and asparagine transaminase were stimulated. Alanine transaminase was inhibited by day 30. The abstract reported no additional experimental data.

Ekshtat et al. (1975) reported that daily oral doses of 1,2-dichloropropane at 8.8, 44, and 220 mg/kg administered to

an unspecified number of rats for 20 days disturbed protein formation and enzyme and lipid metabolism by the liver. Of the four main components of the nematocide fumigant D-D, 1,2-dichloropropane was reported to have the greatest cumulative toxicity. No other experimental details were reported in the abstract from the Russian article.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

Note: Because of the lack of specific information on 1,2-dichloropropane, information on its ecological effects must be derived from data on the nematocide D-D, a mixture of 1,2-dichloropropane and 1,3-dichloropropene.

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

The Aquatic Toxicity Rating (96-hr TLm, species unspecified) of 1,2-dichloropropane is 100-10 ppm, which is considered slightly toxic (NIOSH 1977). The 96-hr TLms for bluegill sunfish and tidewater silverside were 320 and 240 mg/liter, respectively (Dawson et al. 1977).

4. Invertebrates

Use of D-D at an unspecified concentration completely eliminated the springtail population in soil within 30 days (Edwards 1969). The method of treatment was not reported.

Five annual treatments of soil with D-D at 60 ml/m^2 resulted in a statistically significant increase in the numbers of earth-

worms and mites and a statistically significant decrease in the numbers of phytophagic nematodes. No significant change was noted in populations of enchytraeids, saprophagic nematodes, tylenchus-psilenchus, or collembola (Van den Brande and Heungens 1969).

5. Plants and Algae

No dichloropropane or very small residues were found in potatoes grown in D-D-treated soil (Roberts and Stoydin 1976, Edwards 1969, Karasz and Gamengeim 1971).

Lebbink (1977) reported that soil fumigation with 1,2-dichloropropane resulted in a 52% incidence of ear malformations in winter wheat. The author stated that yield was reduced when the rate of ear malformations exceeded 15%. The "no effect level" for 1,2-dichloropropane was estimated to be 5 liters/hectare when applied in the autumn and 1 liter/hectare when applied in the spring.

6. Bacteria and Other Microorganisms

Several soil bacteria used chlorinated hydrocarbons in D-D as an energy source and, when the bacteria were grown on media containing D-D at 1, 10, and 100 ppm, they produced greater amounts of amino acids (Altman 1969).

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

1,2-Dichloropropane (NCI No. C55141) has been tentatively selected for testing in the National Cancer Institute's carcinogenesis bioassay program (NCI 1978).

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GLYCIDOL AND ITS DERIVATIVES

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GLYCIDOL AND ITS DERIVATIVES

OVERVIEW

The chemicals discussed in this dossier are glycidol, two glycidyl esters and five glycidyl ethers. The glycidyl ethers and esters are not commercially synthesized from glycidol but are considered, in this report, as derivatives for simplicity in assigning a name to the category. All of these compounds contain at least one oxirane (epoxide) group that usually reacts readily with nucleophilic substances. Glycidol and allyl glycidyl ether are soluble in water and lipid solvents. Phenyl glycidyl ether is slightly soluble in water and soluble in lipid solvents. Glycidyl acrylate and n-butyl glycidyl ether are insoluble and slightly soluble in water, respectively.

No production data for glycidol and its derivatives were found in the sources searched. Glycidol is used as a stabilizer in the production of vinyl polymers, glycidyl acrylate in the production of thermosetting acrylic surface-coating resins, and the glycidyl ethers in epoxy resin systems.

It was estimated in the National Occupational Hazard Survey that 105,000 workers in the United States are exposed to glycidol, 105,000 to glycidyl methacrylate, and 118,000 to glycidyl ethers.

Skin contact is the primary route of human exposure to the epoxides discussed in this dossier. Workers exposed to glycidyl ethers have developed dermatitis. Symptoms observed included tenderness, redness, itching, swelling, edema, blister

formation, second-degree burns, and discharge from affected areas. Exposure to the vapors of glycidyl ethers has been found to irritate the eyes, nose, and respiratory tract of humans. These ethers have a sensitizing effect on humans and cross-sensitization may occur. After an initial exposure to a glycidyl ether, exposure to the same compound or another glycidyl ether at previously non-irritating concentrations will cause dermatitis.

In laboratory animals, glycidol and glycidyl ethers caused central nervous system depression. Glycidol, glycidyl acrylate, and the glycidyl ethers have caused skin and eye irritation. Glycidol has been shown to cause temporary sterility in male rats and necrosis of the testes has been reported in rats exposed to the glycidyl ethers. Glycidol, glycidyl methacrylate, and diglycidyl ether of bisphenol A have given negative results in carcinogenicity studies. Glycidol has been tentatively selected for carcinogenesis bioassay by the National Cancer Institute. Glycidol was reported to be mutagenic in Salmonella typhimurium, Drosophila, Neurospora, barley, and yeast. Positive results in Salmonella typhimurium have been reported for the glycidyl ethers. n-Butyl glycidyl ether was mutagenic to mice in the dominant lethal test. Phenyl glycidyl ether gave negative results in a teratogenicity study. No reports on the teratogenicity of the other compounds discussed in this dossier were found.

In goldfish, 96-hour LD50s were reported to be 30 and 43 mg/liter for allyl glycidyl ether and phenyl glycidyl ether, respectively.

GLYCIDOL AND ITS DERIVATIVES

GLYCIDOL

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 556-52-5

2. NIOSH No.: UB43750

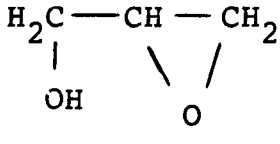
3. Synonyms and Trade Names

Oxiranemethanol
1-Propanol, 2,3-epoxy-
Allyl alcohol oxide
Glycide
Glycidyl alcohol
1-Hydroxy-2,3-epoxypropane
1,2-Epoxy-3-hydroxypropane
2-(Hydroxymethyl)oxirane
3-Hydroxy-1,2-epoxypropane
3-Hydroxypropylene oxide

(NIH/EPA 1978)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_3H_6O_2$ (NIH/EPA 1978)

3. Molecular Weight

74.08 (HCP 1976)

C. Physical Properties

1. Description

Colorless liquid (CCD 1977)

2. Boiling Point

56.5°C at 11 mm (HCP 1976)

3. Melting Point

No information was found in the sources searched.

4. Vapor Pressure

No information was found in the sources searched.

5. Solubility

Soluble in water, alcohol, ether, acetone, benzene, and chloroform (HCP 1976)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.117_4^{20} (HCP 1976)

D. Composition of the Commercial Product

No information was found in the sources searched.

GLYCIDOL

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

Listed by USITC under the section "Miscellaneous Chemicals," but no production data given (USITC 1976)

2. Manufacturers

Dixie Chemical Co. (USITC 1976)

3. Use

As a stabilizer for natural oils; as a demulsifier; as a dye-leveling agent; as a stabilizer for vinyl polymers (CCD 1977)

4. Occupational Exposure

Rank: 1118

Estimated number of persons exposed: 105,000*

* rough estimate

(NOHS 1976)

ACGIH TLV-TWA: 50 ppm (150 mg/m^3) (ACGIH 1978)

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No specific data were found in the sources searched.

Comment: Glycidol is soluble in water (HCP 1976) and will therefore remain in the aquatic medium when discharged into water systems.

3. Bioaccumulation

No specific data were found in the sources searched.

Comment: Glycidol is soluble in both water and lipid solvents (HCP 1976), which suggests a potential for bioaccumulation.

GLYCIDOL

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Organisms

1. Metabolism

Jones (1975) administered glycidol at 200 mg/kg/day by intraperitoneal injection to five male ICI/Swiss mice for 10 days. Three male Wistar rats were given glycidol by intraperitoneal injection at 100 mg/kg/day for 10 days. Urine was collected for 24 hours after dosing, and urinary metabolites were identified as S-(2,3-dihydroxypropyl)cysteine and the corresponding mercapturic acid.

Jones (1975) also gave two rats and three mice single intraperitoneal injections of ^{14}C-labeled glycidol. Rats received 100 mg/kg and mice received 200 mg/kg. In rats 15.3% of the dose was excreted as $^{14}CO_2$ in the first 24 hours after administration. In mice 16.0% was excreted.

When [U-^{14}C]-glycidol was incubated for 3 hours with glutathione and a rat liver supernatant, 50-60% of the radioactivity was identified as S-(2,3-dihydroxy[U-^{14}C]propyl) glutathione and 30-35% was [U-^{14}C]glycerol (Jones 1975). (The supernatant had been obtained by spinning homogenized rat liver at 300 g for 15 minutes and spinning the resultant supernatant at 100,000 g for 1 hour.)

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of glycidol, as reported by the NIOSH RTECS data base (1978a), is given in Table III-1.

TABLE III-1

ACUTE TOXICITY OF GLYCIDOL

Parameter	Dosage	Animal	Route
LD50	850 mg/kg	Rat	Oral
LD50	450 mg/kg	Mouse	Oral
LD50	1,980 mg/kg	Rabbit	Skin
LC50	580 ppm for 8 hr	Rat	Inhalation
LC50	450 ppm for 4 hr	Mouse	Inhalation
LDLo	500 mg/kg	Mouse	Intraperitoneal

Hine et al. (1956) gave mice and rats glycidol intragastrically at a range of doses used to determine the LD50, which was calculated to be 450 mg/kg in mice and 850 mg/kg in rats. CNS depression, incoordination, and ataxia were observed. Animals were often comatose at the time of death.

Hine et al. (1956) also reported that glycidol was a moderate irritant when 0.5 ml of undiluted compound was applied to the skin of rabbits. Glycidol caused severe eye irritation in rabbits

when 0.1 ml of undiluted compound was dropped on the cornea.

b. Carcinogenicity

Van Duuren et al. (1967) applied a 5% glycidol solution in acetone to the skin of 20 female ICH/Ha Swiss mice three times a week for 520 days. No tumors or lesions were observed.

c. Mutagenicity and Cell Transformation

McCann et al. (1976) reported that glycidol induced revertants in Salmonella typhimurium strain TA1535. When glycidol was applied to a plate containing S. typhimurium, 1,730 revertants were observed per 223 µg of the compound.

Wade et al. (1976) reported that glycidol induced revertants in histidine-dependent S. typhimurium strains TA98 and TA100. Glycidol induced more revertants in TA98 (frameshift mutations) than in TA100 (base-pair substitution mutations). Addition of rat liver microsomal enzymes decreased the number of revertants.

Dorange et al. (1977) also studied the mutagenicity of glycidol in S. typhimurium. They found glycidol to be mutagenic in strains TA1535 and TA100, used to detect base-pair substitution. It gave negative results in strains TA1537, TA1538, and TA98. No activation system was used in the tests.

Kucera et al. (1975) reported that 0.3% glycidol induced shortawned (breviaristatum) mutants in barley. No further experimental details were given.

Kolmark and Giles (1955) reported that glycidol induced reversions in the purple adenineless mutant 38701 of Neurospora

crassa. Treatment with 0.5 M glycidol for 60 minutes induced 33.8 reverse mutations per 10^6 viable conidia.

Izard (1973) investigated the mutagenic activity of glycidol in the yeast Saccharomyces cerevisiae. Eighty milliliters of a 10% glycidol solution was incubated at 30°C for 5 days in a medium containing 3 x 10^7 cells of S. cerevisiae/petri dish. Glycidol was mutagenic in the S211 strain of the yeast but not in the S138 strain.

Rapoport (1948 as reported by Fishbein 1977), a Russian investigator, found glycidol to be mutagenic in Drosophila. No further experimental details were given.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Glycidol has been shown to cause temporary sterility in male rats. Jackson et al. (1970) and Cooper et al. (1974) studied the effects of glycidol on the fertility of groups of five male Wistar rats given oral doses for various periods of time. These male rats were serially mated "with females of proven fertility" each week. Rats given single oral doses of 200 mg/kg showed no effect of glycidol on their fertility. Rats given five doses of 100 mg/kg were sterile for 2 weeks. Rats given five doses of 200 mg/kg were sterile for 4 weeks, and two of the five rats exhibited epididymal spermatoceles.

Jones and Jackson (1974) studied the effects of glycidol on spermatozoa of the toad Xenopus laevis and the development

of eggs fertilized in vitro by the glycidol-treated spermatozoa. Male toads were killed and the testes were macerated in Holtfreter's solution to form a sperm suspension. Glycidol at 0.2, 1, 5, and 10 mg/ml was added to the sperm suspension, which was used to fertilize the eggs. Normal development occurred in the two low dose systems. About 50% of the eggs treated for 60 minutes with sperm suspension containing glycidol at 5 or 10 mg/ml failed to cleave. At 5 mg/ml, the cleaving eggs continued to the tadpole stage. At 10 mg/ml, no eggs reached the gastrula stage.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Jones and Jackson (1974) studied the effects of glycidol on spermatozoa of the toad Xenopus laevis and the development of eggs fertilized in vitro by the glycidol-treated spermatozoa. See Glycidol, III.B.2.e for experimental details.

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communitites and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

GLYCIDOL

V. WORK IN PROGRESS

NCI (1978) reported that glycidol has been tentatively selected for carcinogenesis bioassay.

GLYCIDYL ACRYLATE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 106-90-1

2. NIOSH No.: AS92750

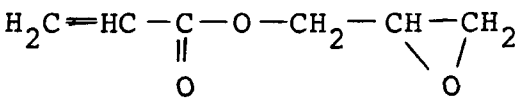
3. Synonyms and Trade Names

2-Propenoic acid, oxiranylmethyl ester
Acrylic acid, 2,3-epoxypropyl ester
Glycidyl propenate
2,3-Epoxypropyl acrylate

(NIH/EPA 1978)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_6H_8O_3$

(NIH/EPA 1978)

3. Molecular Weight

128.13

C. Physical Properties

1. Description

Liquid (CCD 1977)

2. Boiling Point

57°C at 2 mm with polymerization (CCD 1977)

3. Melting Point

-41.5°C (CCD 1977)

4. Vapor Pressure

No information was found in the sources searched.

5. Solubility

Insoluble in water (CCD 1977)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.1074_{20}^{20} (CCD 1977)

D. Composition of the Commercial Product

No information was found in the sources searched.

GLYCIDYL ACRYLATE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

Listed by USITC under the section "Miscellaneous Chemicals," but no production data given (USITC 1975)

2. Manufacturers and Suppliers

American Aniline & Extract Co. (USITC 1975)

Thiokol Corp. (OPD 1977)

3. Use

For the manufacture of thermosetting acrylic surface coating resins (CCD 1977)

4. Occupational Exposure

No information was found in the sources searched.

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No information was found in the sources searched.

3. Bioaccumulation

No information was found in the sources searched.

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Animals

1. Metabolism

No information was found in the sources searched.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of glycidyl acrylate, as reported by the NIOSH RTECS data base (1978a), is given in Table III-1.

TABLE III-1

ACUTE TOXICITY OF GLYCIDYL ACRYLATE

Parameter	Dosage	Animal	Route
LD50	214 mg/kg	Rat	Oral
LD50	400 mg/kg	Rabbit	Skin
LCLo	125 ppm for 4 hr	Rat	Inhalation

Smyth et al. (1962) exposed two groups of six rats (sex unspecified) to glycidyl acrylate vapor at 62.5 and 125 ppm for 4 hours. The rats were observed for 14 days. All the rats exposed at the higher concentration died, and those exposed

at the lower concentration survived. The authors also reported that, in rabbits, the direct application of glycidyl acrylate caused necrosis on the clipped belly and on the cornea.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

No information was found in the sources searched.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

No information was found in the sources searched.

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources seached.

V. WORK IN PROGRESS

No information was found in the sources searched.

GLYCIDYL METHACRYLATE

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 106-91-2

2. NIOSH No.: OZ43750

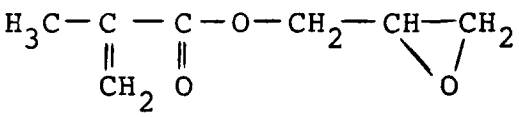
3. Synonyms and Trade Names

2-Propenoic acid, 2-methyl-, oxiranylmethyl ester
Methacrylic acid, 2,3-epoxypropyl ester
Glycidol methacrylate
2,3-Epoxypropyl methacrylate

(NIH/EPA 1978)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_7H_{10}O_3$ (NIH/EPA 1978)

3. Molecular Weight

142.15

C. Physical Properties

1. Description

No information was found in the sources searched.

2. Boiling Point

No information was found in the sources searched.

3. Melting Point

No information was found in the sources searched.

4. Vapor Pressure

No information was found in the sources searched.

5. Solubility

No information was found in the sources searched.

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

No information was found in the sources searched.

D. Composition of the Commercial Product

No information was found in the sources searched.

GLYCIDYL METHACRYLATE

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Source

1. Production and Trends

Listed by USITC under the section "Miscellaneous Chemicals," but no production data given (USITC 1975)

2. Manufacturers and Suppliers

American Aniline and Extract Co. (USITC 1975)

Blemmer Chemical Corp.
Haven Chemical Div.
Thiokol Corp.

(OPD 1977)

3. Use

No information was found in the sources searched.

4. Occupational Exposure

Rank: 1113

Estimated number of persons exposed: 105,000*

* rough estimate

(NOHS 1976)

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No information was found in the sources searched.

3. Bioaccumulation

No information was found in the sources searched.

III. BIOLOGICAL INFORMATON

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Animals

1. Metabolism

No information was found in the sources searched.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of glycidyl methacrylate, as reported by the NIOSH RTECS data base (1978a), is given in Table III-1.

TABLE III-1

ACUTE TOXICITY OF GLYCIDYL METHACRYLATE

Parameter	Dosage	Animal	Route
LD50	770 mg/kg	Rat	Oral
LD50	1,122 mg/kg	Mouse	Intraperitoneal
LD50	450 mg/kg	Rabbit	Skin

b. Carcinogenicity

Hadidian et al. (1968) evaluated the carcinogenicity of glycidyl methacrylate in three groups of rats. The compound

was administered by gavage five times a week for 1 year. The animals were observed for an additional 6 months. The dosages used ranged from 0.001 mg to 3 mg. No apparent difference in the tumor incidence pattern between exposed rats and controls was observed.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Hadidian et al. (1968) administered glycidyl methacrylate by gavage to groups of three weanling male rats, five times a week, for 8 weeks. The doses were 1, 3, 10, 30, 100, and 300 mg/animal/day. The rats given the lowest dose survived, but all rats given the other doses died. The authors did not describe toxic effects.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

No information was found in the sources searched.

4. Invertebrates

Indirect evidence indicates that glycidyl methacrylate inhibits degradation of the juvenile hormone in the blowfly (Calliphora erythrocephala) and the southern armyworm (Prodenia cridanin) through interference with enzymatic epoxide hydration (Slade et al. 1975). This conclusion was based on a study with the following methods and results:

The cyclodiene insecticide HEOM (1,2,3,4,9,9-hexachloro-6,7-epoxy 1,4,4a,5,6,7,8,8a-octahydro-1,4-methanonanaphthalene), which is susceptible to enzymatic epoxide ring cleavage, was used as a substrate. Insect tissues were prepared for epoxide hydrase enzyme incubation, and glycidyl methacrylate was added to the incubation mixture. HEOM was then added. With glycidyl methacrylate at 5.0×10^{-4}M, the activity rate of epoxide hydrase

was decreased by 45%. The authors interpreted this as an indication of a high degree of inhibition (Slade et al. 1975).

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

ALLYL GLYCIDYL ETHER

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 106-92-3

2. NIOSH No.: RR08750

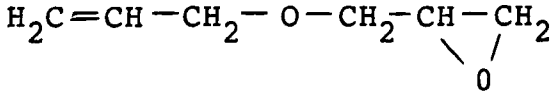
3. Synonyms and Trade Names

Oxirane, [(2-propenyloxy)methyl]-
Propane, 1-(allyloxy)-2,3-epoxy
Allyl 2,3-epoxypropyl ether
1-Allyloxy-2,3-epoxypropane
1,2-Epoxy-3-allyloxypropane

(NIH/EPA 1978)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_6H_{10}O_2$ (NIH/EPA 1978)

3. Molecular Weight

114.14

C. Physical Properties

1. Description

Colorless liquid; characteristic but not unpleasant odor (NIOSH 1978b)

2. Boiling Point

153.9°C (NIOSH 1978b)

3. Melting Point

Forms glass at -100°C (NIOSH 1978b)

4. Vapor Pressure

4.7 mm at 25°C (NIOSH 1978b)

5. Solubility

Soluble in water, acetone, toluene, and octane (NIOSH 1978b)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

0.9698_{4}^{20} (NIOSH 1978b)

D. Composition of the Commercial Product

No information was found in the sources searched.

ALLYL GLYCIDYL ETHER

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

Listed by USITC under the section "Miscellaneous Chemicals," but no production data given (USITC 1976)

2. Manufacturers

Alcoloc Chemical Corp. (USITC 1976)

3. Use

Glycidyl ethers are used chiefly as reactive diluents in epoxy resin systems. (NIOSH 1978b)

4. Occupational Exposure

Glycidyl ethers

Rank: 1020

Estimated number of persons exposed: 118,000*

*rough estimate

(NOHS 1976)

ACGIH TLV-TWA: 5 ppm (22 mg/m^3) (skin) (ACGIH 1978)

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No specific data were found in the sources searched.

Comment: Allyl glycidyl ether is soluble in water (NIOSH 1978b) and will therefore remain in the aquatic medium when discharged into water systems.

3. Bioaccumulation

No specific data were found in the sources searched.

Comment: Allyl glycidyl ether is soluble in both water and lipid solvents (NIOSH 1978b), which suggests a potential for bioaccumulation.

ALLYL GLYCIDYL ETHER

III. BIOLOGICAL INFORMATION

A. Effects on Humans

Hine et al. (1956) reviewed the medical records of workers exposed to allyl glycidyl ether and seeking first-aid treatment at one plant between 1947 and 1956. No worker had more than a total of 300 hours of exposure. Ten cases of dermatitis were reported. The symptoms and signs included tenderness, reddening, itching, swelling, blister formation, and whitish maculae. Exposed workers occasionally became "sensitized" to the compound. One case of eye irritation from allyl glycidyl ether vapor was also reported. Because immediate pain or burning was absent, workers often delayed seeking treatment.

Fregert and Rorsman (1964 as reported by NIOSH 1978b) tested the allergenic property of allyl glycidyl ether on 20 persons known to have contact allergies to epoxy resins of the diglycidyl ethers of bisphenol A. Allyl glycidyl ether at 0.25% in acetone was applied in a patch test for an unspecified exposure period. Two of the twenty test subjects had positive reactions.

B. Tests on Laboratory Organism

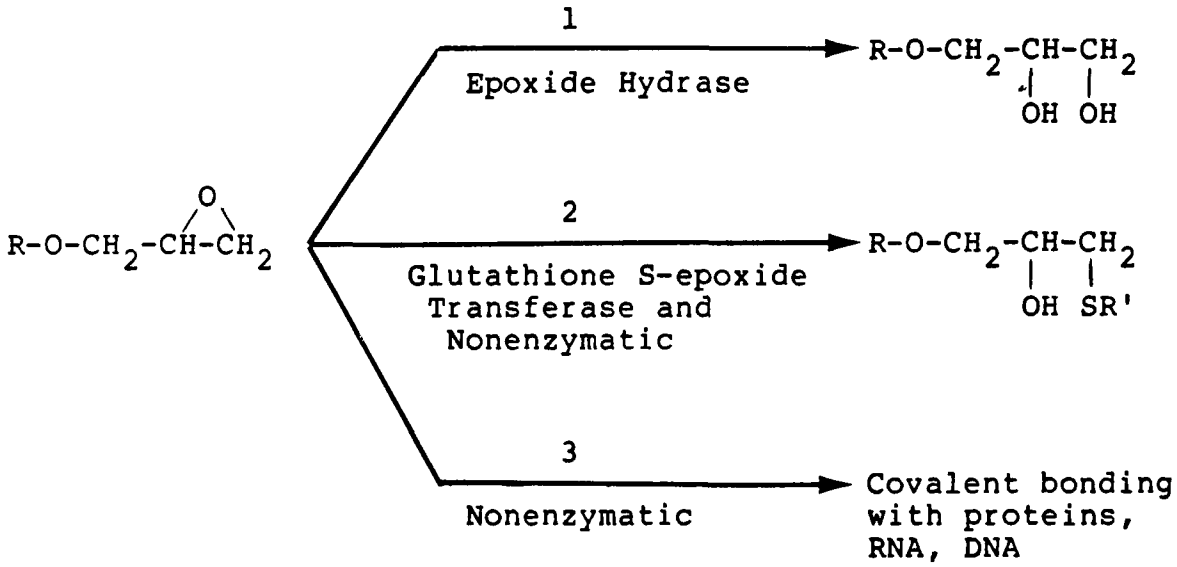
1. Metabolism

Oesch (1972 as reported by NIOSH 1978b) proposed three

types of metabolic reactions for epoxides, which are shown in Figure III-1.

FIGURE III-1

PROPOSED METABOLIC PATHWAYS FOR GLYCIDYL ETHERS*



* Adapted from NIOSH (1978b)

Two of the proposed pathways are enzymatic. One involves the conversion by epoxide hydrase to the corresponding diol. According to NIOSH (1978b), Soellner and Irrgang (1965) presented evidence that ortho-cresyl glycidyl ether was meta-bolized to the corresponding diol, which was apparently more neurotoxic than the parent compound. The second enzymatic pathway proposed by Oesch is conjugation with glutathione. The proposed nonenzymatic reactions of epoxides involve covalent binding to proteins, RNA, and DNA.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of allyl glycidyl ether, as reported by the NIOSH RTECS data base (1978a) and Hine et al. (1956), is given in Table III-1.

TABLE III-1

ACUTE TOXICITY OF ALLYL GLYCIDYL ETHER

Parameter	Dosage	Animal	Route
LD50[1]	922 mg/kg	Rat	Oral
LD50[2]	1,600 mg/kg	Rat	Oral
LD50[1,2]	390 mg/kg	Mouse	Oral
LD50[1,2]	2,550 mg/kg	Rabbit	Skin
LC50[1,2]	270 ppm for 4 hr	Mouse	Inhalation
LCLo[1]	860 ppm for 4 hr	Rat	Inhalation

[1]NIOSH (1978a)
[2]Hine et al. (1956)

Hine et al. (1956) gave mice and rats allyl glycidyl ether intragastrically at a range of doses used to determine the LD50, which was calculated to be 390 mg/kg in mice and 1,600 mg/kg in rats. CNS depression, incoordination, and ataxia were observed. Animals were often comatose at the time of death.

Hine et al. (1956) observed corneal opacity in some of

six rats exposed to allyl glycidyl ether vapors at an unspecified concentration for 8 hours. They also reported that, in rabbits, 0.5 ml of undiluted allyl glycidyl ether applied to the skin caused moderate skin irritation and 0.1 ml dropped on the cornea caused moderate eye irritation.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

Wade et al. (1978 as reported by NIOSH 1978b) studied the mutagenicity of allyl glycidyl ether in Salmonella typhimurium histidine-dependent strains TA98 and TA100. Allyl glycidyl ether was not mutagenic in TA98. Application of 10 mg of allyl glycidyl ether to agar plates containing TA100 induced mutations at 10 times the spontaneous rate. Addition of liver microsomal extract had no effect on the mutagenic activity of of the compound.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Hine et al. (1956) exposed groups of 10 rats to allyl glycidyl ether vapors for 7 hours/day, 5 days/week, for 10 weeks. Control groups were exposed to uncontaminated air. Seven or eight animals from groups exposed at 600 and 900 ppm died between the 7th and 21st exposures. The severe toxic effects necessitated termination of the use of high doses.

The authors observed a statistically significant change in the kidney to body weight ratio in rats exposed at 400 ppm. Eye irritation and respiratory distress were observed in rats exposed at 260 and 400 ppm. One rat exposed at 400 ppm died after 18 exposures, and autopsy revealed emphysema, mottled liver, and enlarged, congested adrenal glands. Bronchial dilatation, bronchopneumonia, and emphysema were observed in rats that survived the entire exposure period.

Kodama et al. (1961) gave five male Long-Evans rats intramuscular injections of allyl glycidyl ether at 400 mg/kg/day for 4 days. Leukocyte counts were significantly reduced in treated rats. Two rats died, and autopsies revealed pulmonary congestion in one and a small spleen and no visible thymus in the other. Necropsy of the three surviving rats showed involuted thymuses. Microscopic examination revealed atrophy of lymphoid tissue, focal necrosis of the pancreas and testes, hemorrhage of the thymus, hemorrhage into the periphery of the liver, and pneumonia.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Verschueren (1977) reported LD50 values for allyl glycidyl ether in goldfish of 78 mg/liter and 30 mg/liter in 24- and 96-hour tests.

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

n-BUTYL GLYCIDYL ETHER

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 2426-08-6

2. NIOSH No.: TX42000

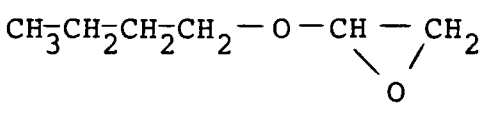
3. Synonyms and Trade Names

Oxirane, (butoxymethyl)-
Propane, 1-butoxy-2,3-epoxy-
ERL 0810
1-Butoxy-2,3-epoxypropane
2,3-Epoxypropyl butyl ether
3-Butoxy-1,2-epoxypropane

(NIH/EPA 1978)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_7H_{14}O_2$ (NIH/EPA 1978)

3. Molecular Weight

130.19

C. Physical Properties

1. Description

Colorless liquid; slight irritating odor (NIOSH 1978b)

2. Boiling Point

164°C (NIOSH 1978b)

3. Melting Point

No information was found in the sources searched.

4. Vapor Pressure

3.2 mm at 25°C (NIOSH 1978b)

5. Solubility

Slightly soluble in water (NIOSH 1978b)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

No information was found in the sources searched.

D. Composition of the Commercial Product

No information was found in the sources searched.

n-BUTYL GLYCIDYL ETHER

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

Listed by USITC under the section "Miscellaneous Chemicals," but no production data given (USITC 1974)

2. Manufacturers and Suppliers

Dow Chemical Co. (USITC 1974)

CPS Chemical Co.
Ciba-Geigy Corp.
Shell Chemical Co.

(OPD 1977)

3. Use

See Allyl Glycidyl Ether, Section II.A.3.

4. Occupational Exposure

See Allyl Glycidyl Ether, Section II.A.4.

ACGIH TLV-TWA: 50 ppm (270 mg/m^3) (ACGIH 1978)

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No information was found in the sources searched.

3. Bioaccumulation

No information was found in the sources searched.

n-BUTYL GLYCIDYL ETHER

III. BIOLOGICAL INFORMATION

A. Effects on Humans

Several studies on the irritating and sensitizing properties of n-butyl glycidyl ether have been reported. Kligman (1966 as reported by NIOSH 1978b) tested the sensitization potential of the compound in 24 healthy adults. One milliliter of a 1% suspension in mineral oil on a cloth patch, 1.5 inches square, was applied to the forearm or lower leg of each subject. The patch was covered with plastic tape and left in place 24 hours. This exposure was repeated five times, with 24-hour rest periods between patch tests. The 24 subjects were then each exposed to a challenge dose of 0.4 ml of 10% n-butyl glycidyl ether in mineral oil on a 1-square-inch patch left in place for 48 hours on the lower back or forearm; 19 showed sensitization.

Lea et al. (1958 as reported by NIOSH 1978b) applied n-butyl glycidyl ether on cotton pads to the backs of subjects. The pads were covered with cellophane and left in place 48 hours. Irritation was elicited in 5 of 5 subjects exposed to n-butyl glycidyl ether at 100% and in 17, 8, 1, and 0 of 25 subjects exposed to the substance at 10%, 5%, 2.5%, and 1.25%, respectively. Severity of response was dose-related; reactions ranged from mild irritation to erythema, edema, multiple vesiculation, and superficial ulceration.

Fregert and Rorsman (1964 as reported by NIOSH 1978b) tested the allergenic properties of n-butyl glycidyl ether

on 20 persons who were allergic to epoxy resins of the diglycidyl ethers of bisphenol A. n-Butyl glycidyl ether at 0.25% in acetone was applied in a patch test. Three of twenty subjects had allergic responses.

No reports on systemic effects of n-butyl glycidyl ether in humans were found in sources searched. However, toxic side effects have been reported in patients receiving triethylene glycol diglycidyl ether as an antitumor agent, which according to NIOSH (1978b) suggests that other lower-molecular-weight glycidyl ethers may also attack rapidly dividing tissues.

B. Tests on Laboratory Organisms

1. Metabolism

See Allyl Glycidyl Ether, Section III.B.1.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of n-butyl glycidyl ether, as reported by the NIOSH RTECS data base (1978a) and Hine et al. (1956), is given in Table III-1.

Hine et al. (1956) gave mice and rats n-butyl glycidyl ether intragastrically at a range of doses used to determine the LD50, which was calculated to be 1,530 mg/kg in mice and 2,260 mg/kg in rats. CNS depression, incoordination, and ataxia were observed. Death was preceded by agitation and excitement. The authors also exposed six rats to vapor concentrations used to calculate an LC50 of 1,030 ppm. Some rats developed focal

inflammatory cells with moderate congestion in the liver and hyperemia of the adrenal glands.

Hine et al. (1956) also reported that, in rabbits, 0.5 ml of undiluted n-butyl glycidyl ether applied to the skin caused moderate skin irritation and 0.1 ml dropped on the cornea caused moderate eye irritation.

TABLE III-1

ACUTE TOXICITY OF n-BUTYL GLYCIDYL ETHER

Parameter	Dosage	Animal	Route
LD50[1]	2,050 mg/kg	Rat	Oral
LD50[2]	2,260 mg/kg	Rat	Oral
LD50[1]	1,520 mg/kg	Mouse	Oral
LD50[2]	1,530 mg/kg	Mouse	Intragastric
LD50[1,2]	700 mg/kg	Mouse	Intraperitoneal
LD50[1,2]	1,140 mg/kg	Rat	Intraperitoneal
LD50[1]	2,520 mg/kg	Rabbit	Skin
LC50[2]	1,030 ppm for 8 hr	Rat	Inhalation
LCLo[1,2]	670 ppm	Rat	Inhalation

[1]NIOSH (1978a)
[2]Hine et al. (1956)

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

Wade et al. (1978 as reported by NIOSH 1978b) studied the mutagenicity of n-butyl glycidyl ether in Salmonella typhimurium strains TA98 and TA100 with and without the addition of liver microsomal extracts from rats pretreated with phenobarbital. In TA100, 10 µg of n-butyl glycidyl ether caused mutations at over 10 times the spontaneous rate. Liver microsomes had little effect on the mutagenic activity. n-Butyl glycidyl ether did not show mutagenic activity in strain TA98.

The mutagenicity of n-butyl glycidyl ether was examined by Pullin and Legator (1977) in a study performed for Dow Chemical USA and reported by NIOSH (1978b). n-Butyl glycidyl ether was significantly mutagenic in mice in a dominant lethal assay in which male mice were treated topically with the undiluted compound at 1.5 g/kg body weight, three times a week, for a minimum of 8 weeks before mating. This treatment caused a significant increase in the number of fetal deaths. In the Ames test, n-butyl glycidyl ether (0.5-2.0 µmoles/plate) produced mutations in S. typhimurium strain TA1535 at 4-13 times the spontaneous rate. Its mutagenic activity was markedly decreased by the addition of microsomal liver extract. The compound also caused a significant increase in unscheduled DNA synthesis in human mononucleated white blood cells. Pullin and Legator classified this compound as mutagenic despite a lack of demonstrated mutagenicity in three other tests:

(1) Body fluid analysis, in which the urine of mice given

oral doses (125-1,000 mg/kg/day) for 4 days was tested for mutagenicity against S. typhimurium

(2) The host mediated assay, in which S. typhimurium were injected into the peritoneal cavity of mice given oral doses (125-1,000 mg/kg/day) for 5 days

(3) The micronucleus test, in which bone marrow from mice given unspecified oral doses for 5 days was examined for the presence of micronuclei. The authors suggested that the doses might have been too low to cause mutagenic activity in these three tests. The dosage in the dominant lethal test was much higher.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Weil et al. (1963) gave 17 guinea pigs intracutaneous injections of 0.1 ml of n-butyl glycidyl ether at an unspecified concentration. The injections were given three times a week for a total of eight injections during a 3-week period. An unspecified challenge dose was given 3 weeks after the eighth injection. Sixteen of the guinea pigs became sensitized within 48 hours of receiving the challenge dose.

Anderson et al. (1957 as reported by NIOSH 1978c) exposed rats to n-butyl glycidyl ether by inhalation at 38, 75, 150, and 300 ppm for 7 hours/day, 5 days/week, for a total of 50 exposures. Slight testicular atrophy was observed in 1 of 10 rats exposed at 75 ppm. Anderson et al. described the testes

from 5 of 10 rats exposed at 300 ppm as "atrophic" and those from 1 of the 10 rats as "very small."

Kodama et al. (1961) observed increased leucocyte counts in five male rats given intramuscular injections of n-butyl glycidyl ether at 400 mg/kg/day for 3 days.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

No information was found in the sources searched.

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

Tox-Tips (1978) reported that a study of the "genetic toxicity" of butyl glycidyl ether in Swiss-Webster mice is being conducted by Dr. Marvin Legator at the University of Texas Medical Branch, Division of Environmental Toxicology, in Galveston, Texas. Mice are receiving low to toxic doses of butyl glycidyl ether topically or by intramuscular injection five times a week for up to 3 months. Dominant lethal tests and cytogenetic analyses will be performed. No starting or completion time is specified.

para-CRESYL GLYCIDYL ETHER

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 2186-24-5

2. NIOSH No.:

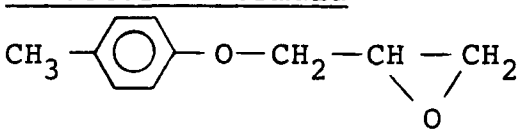
3. Synonyms and Trade Names

Propane, 1,2-epoxy-3-(p-tolyloxy)-
p-Tolyl glycidyl ether
Oxirane, ((4-methylphenoxy)methyl)-
Glycidyl p-tolyl ether
3-(4-Methylphenoxy)-1,2-epoxypropane
Glycidyl p-methylphenyl ether
2,3-Epoxypropyl p-tolyl ether
p-Cresol glycidyl ether

(CHEMLINE 1978)

B. Formulas and Molecular Weight

1. Structural Formula



2. Empirical Formula

$C_{10}H_{12}O_2$

3. Molecular Weight

164.20

C. Physical Properties

1. Description

No information was found in the sources searched.

2. Boiling Point

No information was found in the sources searched.

3. Melting Point

No information was found in the sources searched.

4. Vapor Pressure

No information was found in the sources searched.

5. Solubility

No information was found in the sources searched.

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

No information was found in the sources searched.

D. Composition of the Commercial Product

No information was found in the sources searched.

para-CRESYL GLYCIDYL ETHER

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

No information was found in the sources searched.

2. Manufacturers and Suppliers

CPS Chemical Co. (OPD 1977)

3. Use

See Allyl Glycidyl Ether, Section II.A.3.

4. Occupational Exposure

See Allyl Glycidyl Ether, Section II.A.4.

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No information was found in the sources searched.

3. Bioaccumulation

No information was found in the sources searched.

para-CRESYL GLYCIDYL ETHER

III. BIOLOGICAL INFORMATION

A. Effects on Humans

No information was found in the sources searched.

B. Tests on Laboratory Organisms

1. Metabolism

See Allyl Glycidyl Ether, Section III.B.1.

2. Toxic Effects

a. Acute Toxicity

No information was found in the sources searched.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

No information was found in the sources searched.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

No information was found in the sources searched.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

No information was found in the sources searched.

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

PHENYL GLYCIDYL ETHER

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS NO.: 122-60-1

2. NIOSH No.: TZ36750

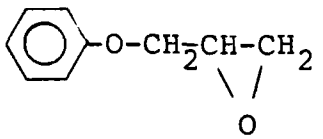
3. Synonyms and Trade Names

gamma-Phenoxypropylene oxide
(Phenoxymethyl)oxirane
Glycidol phenyl ether
Phenol glycidyl ether
Phenyl 2,3-epoxypropyl ether
1-Phenoxy-2,3-epoxypropane
1,2-Epoxy-3-phenoxypropane
2,3-Epoxypropyl phenyl ether
3-Phenoxy-1,2-epoxypropane
3-Phenoxy-1,2-propylene oxide
3-Phenyloxy-1,2-epoxypropane

(NIH/EPA 1978)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_9H_{10}O_2$ (NIH/EPA 1978)

3. Molecular Weight

150.18

C. Physical Properties

1. Description

Colorless liquid (CCD 1977)

2. Boiling Point

245°C (CCD 1977)

3. Melting Point

3.5°C (CCD 1977)

4. Vapor Pressure

0.01 mm at 25°C (NIOSH 1978b)

5. Solubility

Slightly soluble in water; soluble in all proportions in acetone and toluene (NIOSH 1978b)

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.11 (CCD 1977)

D. Composition of the Commercial Product

No information was found in the sources searched.

PHENYL GLYCIDYL ETHER

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

Listed by USITC under the section "Miscellaneous Chemicals," but no production data given (USITC 1976)

2. Manufacturers

No manufacturers listed by USITC (1976)

3. Use

See Allyl Glycidyl Ether, Section II.A.3.

4. Occupational Exposure

See Allyl Glycidyl Ether, Section II.A.4.

ACGIH TLV-TWA: 10 ppm (60 mg/m^3) (ACGIH 1978)

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

Lee et al. (1977) suggested that, as an acid acceptor,

phenyl glycidyl ether is very effective in stabilizing halogenated compounds.

3. Bioaccumulation

No specific data were found in the sources searched.

Comment: Phenyl glycidyl ether is soluble in lipid solvents and slightly soluble in water, suggesting that significant bioaccumulation may occur.

PHENYL GLYCIDYL ETHER

III. BIOLOGICAL INFORMATION

A. Effects on Humans

Hine et al. (1956) reviewed the medical records of workers exposed to phenyl glycidyl ether and seeking first-aid treatment at one plant between 1947 and 1956. Exposure to phenyl glycidyl ether was limited to about 20 workers for about 2 months a year, with no more than 600 hours exposure per worker. Thirteen cases of dermatitis were reported from this group. Symptoms observed in workers included second-degree burns, blister formation, brownish lesions, diffuse or vesicular erythematous rash, dry and defatted areas, watery discharge, macular rash and papules, swelling of connective tissue, and edema. Because immediate pain or burning was absent, workers often delayed seeking treatment. Some of the workers with occupational dermatitis developed sensitivity reactions.

Zschunke and Behrbohn (1965 as reported by NIOSH 1978b) reported 15 cases of occupational dermatitis in workers exposed to phenyl glycidyl ether being used as a chemical stabilizer in two cable-manufacturing plants. Eczema in 12 of 18 workers in one plant was reported. In the other plant, 3 persons were referred to a physician because of suspected occupational eczema, which had developed on the hands, lower arms, and right side of the abdomen. These were all parts of the body that had come in contact with cable-coating material. These areas were reddened, itchy, and contained papules and papulo-vesicles.

Ten out of the 15 cases were severe enough to result in work loss; 8 of the 15 affected workers reacted positively to a 24-hour patch test with phenyl glycidyl ether at 0.001-1.0%. Patch testing with pure and industrial grade phenyl glycidyl ether also produced positive reactions. The authors concluded that it was the ether itself and not its impurities that caused the skin reactions. Patch tests on 58 persons not previously exposed to phenyl glycidyl ether produced no positive reactions; however, 7 persons with eczema and exposure to epoxy resins but no known exposure to phenyl glycidyl ether had positive sensitivity reactions. The authors concluded that either the epoxy resins contained phenyl glycidyl ether or cross-sensitivity had occurred.

Fregert and Rorsman (1964 as reported by NIOSH 1978b) tested the allergenic properties of phenyl glycidyl ether on persons known to have contact allergies to epoxy resins of the diglycidyl ethers of bisphenol A. When phenyl glycidyl ether at 0.25% in acetone was applied in patch tests, 14 of 20 persons reacted positively. The details of the study were unspecified. Ten persons not allergic to epoxy resins were patch tested with 1.0% phenyl glycidyl ether and two became sensitized, but the concentration used did not cause primary irritation. The authors concluded that sensitization to phenyl glycidyl ether may occur after exposure to epoxy resins and that cross-sensitizations between glycidyl ethers may also develop.

No reports describing systemic effects of phenyl glycidyl

ether in humans were found in the sources searched. However, toxic side effects have been reported in patients receiving triethylene glycol diglycidyl ether as an antitumor agent, which according to NIOSH (1978b) suggests that other lower-molecular-weight glycidyl ethers may also attack rapidly dividing tissues.

B. Tests on Laboratory Animals

1. Metabolism

See Allyl Glycidyl Ether, Section III.B.1.

2. Toxic Effects

A. Acute Toxicity

The acute toxicity of phenyl glycidyl ether, as reported by the NIOSH RTECS data base (1978a) and Hine et al. (1956), is given in Table III-1.

TABLE III-1

ACUTE TOXICITY OF PHENYL GLYCIDYL ETHER

Parameter	Dosage	Animal	Route
LD50[1,2]	3,850 mg/kg	Rat	Oral
LD50[1,2]	1,400 mg/kg	Mouse	Oral
LD50[1]	1,500 mg/kg	Rabbit	Skin

[1]NIOSH (1978a)
[2]Hine et al. (1956)

Hine et al. (1956) gave mice and rats phenyl glycidyl ether intragastrically at a range of doses used to determine the LD50, which was calculated to be 1,400 mg/kg in mice and 3,850 mg/kg in rats. CNS depression, incoordination, and ataxia were observed. Animals were often comatose at the time of death. Animals surviving exposure showed reversal of depression with an increase in CNS activity. The authors also reported that, in rabbits, 0.5 ml of undiluted phenyl glycidyl ether caused mild skin irritation and 0.1 ml caused mild eye irritation.

Terrill and Lee (1977) exposed six male Sprague-Dawley rats during a single 4-hour session to phenyl glycidyl ether at various unspecified concentrations. The authors observed weight loss and severe scrotal irritation in the rats surviving during the 14-day observation period. The approximate lethal concentration in this experiment was 323 ppm.

Czajkowska and Stetkiewicz (1972 as reported by NIOSH 1978b) reported that oral administration of an unspecified dose of phenyl glycidyl ether to rats resulted in death within 6-24 hours. Rats exposed dermally died in 12-48 hours. Rats exposed by either route showed narcosis. Hyperemia of internal organs, hemorrhaging in the submeningeal and subpleural regions, and darkening of the epithelium in the kidney tubules and liver tissue were seen in gross and microscopic examination of rats that died or were sacrificed either 6-72 hours or 14 days after exposure. The authors concluded that phenyl glycidyl ether was extremely toxic at the site of administration, because it caused necrosis of the mucous membranes or skin. In addition,

circulatory disorders resulting in hyperemia, increased permeability of the capillaries, and damage to parenchymatous organs were observed in rats exposed by either route.

b. Carcinogenicity

No information was found in the sources searched.

c. Mutagenicity and Cell Transformation

An abstract of a paper presented at an August 1978 meeting of the American Society for Pharmacology and Experimental Therapeutics by M. A. Friedman et al. (1978) reported the following results:

1. Phenyl glycidyl ether induced concentration-dependent reversion in S. typhimurium strains TA1535 and TA100 used to detect base-substitution mutations but not in TA1537, TA1538, or TA98. The compound was mutagenic with and without the presence of rat liver microsomes.

2. Phenyl glycidyl ether at 6.2 µg/ml and higher concentrations transformed hamster embryo cells in a dose-dependent manner.

3. Phenyl glycidyl ether was tested at an oral dose of 2,500 mg/kg in the host-mediated assay in C57Bl/6X6C3H mice with S. typhimurium TA1535. The mutant frequency was increased from 0.022 to 0.298 x 10^{-6}. According to the authors, however, this represents a positive response in only two of five animals.

4. Phenyl glycidyl ether did not inhibit murine testicular DNA synthesis.

E. I. du Pont de Nemours & Co. (1978) reported the results of studies performed between 1974 and 1976:

1. The effects of inhaled phenyl glycidyl ether on the mitotic processes of somatic cells in male ChR-CD rats were examined. Three groups of six rats each were exposed for 6 hours/day for 19 days to heated phenyl glycidyl ether at 1.75, 5.84, and 11.2 ppm. Another group of six rats was exposed to air. In the treated groups, no abnormal effects were observed on the mitotic processes of somatic (bone marrow) cells and no chromosome breaks were evident. The authors concluded that phenyl glycidyl ether was not mutagenic under the conditions of this test.

2. Phenyl glycidyl ether was tested in S. typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 in the presence and absence of rat liver homogenate. The compound was found to be mutagenic in strains TA1535 and TA100 in both activated and nonactivated systems.

3. In a dominant-lethal and reproduction study, three groups of eight male ChR-CD rats were exposed by inhalation to heated phenyl glycidyl ether at 1.75, 5.84, and 11.2 ppm, 6 hours/day, for 19 days. Eight other rats were controls. Each week for 6 weeks, after the last exposure, each male rat was mated with three virgin females. One of these three females was sacrificed on the 18th day of pregnancy, and the ovaries, uterus, and fetuses were examined. No significant increase in the incidence of early or late fetal death or preimplantation

loss among these females was observed. The other female rats gave birth to pups with no genetic abnormalities.

d. Teratogenicity, Embryotoxicity, and Fetotoxicity

E. I. du Pont de Nemours & Co. (1978) reported a study in which the teratogenic potential of phenyl glycidyl ether was evaluated in groups of mated female ChR-CD rats. Twenty-five rats were controls, and 3 groups of 25 rats were exposed to heated phenyl glycidyl ether daily for 6 hours on the 4th-15th days of gestation. The exposure concentrations were 1.7, 5.7, and 11.5 ppm. No significant differences were observed in the maternal body weight, mortality, and gross pathology between the control and exposed rats. There were no significant differences in fetal malformations or survival or in implantation efficiency between the control and exposed groups.

e. Other Toxicity

Three groups of eight male rats were exposed by inhalation to heated phenyl glycidyl ether in the du Pont (1978) dominant-lethal and reproduction study described in Section III.B.2.C. The exposures were at 1.75, 5.84, and 11.2 ppm, 6 hours/day, for 19 days. Focal degenerative changes in the seminiferous tubules in both testes were observed in one rat in the low dose group, one rat in the medium dose group, and three rats in the high dose group. According to the report, one animal in each group had marked changes in the gonads.

Terrill and Lee (1977) exposed six male Sprague-Dawley rats to phenyl glycidyl ether at 29 ppm by inhalation for 4 hours

a day, 5 days/week, for 2 weeks. The rats were observed for an additional 2 weeks. The exposed rats showed decreased weight gain, atrophic changes in the kidney, liver, spleen, thymus, and testes, depletion of hepatic glycogen, and chronic catarrhal tracheitis.

In related studies, Terrill and Lee (1977) and Lee et al. (1977) reported the effects of phenyl glycidyl ether on groups of 24 male and 24 female Sprague-Dawley rats and 6 male beagle dogs. The animals were exposed to phenyl glycidyl ether at concentrations of 1, 5, and 12 ppm for 6 hours a day, 5 days a week, for 90 days. No toxic effects were seen in dogs exposed at any of the concentrations or in rats at the lowest concentration. Alopecia was observed in two male and seven female rats in the 5 ppm group and in one male and five females at 12 ppm. The authors also noticed perifollicular inflammation, keratotic follicles, and disturbances of the keratinization of the hair follicles.

Hine et al. (1956) exposed 10 rats to phenyl glycidyl ether at 100 ppm by inhalation 7 hours/day, 5 days/week, for a total of 50 exposures. At necropsy, tissues appeared normal in most rats, but the authors observed pulmonary inflammatory cell infiltration and "cloudy swelling" in the liver in two rats.

Kodama et al. (1961) observed increased leukocyte counts in five male rats given phenyl glycidyl either by intramuscular injection at 400 mg/kg/day for 3 days.

Stevens (1967) investigated sensitization to phenyl glycidyl

ether in guinea pigs. On each of 3 days, 0.01 ml of phenyl glycidyl ether was applied to the outer surface of one ear on each of six Alderly-Park albino guinea pigs. Four days after the last exposure, the guinea pigs received challenge doses of 0.2 ml on a clipped flank. A group of control guinea pigs with no previous exposure to phenyl glycidyl ether also were given 0.2 ml on a clipped flank. No irritation was seen in the controls, but two pretreated guinea pigs showed "light pink" erythema. Erythema on the four others was just barely visible. The author concluded that phenyl glycidyl ether caused sensitization.

Tang (1971) found that phenyl glycidyl ether completely inactivated porcine pepsin in vitro in 70 hours. The compound also inactivated human gastricsin, human pepsin, and bovine rennin, but it had no effect on bovine pepsinogen.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

Twenty-four and ninety-six hour LD50s for goldfish were reported to be 69 and 43 mg/liter, respectively (Verschueren 1977).

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

The bacteriostatic concentration of alpha-phenyl glycidyl ether for Escherichia coli was reported to be 3.2×10^{-5} moles/ml (Kilpatrick and Lambooy 1967).

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. WORK IN PROGRESS

No information was found in the sources searched.

DIGLYCIDYL ETHER OF BISPHENOL A

I. CHEMICAL AND PHYSICAL INFORMATION

A. Identification

1. CAS No.: 1675-54-3

2. NIOSH No.: TX38000

3. Synonyms and Trade Names

Oxirane, 2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bis-

Propane, 2,2-bis[p-(2,3-epoxypropoxy)phenyl]-

Bis(4-glycidyloxyphenyl)dimethylmethane

Bis(4-hydroxyphenyl)dimethylmethane diglycidyl ether

Bisphenol A diglycidyl ether

Dian diglycidyl ether

Diglycidyl bisphenol A

Diglycidyl diphenylolpropane ether

Diomethane diglycidyl ether

2,2-Bis(p-glycidyloxyphenyl)propane

2,2-Bis(p-hydroxyphenyl)propane diglycidyl ether

2,2-Bis(4-glycidyloxyphenyl)propane

2,2-Bis(4-hydroxyphenyl)propane diglycidyl ether

2,2-Bis(4'-glycidyloxyphenyl) propane

2,2-Bis[p-(2,3-epoxypropoxy)phenyl]propane

2,2-Bis[4-(2,3-epoxypropoxy)phenyl]propane

2,2-Bis[4-(2,3-epoxypropyloxy)phenyl]propane

4,4'-Bis(2,3-epoxypropoxy)diphenyldimethylmethane

4,4'-Isopropylidenebis[1-(2,3-epoxypropoxy)benzene]

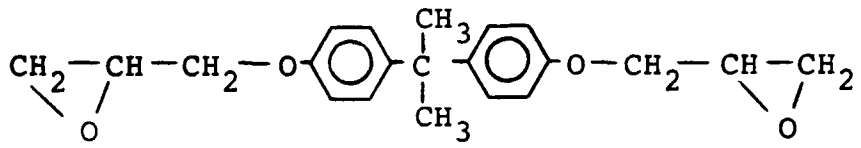
4,4'-Isopropylidenediphenol diglycidyl ether

Diphenylol propane diglycidyl ether

(NIH/EPA 1978, NIOSH 1978b)

B. Formulas and Molecular Weight

1. Structural Formula



(NIH/EPA 1978)

2. Empirical Formula

$C_{21}H_{24}O_4$ (NIH/EPA 1978)

3. Molecular Weight

340.40

C. Physical Properties

1. Description

Odorless liquid; sticky and tacky when handled

(TDB 1978)

2. Boiling Point

No information was found in the sources searched.

3. Melting Point

8-12°C (TDB 1978)

4. Vapor Pressure

No information was found in the sources searched.

5. Solubility

No information was found in the sources searched.

6. Octanol/Water Partition Coefficient

No information was found in the sources searched.

7. Specific Gravity

1.168 (TDB 1978)

D. Composition of the Commercial Product

No information was found in the sources searched.

DIGLYCIDYL ETHER OF BISPHENOL A

II. SOURCE AND FATE IN THE ENVIRONMENT

A. Sources

1. Production and Trends

No information was found in the sources searched.

2. Manufacturers

No information was found in the sources searched.

3. Use

As a basic active ingredient for epoxy resins which are used for sealing and encapsulating, for making castings and pottings, for formulating light-weight foams, and as binders in laminates of fiber glass, paper, wood sheets, and polyester cloth

(Patty 1963, NIOSH 1978c)

4. Occupational Exposure

Rank: 1677

Estimated number of persons exposed: 37,000*

* rough estimate

(NOHS 1976)

5. Release

No information was found in the sources searched.

B. Environmental Fate

1. Occurrence

No information was found in the sources searched.

2. Transformation

No information was found in the sources searched.

3. Bioaccumulation

No information was found in the sources searched.

III. BIOLOGICAL INFORMATION

A. Effects on Humans

Fregert and Thorgeirsson (1977) conducted patch tests with a 1% solution of diglycidyl ether of bisphenol A in acetone on 27 men and 7 women sensitive to epoxy resins. All 34 patients showed positive reactions.

B. Tests on Laboratory Organisms

1. Metabolism

No information was found in the sources searched.

2. Toxic Effects

a. Acute Toxicity

The acute toxicity of diglycidyl ether of bisphenol A, as reported by the NIOSH RTECS data base (1978a) and Hine and Rowe (1963), is given in Table III-1.

b. Carcinogenicity

According to Hine and Rowe (1963), skin painting with diglycidyl ether of bisphenol A for up to 2 years did not cause any tumors in mice and rabbits. Repeated subcutaneous injections in rats resulted in sarcomas in 25% of the animals. No further details were given.

Weil et al. (1963) gave 30-40 mice topical applications of diglycidyl ether of bisphenol A three times a week for the

life span of the animals. Each application amounted to "one brushful" of the undiluted compound, and the maximum period of treatment was 23 months. One papilloma was observed at 16 months. When the compound was retested by the same procedure, no tumors were found. Maximum treatment time was 27 months.

TABLE III-1

ACUTE TOXICITY OF DIGLYCIDYL ETHER OF BISPHENOL A

Parameter	Dosage	Animal	Route
LD50[1]	11,000 mg/kg	Rat	Oral
LD50[2]	11,400 mg/kg	Rat	Intragastric
LD50[2]	2,400 mg/kg	Rat	Intraperitoneal
LD50[2]	15,600 mg/kg	Mouse	Intragastric
LD50[2]	4,000 mg/kg	Mouse	Intraperitoneal
LD50[2]	19,800 mg/kg	Rabbit	Intragastric

[1]NIOSH RTECS (1978a)
[2]Hine and Rowe (1963)

c. Mutagenicity and Cell Transformation

Wade et al. (1978 as reported by NIOSH 1978b) reported that diglycidyl ether of bisphenol A was not mutagenic in Salmonella typhimurium TA98 and TA100. The compound was tested with and without liver microsomal extract from rats pretreated with phenobarbital.

Pullin and Legator (1977 as reported by NIOSH 1978b) reported that diglycidyl ether of bisphenol A gave weakly positive results

in the Ames test with S. typhimurium TA1535 but gave negative results in TA98. The compound was mutagenic both in the absence and presence of rat liver microsomes.

Pullin and Legator (1977 as reported by NIOSH 1978b) reported that diglycidyl ether of bisphenol A showed some activity in a host-mediated assay. Mutant strains of S. typhimurium were injected into the peritoneal cavity of mice that had been given diglycidyl ether of bisphenol A orally at doses between 125 and 1,000 mg/kg/day for 5 days. The authors attributed the activity of the compound to a decrease in the growth of microorganisms in the host animals. Pullin and Legator also reported that diglycidyl ether of bisphenol A was negative in a dominant lethal assay. Male mice were treated topically with the undiluted compound at 3 g/kg three times a week for a minimum of 87 weeks before mating. A control group was treated with saline. Thirteen to fourteen days after presumptive mating with the males, female mice were sacrificed and their uteri examined. No significant differences in the percentage of pregnancies, the total number of implants, and the number of fetal deaths were observed between control and experimental groups.

d. Teratogencity, Embryotoxicity, and Fetotoxicity

No information was found in the sources searched.

e. Other Toxicity

Thorgeirsson and Fregert (1977) reported that diglycidyl ether of bisphenol A caused sensitization in female guinea pigs. Twenty animals received intradermal injections of 0.1 ml of

5% (wt/vol) diglycidyl ether of bisphenol A in acetone and 0.1 ml of 5% (wt/vol) diglycidyl ether of bisphenol A in an equal mixture of complete Freund's adjuvant and acetone. Skin patch tests with 0.1 ml of the compound at 5% (wt/vol) in acetone were performed 1 and 3 weeks later. All of the treated guinea pigs were sensitized. No animals in a control group showed positive reactions.

Thorgeirsson et al. (1978) in a similar study also observed sensitization in 10 of 15 guinea pigs exposed to diglycidyl ether of bisphenol A at one-tenth the concentration used in the earlier study by Thorgeirsson and Fregert.

IV. ENVIRONMENTAL EFFECTS

A. Ecological Effects

1. Wild and Domestic Mammals

No information was found in the sources searched.

2. Wild and Domestic Birds

No information was found in the sources searched.

3. Fish, Amphibians, and Reptiles

No information was found in the sources searched.

4. Invertebrates

No information was found in the sources searched.

5. Plants and Algae

No information was found in the sources searched.

6. Bacteria and Other Microorganisms

No information was found in the sources searched.

7. Ecological Communities and Processes

No information was found in the sources searched.

B. Other Environmental Effects

No information was found in the sources searched.

V. Work in Progress

No information was found in the sources searched.

SUMMARY TABLE

CHARACTERISTICS OF GLYCIDOL AND ITS DERIVATIVES

Name	Solubility	Log P_{oct}	Estimated Environmental Release	Production	Estimated No. of Persons Exposed (Occupational)	Use
Glycidol	s in H_2O, alc, eth, ace, bz, and chl	*	*	*	∿105,000	As a stabilizer, demulsifier, dye-leveling agent
Glycidyl acrylate	i in H_2O	*	*	*	*	In manufacture of resins
Glycidyl methacrylate	*	*	*	*	∿105,000	*
Allyl glycidyl ether	s in H_2O, ace, tol, and oct	*	*	*	**	Diluent in resin systems
Butyl glycidyl ether	ss in H_2O	*	*	*	**	Diluent in resin systems
Cresyl glycidyl ether	*	*	*	*	**	Diluent in resin systems

SUMMARY TABLE (continued)

Name	Solubility	Log P_{oct}	Estimated Environmental Release	Production	Estimated No. of Persons Exposed (Occupational)	Use
Phenyl glycidyl ether	ss in H_2O; ∞ in ace and tol	*	*	*	**	Diluent in resin systems
Diglycidyl ether of bisphenol A	*	*	*	*	∿37,000	Active ingredient for epoxy resins

* No information was found in the sources searched.
** ∿118,000 for "glycidyl ethers"

Key to abbreviations:

s--soluble
ss--slightly soluble
∞--soluble in all proportions
i--insoluble
ace--acetone
alc--alcohol
bz--benzene
chl--chloroform
eth--ethane
H_2O--water
oct--octanol
tol--toluene

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APPENDIX A

ABSTRACTS AND AUTOMATED DATA BASES SEARCHED

Air Pollution Abstracts (APTIC)

CANCERLIT

CANCERPROJ

Chemical Abstracts (1978)

CHEMLINE

Environmental Mutagen Information Center File (EMIC)

Enviromental Teratology Information Center File (ETIC)

National Occupational Hazard Survey (NOHS)

NIH/EPA Substructure Search System

National Technical Information Service Data Base (NTIS)

Pollution Abstracts

Registry of Toxic Effects of Chemical Substances (RTECS)

Toxicology Data Bank (TDB)

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APPENDIX C

KEY TO ABBREVIATIONS

LD50 Median Lethal Dose
The dose of a test material, introduced by any route other than inhalation, that kills 50% of an experimental animal population within a given period of time

LC50 Median Lethal Concentration
The concentration of a test material in air or water that kills 50% of an experimental animal population within a given period of time

LDLo Lowest Published Lethal Dose
The lowest dose of a substance, introduced by any route other than inhalation over a given period of time, that has been reported to have killed members of a given species

LCLo Lowest Published Lethal Concentration
The lowest concentration of a substance in air or water that has been reported to have killed members of a given species over a given exposure time

TLV-TWA Threshold Limit Value-Time Weighted Average
The time-weighted average airborne concentration of a substance for an 8-hour workday or 40-hour workweek recommended by the American Conference of Governmental Hygienists as safe for nearly all workers

TLm Median Tolerance Limit
The concentration of a test material at which 50% of an experimental animal population survives for a specified time period

BOD_x Biochemical Oxygen Demand
A measure of the extent of biodegradation of an organic chemical by biota in water in a specific number of days (x)

NOHS Occupational Exposure

Rank: A number indicating the chemical's place in a list of approximately 7,000 occupational hazards ranked in order of the number of workers exposed. The lower the number, the more common the hazard.

Estimated number of persons exposed: This figure includes full- and part-time workers. For hazards ranked 1-200, the figure given is a

ADDENDUM TO
INFORMATION DOSSIERS ON SUBSTANCES
DESIGNATED BY
TSCA INTERAGENCY TESTING COMMITTEE
(October 1978)

CHLOROBENZENES

PENTACHLOROBENZENE

III.B.1. Metabolism

Villeneuve and Khera (1975) reported a study in which four groups, each containing five pregnant Wistar rats, received single daily oral doses of pentachlorobenzene at 25, 50, 100, and 200 mg/kg on days 6-15 of gestation. The rats were sacrificed on day 25 of pregnancy. The accumulation of pentachlorobenzene in the maternal and fetal viscera appeared to be dose-related. The highest concentration in maternal tissue was in the fat. The compound was also present in liver, brain, heart, kidney, and spleen. The mean concentrations in tissues from females given 200 mg/kg were 3,350 ppm in fat, 91.1 ppm in liver, 62.5 ppm in brain, 57.5 ppm in heart, 43.5 ppm in kidney, and 46.2 ppm in spleen. In the fetuses from these females, the brain contained pentachlorobenzene at 4.37 ppm and the liver contained 3.08 ppm.

Leber et al. (1977) examined the metabolic fate of pentachlorobenzene in rhesus monkeys each given an oral dose of 20 mg. The major urinary metabolites included two isomers of tetrachlorophenol, and the feces contained a substantial amount of unmetabolized pentachlorobenzene. The authors stated the pentachlorobenzene might have a prolonged retention time in rhesus monkeys.

REFERENCES

LEBER, A.P., FREUDENTHAL, R.I., BARON, R.L., and CURLEY, A. 1977. Pharmacokinetics and metabolism of pentachlorobenzene in rhesus monkeys. Toxicol. Appl. Pharmacol. 41:45 (Abstract)

VILLENEUVE, D.C., and KHERA, K.S. 1975. Placental transfer of halogenated benzenes (pentachloro-, pentachloronitro-, and hexabromo-) in rats. Environ. Physiol. Biochem. 5:328-331

HEXACHLOROBENZENE

On page 8 of the Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, the statement is made that "hexachlorobenzene is a demonstrated animal carcinogen." The following articles are relevant to the evaluation of the carcinogenicity of this compound:

CABRAL, J.R.P., SHUBIK, P., MOLLNER, T., and RAITANO, F. 1977. Carcinogenic activity of hexachlorobenzenes in hamsters. Nature 269:510-511

CABRAL, J.R.P., MOLLNER, T., RAITANO, F., and SHUBIK, P. 1978. Carcinogenesis study in mice with hexachlorobenzene. Abstracts of Papers for the Seventeenth Annual Meeting of the Society of Toxicology, San Francisco, Calif., March 12-16

1,2-DICHLOROPROPANE

II.A.1. Production and Trends

58.5 million lb (USITC 1977)

III.B.2.c. Mutagenicity and Cell Transformation

DeLorenzo et al. (1977) reported that 1,2-dichloropropane at 10-50 mg/plate was mutagenic in Salmonella typhimurium TA1535 and TA100 with and without microsomal activation. The compound was reported to be nonmutagenic in S. typhimurium TA1978.

REFERENCES

DeLORENZO, F., DEGL'INNOCENTI, S., RUOCCO, A., SILENGO, L., and CORTESE, R. 1977. Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res. 37:1915-1917

U.S. INTERNATIONAL TRADE COMMISSION (USITC). 1977. Synthetic Organic Chemicals, United States Production and Sales. Washington, D.C. USITC Publication 833

GLYCIDOL AND ITS DERIVATIVES

GLYCIDOL

II.A.1. Production and Trends

0.1 million lb (SRI 1977)

II.A.4. Occupational Exposure

Estimated number of persons exposed: 61,147 (NIOSH 1978a)

(Comment: This estimate of occupational exposure was based on statistical extrapolation. It replaces the rougher estimate given in the dossier.)

GLYCIDYL ETHERS

II.A.4. Occupational Exposure

Data on occupational exposure to the glycidyl ethers are given in Table 1:

TABLE 1

OCCUPATIONAL EXPOSURE TO GLYCIDYL ETHERS*

Compound	Estimated Number of Workers Potentially Exposed**
Glycidyl ethers***	71,000
Diglycidyl ether of bisphenol A	36,000
n-Butyl glycidyl ether	13,000

TABLE 1 (continued)

Compound	Estimated Number of Workers Potentially Exposed**
Phenyl glycidyl ether	8,000
Allyl glycidyl ether	2,000

*Adapted from NIOSH (1978b)
**A worker may be exposed to more than one glycidyl ether. Thus the exposure estimates are not additive. Because of the difficulty of obtaining data on the composition of trade name products, these estimates may be low (NIOSH 1978b).
***Exposures were entered into the NOHS data base either under the specific glycidyl ether (when the information was available) or under the general term "glycidyl ethers" (when more specific information was not available). To the extent that an exposure to a specific glycidyl ether was reported as exposure to "glycidyl ethers," the estimates for occupational exposure to individual glycidyl ethers may be low (NIOSH 1978b)

REFERENCES

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1978a. National Occupational Hazard Survey Print-Outs. Enclosed in letter from Joseph A. Seta, Hazard Section, Surveillance Branch, NIOSH, Cincinnati, Ohio, to Clement Associates, August 3, 1978

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1978b. NIOSH Current Intelligence Bulletin No. 29: Glycidyl Ethers. Prepublication copy. October 12, 1978

SRI INTERNATIONAL. 1977. Glycidol: Summary of data for chemical selection. Menlo Park, Calif. September 1977

On page 11 of the Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, reference is made to the "demonstrated carcinogenicity of certain members" of the category of glycidol and its derivatives.

The following articles are relevant to the evaluation of the carcinogenicity of two examples of these compounds:

Triethylene glycol diglycidyl ether (CAS No. 1954-28-5)

SHIMKIN, M.B., WEISBURGER, J.H., WEISBURGER, E.K., GUBAREFF, N., and SUNTZEFF, V. 1966. Bioassay of 29 alkylating chemicals by the pulmonary-tumor response in strain A mice. J. Natl. Cancer Inst. 36:915-935

Glycidal (CAS No. 765-34-3)

VAN DUUREN, B.L., ORRIS, L., and NELSON. 1965. Carcinogenicity of epoxides, lactones and peroxy compounds. II. J. Natl. Cancer Inst. 35:707-717

VAN DUUREN, B.L., LANGSETH, L., ORRIS, L., TEEBOR, G., NELSON, N. and KUSCHNER, M. 1966. Carcinogenicity of epoxides, lactones and peroxy compounds. IV. Tumor response in epithelial and connective tissue in mice and rats. J. Natl. Cancer Inst. 37:825-834

VAN DUUREN, B.L., LANGSETH, L., GOLDSCHMIDT, B.M., and ORRIS, L. 1967a. Carcinogenicity of epoxides, lactones and peroxy compounds. VI. Structure and carcinogenic activity. J. Natl. Cancer Inst. 39:1217-1228

VAN DUUREN, B.L., LANGSETH, L., ORRIS, L., BADEN, M. and KUSCHNER, M. 1967b. Carcinogenicity of epoxides, lactones and peroxy compounds. V. Subcutaneous injection in rats. J. Natl. Cancer Inst. 39:1213-1216