United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Criteria and Standards Division
Washington DC 20460

EPA 440/5-80-039
October 1980

EPA

Ambient Water Quality Criteria for Dichlorobenzenes

AMBIENT WATER QUALITY CRITERIA FOR

DICHLOROBENZENE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

DISCLAIMER

This report has been reviewed by the Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

AVAILABILITY NOTICE

This document is available to the public through the National Technical Information Service, (NTIS), Springfield, Virginia 22161.

FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

ACKNOWLEDGEMENTS

Aquatic Life Toxicology

William A. Brungs, ERL-Narragansett
U.S. Environmental Protection Agency

David J. Hansen, ERL-Gulf Breeze
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects

Kirby Campbell (author), HERL
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

Terence M. Grady (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

Penelope A. Fenner-Crisp
U.S. Environmental Protection Agency

Donna Sivulka, ECAO-Cin
U.S. Environmental Protection Agency

Si Duk Lee, EPA-Cin
U.S. Environmental Protection Agency

Eliot Lomnitz
U.S. Environmental Protection Agency

Steven D. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

Myron Mehlman
Mobil Oil Corporation

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, C. Russom, R. Rubinstein.

TABLE OF CONTENTS

CRITERIA DOCUMENT

DICHLOROBENZENES

CRITERIA

Aquatic Life

The available data for dichlorobenzenes indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 1,120 and 763 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for dichlorobenzenes indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 1,970 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of dichlorobenzenes to sensitive saltwater aquatic life.

Human Health

For the protection of human health from the toxic properties of dichlorobenzene ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 400 µg/l

For the protection of human health from the toxic properties of dichlorobenzenes ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 2.6 mg/l.

INTRODUCTION

The dichlorobenzenes are a class of halogenated aromatic compounds represented by three structurally similar isomers: 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzene. Dichlorobenzenes have the molecular formula $C_6H_4Cl_2$ and a molecular weight of 147.01 (Weast, et al. 1975).

1,2-Dichlorobenzene (1,2-DCB) and 1,3-dichlorobenzene (1,3-DCB) are liquids at normal environment temperatures, while 1,4-dichlorobenzene (1,4-DCB) is a solid. Melting points (MP), boiling points (BP), and densities for the three isomers are presented in Table 1 (Weast, et al. 1975).

The dichlorobenzenes are soluble in water at concentrations which are toxic to aquatic organisms. The solubilities in water of the 1,2-, 1,3-, and 1,4-dichlorobenzene isomers at 25°C are 145,000 µg/l, 123,000 µg/l, and 80,000 µg/l, respectively (Jacobs, 1957). The dichlorobenzenes also are readily soluble in natural fats or fat soluble substances (Windholz, 1976). The logs of the octanol/water partition coefficients for 1,3-dichloro- and 1,4-dichlorobenzene are 3.44 and 3.37, respectively (U.S. EPA, 1978). All three dichlorobenzene isomers are relatively volatile. The vapor pressure of 1,2-dichlorobenzene at 20°C is 1 mm Hg; the vapor pressure of 1,3-dichlorobenzene at 39°C is 5 mm Hg; and the vapor pressure of 1,4-dichlorobenzene at 25°C is 0.4 mm Hg (Jordan, 1954; Kirk and Othmer, 1963).

The major uses of 1,2-DCB are as a process solvent in the manufacturing of toluene diisocyanate and as an intermediate in the synthesis of dyestuffs, herbicides, and degreasers (West and Ware, 1977). 1,4-Dichlorobenzene is used primarily as an air deodorant and an insecticide, which account for 90 percent of the total production of this isomer (West and Ware, 1977). Information is not available concerning the production and use of 1,3-DCB.

TABLE 1

Physical Properties of Dichlorobenzenes*

Compound/Isomer	MP (°C)	BP (°C)	Density (°C)
1,2-Dichlorobenzene	-17.6	179	1.30 g/ml (20)
1,3-Dichlorobenzene	-24.2	172	1.29 g/ml (20)
1,4-Dichlorobenzene	-53.0	174	1.25 g/ml (20)

*Source: Weast, et al. 1975

However, it may occur as a contaminant of 1,2- or 1,4-DCB formulations. Both 1,2-dichloro- and 1,4-dichlorobenzene are produced almost entirely as by-products during the production of monochlorobenzene. Combined annual production of these two isomers in the United States approaches 50,000 metric tons (West and Ware, 1977).

REFERENCES

Jacobs, S. 1957. The Handbook of Solvents. D. Van Nostrand Co., Inc., New York.

Jordan, T.E. 1954. Vapor Pressure of Organic Compounds. Interscience Publishers, Inc., New York.

Kirk, R.E. and D.E. Othmer. 1963. Kirk-Othmer Encyclopedia of Chemical Technology. 8th ed. John Wiley and Sons, Inc., New York.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. EPA Contract No. 68-01-4646. U.S. Environ. Prot. Agency, Washington, D.C.

Weast, R.C., et al. 1975. Handbook of Chemistry and Physics. 56th ed. CRC Press, Cleveland, Ohio.

West, W.L. and S.A. Ware. 1977. Investigation of selected potential environmental contaminants: Halogenated benzenes. U.S. Environ. Prot. Agency, Washington, D.C.

Windholz, M. (ed.) 1976. The Merck Index. 9th ed. Merck and Co., Rahway, New Jersey.

Aquatic Life Toxicology*

INTRODUCTION

Comparable data for the bluegill, Daphnia magna, and Selenastrum capricornutum (an alga) are available for 1,2-, 1,3-, and 1,4-dichlorobenzene. Most of these tests were conducted under static conditions and the test concentrations were not measured. The alga, based on chlorophyll a and cell numbers, has higher 96-hour EC_{50} values.

As with the freshwater species, the saltwater data base for the dichlorobenzenes is limited to results of acute exposures of fish and invertebrate species, predominantly performed with unmeasured concentrations under static test conditions. The LC_{50} and plant values range from 1,970 to greater than 100,000 µg/l; the mysid shrimp was most sensitive. Although differences in acute toxicity of the dichlorobenzenes exist among species, the toxicity of different dichlorobenzenes to individual species is similar so for practical purposes they may be considered to be equally toxic.

EFFECTS

Acute Toxicity

Daphnia magna and a midge are the only freshwater invertebrate species for which data for dichlorobenzenes are available (Table 1). The data for Daphnia magna were obtained using similar methods (U.S. EPA, 1978) and the 48-hour EC_{50} values are 2,440, 28,100, and 11,000 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively. As will be seen, there is no great difference in sensitivity between the bluegill and Daphnia magna. Comparable test results (U.S. EPA, 1978) with other chlorinated benzenes and Daphnia

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

magna are available. The 48-hour EC_{50} values range from 86,000 µg/l for chlorobenzene to 5,280 µg/l for pentachlorobenzene, indicating an increase in toxicity of the chlorinated benzenes with increasing chlorination. The midge 48-hour EC_{50} values are 11,760 and 13,000 µg/l for 1,2- and 1,4-dichlorobenzene, respectively.

The bluegill has been tested (U.S. EPA, 1978) and the 96-hour LC_{50} values, obtained under static and unmeasured test conditions, are 5,590, 5,020, and 4,280 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively (Table 1). These results indicate that the position of the chlorine atoms on the benzene ring probably does not influence the toxicity of dichlorobenzenes very much. Dawson, et al. (1977) also tested the bluegill and their 96-hour LC_{50} was 27,000 µg/l for 1,2-dichlorobenzene which result is different from that (5,590 µg/l) for the same species by different investigators (U.S. EPA, 1978). This difference may be due to the fact that Dawson, et al. (1977) added 1,2-dichlorobenzene to the surface of the test water without the subsequent mixing usually done for such tests.

Two flow-through measured tests were conducted with the fathead minnow and the rainbow trout (U.S. EPA, 1980); the 96-hour LC_{50} values for 1,3- and 1,4-dichlorobenzene were 7,790 and 4,000 µg/l, respectively. For the minnow and the rainbow trout the 96-hour LC_{50} values were 1,580 and 1,120 µg/l for 1,2- and 1,4-dichlorobenzene, respectively.

When the 96-hour LC_{50} values obtained for the bluegill under similar conditions (U.S. EPA, 1978) for the dichlorobenzenes and a variety of other chlorinated benzenes (chlorobenzene, trichlorobenzene, tetrachlorobenzene and pentachlorobenzene) are compared, there is good correlation between the degree of chlorination and acute toxicity. (See the criterion document for

chlorinated benzenes for details.) These LC_{50} values range from 15,900 µg/l for chlorobenzene to 250 µg/l for pentachlorobenzene with the dichlorobenzenes being approximately three times more toxic than chlorobenzene.

The mysid shrimp was more sensitive to the dichlorobenzenes in 96-hour acute exposures (Table 1) than were the fish; LC_{50} values ranged from 1,970 to 2,850 µg/l. As with the freshwater test species, comparable results (U.S. EPA, 1978) with other chlorinated benzenes and the mysid shrimp are also available. The LC_{50} values range from 16,400 µg/l for chlorobenzene to 160 µg/l for pentachlorobenzene, again indicating an increase in toxicity of the chlorinated benzenes with increasing chlorination.

The sheepshead minnow was similarly sensitive to the dichlorobenzenes; 96-hour LC_{50} values ranged from 7,400 to 9,660 µg/l (Table 1). Toxicity of these compounds to fishes may be inadequately estimated by these results since data on only one other fish species are available. The tidewater silverside (Dawson, et al. 1977) was as sensitive as the sheepshead minnow with a 96-hour LC_{50} of 7,300 µg/l.

Comparable data (U.S. EPA, 1978) are available for the sheepshead minnow and other chlorinated benzenes. (See the criterion document for chlorinated benzenes for details.) These LC_{50} values range from 10,500 µg/l for chlorobenzene to 830 µg/l for pentachlorobenzene and indicate, again, a good correlation between the degree of chlorination and acute toxicity.

Chronic Toxicity

An embryo-larval test with fathead minnows and 1,2-dichlorobenzene has been conducted (U.S. EPA, 1978) and the chronic value for this test is 2,000 µg/l (Table 2). Embryo-larval tests have also been conducted with the fathead minnow and 1,3- and 1,4-dichlorobenzene (ERL-D, 1980) and the acute-

chronic ratios for these compounds are both 5.2 (Table 2). No other data on chronic effects on freshwater or saltwater fish or invertebrate species are available.

This range of chronic values for the dichlorobenzenes (763 to 2,000 µg/l) and the fathead minnow demonstrate that these chemicals are less chronically toxic than the more highly chlorinated chemicals. The fathead minnow chronic values for 1,2,4-trichlorobenzene (two tests) and 1,2,3,4-tetrachlorobenzene were 287,000, and 318 µg/l, respectively.

Plant Effects

The freshwater alga, Selenastrum capricornutum, has been tested for the effects of dichlorobenzenes on chlorophyll a and cell numbers (Table 3). The EC_{50} values range from 91,600 to 179,000 µg/l for the dichlorobenzenes, which results indicate little if any relationship to the location of chlorine atoms on the benzene ring.

Comparable test procedures (U.S. EPA, 1978) were used for other chlorinated benzenes and, as with the fish and invertebrate species, toxicity is increased with an increase in chlorination.

The saltwater algal species, Skeletonema costatum, has also been tested (U.S. EPA, 1978) for acute effects of exposure to the dichlorobenzenes (Table 3). The EC_{50} values for cell number or chlorophyll a ranged from 44,100 to 59,100 µg/l.

Comparable test procedures (U.S. EPA, 1978) were used for other chlorinated benzenes and this saltwater alga, and toxicity generally increases with an increase in chlorination.

Residues

Bioconcentration by the bluegill (Table 4) has been studied using ^{14}C-labeled dichlorobenzenes, with thin layer chromatography for verification (U.S. EPA, 1978). The bioconcentration factors were 89, 66, and 60 for

1,2-, 1,3-, and 1,4-dichlorobenzene, respectively. Equilibrium occurred within 14 days and the half-life for each dichlorobenzene was less than 1 day. These results suggest that the dichlorobenzenes are unlikely to be a tissue residue problem in the aquatic environment.

Additional comparable data (U.S. EPA, 1978) are available in the chlorinated benzenes criterion document for tetrachlorobenzene and pentachlorobenzene and the bluegill. These compounds are much more lipophilic than the dichlorobenzenes with bioconcentration factors of 1,800 for tetrachlorobenzene and 3,400 for pentachlorobenzene. Hexachlorobenzene has been tested with the fathead minnow and the pinfish and the bioconcentration factors were 22,000 and 23,000, respectively. In addition, the half-lives of chlorinated benzenes increase with chlorination from less than 1 day for the dichlorobenzenes, to 2 to 4 days for tetrachlorobenzene, and greater than 7 days for pentachlorobenzene. These results indicate that the environmental risk due to tissue residues increases with increasing chlorination and support the conclusion above that dichlorobenzenes will not likely cause a serious residue problem for aquatic life.

Miscellaneous

Neely, et al. (1974) estimated a steady-state bioconcentration factor for p-dichlorobenzene (1,4-dichlorobenzene) using a short exposure and depuration study with the rainbow trout. This estimated value was 210 (Table 5).

Two polychaete species and clam embryos and larvae were relatively insensitive to exposures to 1,2- and 1,4-dichlorobenzene (Table 5). The LC_{50} values for 1,2-dichlorobenzene and clam embryos and larvae were greater than 100,000 µg/l (Davis and Hindu, 1969). Acute exposures to 1,2- and 1,4-di-

chlorobenzene at 100,000 µg/l were responsible for 55-100 percent emergence of two polychaete species from parasitized oysters (Mackenzie and Shearer, 1959).

Summary

The 48-hour EC_{50} values for Daphnia magna and a midge for 1,2-, 1,3-, and 1,4-dichlorobenzene ranged from 2,440 to 28,100 µg/l with no consistent difference due to location of the chlorine atoms or sensitivity of the two species. The range of LC_{50} values for three fish species and the same dichlorobenzenes was 1,120 to 27,000 µg/l, and the rainbow trout appears to be a little more sensitive than the two warmwater fish species. Embryo-larval tests with the fathead minnow and 1,2-, 1,3-, and 1,4-dichlorobenzene have been conducted and the chronic values ranged from 763 to 2,000 µg/l. The acute-chronic ratio for both 1,3- and 1,4-dichlorobenzene was 5.2. The freshwater alga, Selenastrum capricornutum, is less sensitive to the dichlorobenzenes with EC_{50} values that range from 91,600 to 179,000 µg/l. The measured steady-state bioconcentration factors for the three dichlorobenzenes are in the range of 60 to 89 for the bluegill. There appears to be little if any difference in toxicity to freshwater organisms among the dichlorobenzenes.

The saltwater mysid shrimp has been exposed to 1,2-, 1,3-, and 1,4-dichlorobenzene and the 96-hour LC_{50} values were 1,970, 2,850, and 1,990 µg/l, respectively. For the sheepshead minnow and the same chemicals, the 96-hour LC_{50} values were in the range of 7,400 to 9,660 µg/l. No chronic toxicity data are available for any saltwater species. The 96-hour EC_{50} for a saltwater alga and 1,2-, 1,3-, and 1,4-dichlorobenzene ranged from 44,100 to 59,100 µg/l. The saltwater data suggest that there is no difference in toxicity among the three dichlorobenzenes.

CRITERIA

The available data for dichlorobenzenes indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 1,120 and 763 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for dichlorobenzenes indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 1,970 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of dichlorobenzenes to sensitive saltwater aquatic life.

Table 1. Acute values for dichlorobenzenes

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	1,2-dichloro-benzene	2,440	2,440	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	1,3-dichloro-benzene	28,100	28,100	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	1,4-dichloro-benzene	11,000	11,000	U.S. EPA, 1978
Midge, *Tanytarsus dissimilis*	S, M	1,2-dichloro-benzene	11,760	11,800	U.S. EPA, 1980
Midge, *Tanytarsus dissimilis*	S, M	1,4-dichloro-benzene	13,000	13,000	U.S. EPA, 1980
Rainbow trout, *Salmo gairdneri*	FT, M	1,2-dichloro-benzene	1,580	1,580	U.S. EPA, 1980
Rainbow trout, *Salmo gairdneri*	FT, M	1,4-dichloro-benzene	1,120	1,120	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	1,3-dichloro-benzene	7,790	7,790	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	1,4-dichloro-benzene	4,000	4,000	U.S. EPA, 1980
Bluegill, *Lepomis macrochirus*	S, U	1,2-dichloro-benzene	27,000	--	Dawson, et al. 1977
Bluegill, *Lepomis macrochirus*	S, U	1,2-dichloro-benzene	5,590	12,000	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,3-dichloro-benzene	5,020	5,020	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,4-dichloro-benzene	4,280	4,280	U.S. EPA, 1978

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	S, U	1,2-dichloro-benzene	1,970	1,970	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,3-dichloro-benzene	2,850	2,850	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,4-dichloro-benzene	1,990	1,990	U.S. EPA, 1978
Tidewater silverside, *Menidia beryllina*	S, U	1,2-dichloro-benzene	7,300	7,300	Dawson, et al. 1977
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,2-dichloro-benzene	9,660	9,660	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,3-dichloro-benzene	7,770	7,770	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,4-dichloro-benzene	7,400	7,400	U.S. EPA, 1978

* S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for dichlorobenzenes

Species	Test*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Fathead minnow, Pimephales promelas	ELS	1,2-dichloro-benzene	1,600-2,500	2,000	U.S. EPA, 1978
Fathead minnow, Pimephales promelas	ELS	1,3-dichloro-benzene	1,000-2,270	1,510	U.S. EPA, 1980
Fathead minnow, Pimephales promelas	ELS	1,4-dichloro-benzene	560-1,040	763	U.S. EPA, 1980

* ELS = Early life stage

Acute-Chronic Ratios

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Fathead minnow, Pimephales promelas	1,3-dichloro-benzene	7,790**	1,510	5.2
Fathead minnow, Pimephales promelas	1,4-dichloro-benzene	4,000	763	5.2

**These values were selected to calculate the acute-chronic ratio because tests were conducted in the same dilution water (Lake Superior).

Table 3. Plant values for dichlorobenzenes (U.S. EPA, 1978)

Species	Chemical	Effect	Result (µg/l)
	FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	1,2-dichloro-benzene	EC50 96-hr chlorophyll *a*	91,600
Alga, *Selenastrum capricornutum*	1,2-dichloro-benzene	EC50 96-hr cell number	98,000
Alga, *Selenastrum capricornutum*	1,3-dichloro-benzene	EC50 96-hr chlorophyll *a*	179,000
Alga, *Selenastrum capricornutum*	1,3-dichloro-benzene	EC50 96-hr cell number	149,000
Alga, *Selenastrum capricornutum*	1,4-dichloro-benzene	EC50 96-hr chlorophyll *a*	98,100
Alga, *Selenastrum capricornutum*	1,4-dichloro-benzene	EC50 96-hr cell number	96,700
	SALTWATER SPECIES		
Alga, *Skeletonema costatum*	1,2-dichloro-benzene	EC50 96-hr chlorophyll *a*	44,200
Alga, *Skeletonema costatum*	1,2-dichloro-benzene	EC50 96-hr cell number	44,100
Alga, *Skeletonema costatum*	1,3-dichloro-benzene	EC50 96-hr chlorophyll *a*	52,800
Alga, *Skeletonema costatum*	1,3-dichloro-benzene	EC50 96-hr cell number	49,600
Alga, *Skeletonema costatum*	1,4-dichloro-benzene	EC50 96-hr chlorophyll *a*	54,800
Alga, *Skeletonema costatum*	1,4-dichloro-benzene	EC50 96-hr cell number	59,100

Table 4. Residues for dichlorobenzenes (U.S. EPA, 1978)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)
		FRESHWATER SPECIES		
Bluegill, Lepomis macrochirus	whole body	1,2-dichloro-benzene	89	14
Bluegill, Lepomis macrochirus	whole body	1,3-dichloro-benzene	66	14
Bluegill, Lepomis macrochirus	whole body	1,4-dichloro-benzene	60	14

Table 5. Other data for dichlorobenzenes

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Rainbow trout, *Salmo gairdneri*	1,4-dichloro-benzene	--	Estimated steady-state bioconcentration factor = 210	--	Neely, et al. 1974
		SALTWATER SPECIES			
Polychaete, *Polydora websteri*	1,2-dichloro-benzene	3 hrs	65% emergence from parasitized oysters	100,000	Mackenzie & Shearer, 1959
Polychaete, *Nerlis* sp.	1,2-dichloro-benzene	3 hrs	70% emergence from parasitized oysters	100,000	Mackenzie & Shearer, 1959
Clam (embryo), *Mercenaria mercenaria*	1,2-dichloro-benzene	48 hrs	LC50	>100,000	Davis & Hindu, 1969
Clam (larva), *Mercenaria mercenaria*	1,2-dichloro-benzene	12 days	LC50	>100,000	Davis & Hindu, 1969
Polychaete, *Polydora websteri*	1,4-dichloro-benzene	3 hrs	55% emergence from parasitized oysters	100,000	Mackenzie & Shearer, 1959
Polychaete, *Nereis* sp.	1,4-dichloro-benzene	3 hrs	100% emergence from parasitized oysters	100,000	Mackenzie & Shearer, 1959

REFERENCES

Davis, H.C. and H. Hindu. 1969. Effects of pesticides on embryonic development of clams and oysters and on survival and growth of the larvae. U.S. Fish Wildl. Serv. Fish. Bull. 67: 393.

Dawson, G.W., et al. 1977. The toxicity of 47 industrial chemicals to fresh and saltwater fishes. Jour. Hazard. Mater. 1: 303.

MacKenzie, C.L., Jr. and L.W. Shearer. 1959. Chemical control of Polydora websteri and other annelids inhabiting oyster shells. Proc. Natl. Shellfish Assoc. 50: 105.

Neely, W.B., et al. 1974. Partition coefficient to measure bioconcentration potential of organic chemicals in fish. Environ. Science Tech. 8: 1113.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

U.S. EPA. 1980. Unpublished laboratory data. Environmental Research Laboratory - Duluth.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

The production, use, transport, and disposal of dichlorobenzenes result in widespread dispersal to, and therefore contamination of, environmental media, with resulting opportunity for exposure of the biosphere (including man). Dichlorobenzenes (DCBs) have been detected or quantified in rivers, ground water, municipal and industrial discharges, drinking water, air, and soil. They have also been detected in tissues of lower organisms living in contaminated waters and in exposed higher animals. Persistence in the environment varies among compounds and with conditions. The more highly halogenated benzenes are more generally resistant to biodegradation and are therefore more persistent.

Table 1 shows detection and concentration of DCBs in raw and contaminated waters. 1,2-DCB has been reported as entering water systems at average levels of 2 mg/l as a result of its use by industrial wastewater treatment plants for odor control (Ware and West, 1977). 1,4-DCB enters wastewater systems because of its use in toilet blocks (Ware and West, 1977). Table 2 summarizes the data on DCBs in drinking water samples. Reported DCB levels in drinking water samples have thus far been relatively low (i.e., compared to trihalomethanes).

As with halomethanes, new chlorinated organic compounds including chlorinated benzenes have been reported from chlorination of raw and waste waters containing organic precursor material.

TABLE 1

Dichlorobenzenes in Raw and Discharge Waters[+*]

Medium or Sample	Location	1,2-DCB	1,3-DCB	1,4-DCB	DCB
Ground water	Miami, Fla.	1(cce) d(voa)	0.5(cce) d(voa)	0.5(cce) d(voa)	
Raw water contam. with municipal waste	Philadelphia, Pa.	d(voa)	d(voa)	d(voa)	
Raw water contam. with municipal waste	Cincinnati, Ohio		d(voa)		
Raw water contam. with indust. discharge	Cincinnati, Ohio	d(voa)	d(voa)		
Raw water contam. with indust. discharge	Lawrence, Mass.		d(voa)		
Industrial discharge	Lawson's Fork Creek, N.C.				32,12(fid)
Industrial discharge	Catawba River	690(fid)			33(fid)
Industrial waste holding	Kentucky	15(ecd)			0.9(ecd)
Ground water	Kentucky	1.2,71(ecd)			1.2,12(ecd)
Industrial discharge	Big Bigby Creek, Tenn.	40(fid)		58(fid)	
Submarine outfall, sew. treatment effluent	Point Loma, Calif.	< .01,2.2		0.42,1	
Submarine outfall, sew. treatment effluent	Oxnard, Calif.	4.7, 2.3		9.3, 3.1	
Submarine outfall, sew. treatment effluent	Joint Wat. Plant, So. Calif.	5.1(ec) 3.3(ms) 7.3, 12		7.6(ec) 7.4(ms) 7.4, 12	
Submarine outfall, sew. treatment effluent	Orange Co. Sew. Dep.	1.3(ec) 2.4		2.8(ec) 4.9	
Submarine outfall, sew. treatment effluent (5 miles)	Hyperion Sew. Treat. Works, Los Angeles, Calif.	1.9, 4		3.4, 5.1	

TABLE 1 (Continued)

Medium or Sample	Location	1,2-DCB	1,3-DCB	1,4-DCB	DCB
Submarine outfall, sew. (7 miles) effluent	Los Angeles River	183(ec) 14(ms) 30, 440		90(ec) 7.8(ms) 34, 230	
River, rec. surface run-off after storm (4 day period)	Los Angeles River	0.01		0.05	
Chemical plant waste-water (seepage and cooling)	Michigan				10
Textile waste effluents	U.S.			detected	

+In mg x 10^{-3}; (cce) = carb. chlorof. extract; (voa) = vol. org. anal.; (ecd) = elect. conduct. detect. (fid) = flame ioniz. det.; (ec) = electron capt.; (ms) = mass spec; (d) = detected.

*Source: Ware & West 1977

TABLE 2

Dichlorobenzenes in U.S. Drinking Waters, mg x 10^{-3}/l

	1,2-DCB	1,3-DCB	1,4-DCB	Reference
Highest concentrations reported as of 1975	1	<3	1	U.S. EPA, 1975
National Organics Reconnaisance Survey				
Miami, Fla.	1	0.5	0.5	U.S. EPA, 1975
Philadelphia, Pa.	d*	d	d	
Cincinnati, Oh.	d	d	d	
Lawrence, Mass.		d	d	

Concentrations reported in U.S. EPA's NOMS study during 1976 and 1977	Phase+ II	Phase+ III	Phase II	Phase III	Phase I	Phase II	Phase III	Reference
No. pos/no. anal.	0/113	4/110	0/113	2/110	2/111	20/113	29/110	U.S. EPA, 1978a
Mean of pos. analyses, µg/l	-	2.5	-	0.10	2.0	0.14	0.07	
Median, all results, µg/l	<0.005	<0.005	<0.005	<0.005	<1	<0.005	<0.005	

*d = detected but not quantified.

+Phase I: samples shipped and stored at 2 to 8°C for 1 to 2 weeks prior to analyses; Phase II: samples held at 20 to 25°C for 3 to 6 weeks prior to analyses permitting reactions to proceed to end points (terminal values); Phase III: samples processed with or without chlorine reducing agent - in these data, samples were processed without quenching additive, so were permitted to react to terminal values.

Glaze, et al. (1976) reported the formation of many new chlorinated organic compounds as a result of chlorine treatment of secondary municipal wastewater effluents. Total organic-bound (TOCl) levels in concentrated extracts of effluents increased significantly after chlorination. Some of the aromatic halides identified were chlorobenzenes. Kopperman, et al. (1976) reported higher levels of chlorinated organic compounds (including dichlorobenzenes) in fish exposed (90 days) to chlorinated wastewater treatment plant effluent than in those exposed to nondisinfected effluent. They interpreted their data as indicating that even gentle chlorination conditions cause chlorine to be incorporated into organic molecules. Gaffney (1976) studied removal and formation of organic compounds at waste treatment plants processing waters containing effluents from textile processing plants. His data indicated that chlorinated components were formed by chlorination in the disinfection process at the treatment plant. In water purification plant samples the concentration of DCBs tended to increase in a downstream pattern. In two case studies the concentration of DCB in finished water was higher than in the raw water supply.

Data on air concentrations of DCBs are very limited, but they suggest the potential for inhalation exposure. Dichlorobenzenes were measured in aerial fallout and high-volume samples taken at various locations in the Los Angeles area (Ware and West, 1977). Fallout samples were obtained at El Segundo, Catalina Island, San Clemente Island, La Jolla, and Santa Barbara. Levels of 1,2-DCB were reported as less than 8, 27, and less than 53 ng/m^2 ($mg \times 10^{-6}/m^2$) for Catalina Island, San Clemente, and Santa

Barbara, respectively. Apparently no 1,4-DCB was detected in fallout samples from any of the sites. DDT, Aroclor 1254®, and Aroclor 1242® were present in samples from all sites and at levels much greater than for DCB. High-volume air samples were collected at the El Segundo, Catalina Island, and San Clemente sites. The 1,2-DCB level in air at El Segundo (estimated from reported filter analytic values at approximately 0.3 x 10^{-6} mg/m^3) was higher than that at Catalina Island and at San Clemente (similarly estimated at approximately 0.04 x 10^{-6} mg/m, respectively). 1,2-DCB concentrations were considerably lower than for DDT and Aroclor 1254® at all sites. Data for 1,4-DCB were inadequate because of high and variable values in the analytical process blanks. The authors concluded that aerial fallout of chlorinated benzenes is less significant than that of DDT and PCBs because of the higher volatility of chlorinated benzenes. Gas-phase concentrations of DCBs were not reported.

Morita and Ohi (1975) have reported "appreciable" levels of 1,4-DCB in the indoor and ambient air of Tokyo. The results of their survery of air contamination levels are summarized in Table 3. 1,4-DCB concentrations from 2.7 to 4.2 mg x $10^{-3}/m^3$ ($\mu g/m^3$) were measured outdoors in central Tokyo. In the outdoor atmosphere of suburban Tokyo levels from 1.5 to 2.4 mg x $10^{-3}/m^3$ were obtained. Considerably higher levels (from 0.105 to 1.7 mg/m^3) were measured in samples of indoor air (bedroom, closet, wardrobe). 1,4-DCB was also measured in human adipose tissue of residents. Morita and Ohi (1975) collected their airborne 1,4-DCB in the vapor phase by use of cold solvent traps, whereas Young, et al. (1976)

TABLE 3

Atmospheric Concentrations of 1,4-Dichlorobenzene
In and Around Tokyo*

Area		Concentration of 1,4-DCB ($mg \times 10^{-3}/m^3$)
Outdoors Cental Tokyo	a. Residential	4.2
	b. Busy station square	2.7
	c. Main street	2.9
Suburbs	a. Quiet Lake, 50 km west	1.5
	b. Major highway, 30 km west	2.4
	c. Farm 15 km northwest	2.1
Indoors	a. Inside wardrobe	1,700
	b. Inside closet	315
	c. Bedroom	105

*Source: Morita and Ohi, 1975

collected their DCB from the particulate fraction of air in southern California using filter and fallout samplers. The much higher airborne concnetrations reported by Morita and Ohi (1975) may reflect that their Tokyo downtown and suburban air was more contaminated than the air at the California sites and/or that DCB is present in ambient air more as vapor than as a component of suspended particulates. In New Orleans, although all DCB isomers were detected in human blood samples in the area of New Orleans, no DCBs were detected in air or drinking water samples (Ware and West, 1977). The source of DCBs in the blood was not determined.

DCB contamination may exist in certain workplace atmospheres at much higher concentrations than exist in ambient air, presenting a greater exposure to persons in some occupations than to the general public. In workplace atmospheres associated with the manufacture of 1,4-DCB, measurements were made that found 1,4-DCB at air concentrations averaging 204 mg/m^3 (range: from 42 to 288 mg/m^3) near shoveling and centrifuging, and 150 mg/m^3 (range: from 108 to 204 mg/m^3) during pulverizing and packaging. No concentrations of less than 48 mg/m^3 were found (Ware and West, 1977).

In the late 1930's a survey of fulling operations in three mills of the woolen industry using 1,2-DCB as a solvent, vapor concentrations in eight samples of workroom air ranged from 60 to 1,620 mg/m^3 (Hollingsworth, et al. 1958). Concentrations of 1,4-DCB were determined in samples of workplace air associated with manufacture and/or handling of 1,4-DCB (Hollingsworth, et al. 1956). In the 62 samples of the first survey concentrations of 1,4-DCB ranged from 6 to 3,300 mg/m^3 (average, 510 mg/m^3). In the

second survey 15 samples collected under recurrent, severe, unpleasant work conditions ranged from 600 to 4,350 mg/m^3 (average, 630 mg/m^3) in 21 samples collected under conditions associated with worker complaints (eye and nasal irritation). In 25 other samples, collected under no-complaint conditions, concentrations ranged from 90 to 510 mg/m^3 (average, 270 mg/m^3).

Novokovskaya, et al. (1976) reported 1,2-DCB as being among several organic compounds in gaseous emissions from the production of silicone medical tubing. 2,4-Dichlorobenzene peroxide was an ingredient of resins used in the manufacture. Emission gases were said to be below the maximum allowable concentration (MAC). The recommended MAC for 1,2-DCB in the Soviet Union as of 1970 was 20 mg/m^3 (International Agency for Research on Cancer (IARC), 1974).

Ingestion from Food

Dichlorobenzenes may be present in food commodities as a result of direct or indirect contamination from proper or improper uses or accidents. Schmidt (1971) reported the tainting of pork (disagreeable odor and taste) as a result of the use in pig stalls of an odor-control product containing 1,4-DCB. Eggs were tainted within three days of exposure of hens to 1,4-DCB concentrations from 20 to 38 mg/m^3. Neither the hens nor the egg production were affected (Langner and Hilliger, 1971). Morita, et al. (1975) reported detectable levels of 1,4-DCB in fish of the Japanese coastal waters. A species of mackerel (Trachurus trachurus) contained 0.05 mg/kg (wet weight). These authors also reported analyzing 1,4-DCB in human adipose tissue (obtained from central Tokyo hospitals and medical examiners' offices).

Dichlorobenzenes may occur in plant tissues as degradation products of lindane or other chemicals. A DCB was found among several other polychlorinated benzenes constituting a nonpolar group of metabolites of lindane used on lettuce and endives (Kohli, et al. 1976). DCBs were recovered as lindane metabolites in roots of wheat plants grown from lindane-treated seed (Balba and Saha, 1974). 1,3-DCB was reported to be among several metabolites of gamma-pentachloro-1-cycylohexane in corn and pea seedlings (Mostafa and Moza, 1973). There are not enough data to state quantitatively the degree of DCB exposure through total diet. Available evidence indicates that degree of environmental contamination by DCBs as a result of lindane degradation is probably very small (Ware and West, 1977). 1,2-DCB and/or 1,4-DCB have also been measured in soils as products of lindane degradation (Mathur and Saha, 1977).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita

consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

Measured steady-state bioconcentration factors of 89, 66 and 60 were obtained for 1,2-dichlorobenzene, 1,3-dichlorobenzene, and 1,4-dichlorobenzene, respectively, using bluegills (U.S. EPA, 1978b,c). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factors for 1,2-dichlorobenzene, 1,3-dichlorobenzene, and 1,4-diclorobenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans are calculated to be 55.6, 41.2, and 37.5, respectively.

PHARMACOKINETICS

Absorption

The dichlorobenzenes may be absorbed through the lungs, gastrointestinal (GI) tract, and intact skin. Relatively low water solubility and high lipid solubility of halobenzenes favor their penetration of most membranes by diffusion, including pulmonary and GI epithelia, the brain, hepatic parenchyma, renal tubules, and the placenta (Ware and West, 1977).

From their investigation of atmospheric contamination by 1,4-DCB in the Tokyo area (Table 3), Morita and Ohi (1975) suggested that inhalation is a major mode of human exposure to environmental 1,4-DCB. The same authors (Morita, et al. 1975) reported finding 1,4-DCB in all samples of human adipose tissue examined. In 32 samples obtained from local hospitals and medical examiners, representing subjects of both sexes and ages of 13 to 80 years, 1,4-DCB was measured at concentrations of 0.2 to 11.7 mg/kg (mean 2.3). The mean concentration in adipose tissue was 246 times the mean concentration (9.3×10^{-3} mg/l) measured in six samples of whole blood from males and females aged 21 to 35 years. Although 1,4-DCB was also measured at 0.05 and 0.012 mg/kg in samples of fish of the Japanese coastal waters, no concentrations were reported for other food items or for drinking water, so the relative contribution to body burden of 1,4-DCB by various exposure sources and routes is not clear.

Inhalation of DCB vapors was primarily responsible for most (16 of 22) of a series of clinical cases of poisoning reported in the literature (Girard, et al. 1969; Sumers, et al. 1952; Weller and Crellin, 1953; Perrin,1941; Cotter, 1953; Gadrat, et al. 1962; Petit and Champeix, 1948; Nalbandian and Pierce, 1965; Campbell and Davidson, 1970; Downing, 1939; Frank and Cohen, 1961; Ware and West, 1977). 1,2-DCB was the principal or a significant ingredient in five of these case reports and 1,4-DCB was similarly involved in eleven. Of these 16 cases, 10 were occupationally related.

There are no data on the quantitative efficiency of absorption of DCBs via the respiratory route. However, Pagnotto and Walkley

(1966) have measured urinary excretion of the principal DCB metabolite in occupationally exposed (by inhalation) persons and reported that excretion occurred "soon after exposure...began and peaked...at the end of the working shift," indicating that respiratory absorption during inhalation exposure is rapid.

Dichlorobenzenes, as well as other chlorinated benzene derivatives, may be absorbed through the gastrointestinal (GI) tract. Lower halobenzenes are more readily and rapidly absorbed by this route than the higher homologues (Ware and West, 1977; Rimington and Ziegler, 1963). Three of the 22 cases of human DCB poisoning mentioned above resulted from accidentally or deliberately ingesting 1,4-DCB (Campbell and Davidson, 1970; Frank and Cohen, 1961; Hallowell, 1959). These cases clearly indicate significant absorption by the GI route. Data on quantitative absorption efficiency of DCBs are sparse. Azouz, et al. (1955) detected no 1,4-DCB in feces of rabbits dosed intragastrically with the compound in oil. This suggests virtually complete absorption at least under those conditions. Animal experiments indicate that GI absorption of DCBs occurs and is fairly rapid, since metabolites, various effects, and excretion have been observed within one day of oral dosing (Rimington and Ziegler, 1963; Azouz, et al. 1953; Poland, et al. 1971). 1,2-DCB and other components of Rhine River water contamination fed to rats at less than 0.4 to 2 mg/kg/day were absorbed and accumulated in various tissues indicating significant absorption by the GI tract even at low levels of ingestion (Jacobs, et al. 1974a,b).

Evidence in the literature indicates the DCBs are also absorbed via the skin (Ware and West, 1977). Three of the 22 clinical case reports mentioned previously involved dermal exposure and consequent toxicosis (Girard, et al. 1969; Downing, 1939; Nalbandian and Pierce, 1965). Riedel (1941) reported absorption of 1,2-DCB through the skin of rats in lethal amounts after five dermal applications under severe test conditions (painting twice daily directly on a 10 cm^2 area of abdominal skin) (Ware and West, 1977). There were no available data on the quantitative efficiency of absorption by the dermal route in man or animals.

Distribution

As noted previously, the relative insolubility in water and high lipid solubility of DCBs render them able to cross barrier membranes (Ware and West, 1977). This indicates that they (DCBs) would be widely distributed to various tissues. Clinical and experimental data also indicate wide distribution to various tissues. Lipid soluble halobenzenes tend to accumulate in the body, may reach toxic levels, and may recirculate for long periods (Ware and West, 1977).

Cases of human poisonings and animal testing demonstrating changes in blood, blood chemistry, neuromuscular function, liver and kidney structure and function, and bone marrow elements indicate distribution of absorbed DCBs in and by blood to at least the brain, heart, liver, kidney, and bone marrow in multiple mammalian species (references noted: Hollingsworth, et al. 1956, 1958; Ito, et al. 1973; Totaro and Licari, 1964; Totaro, 1961; Salamone and Coppola, 1960; Coppola, et al. 1963; Rimington and Ziegler, 1963;

Azouz, et al. 1953, 1955; Poland, et al. 1971; Girard, et al. 1969; Sumers, et al. 1952; Cotter, 1953; Campbell and Davidson, 1970; Frank and Cohen, 1961; Petit and Champeix, 1948).

In a study by Jacobs, et al. (1974a) 1,2-DCB and other chemicals known to be contaminants in Rhine River water were fed daily in a mixture to rats at 2 mg/kg (each component). Tissue accumulation was greater in fat than in the liver, kidney, heart, and blood. The same investigators (Jacobs, et al. 1974b) fed such a contaminant mixture to rats at two lower dose levels (0.4 and 0.8 mg/day) for 4 to 12 weeks. A dose-related accumulation of all compounds (including 1,2-DCB) in abdominal and renal adipose tissue occurred, and there was no evidence of saturation. The studies of Morita and Ohi (1975) have shown 1,4-DCB in adipose tissue (mean about 1 mg/kg) and blood (mean about 0.01 mg/l) of humans exposed to ambient pollution levels in the Tokyo area.

Injection of DCB intramuscularly into hens at about 50 mg/kg resulted in recovery of 0.4 to 0.6 percent of the dose from yolks of eggs. The egg white contained negligible amounts. An increase in the chlorine content of chlorinated benzenes increased the period from injection to accumulation of residue in the yolk (Kazama, et al. 1972). DCB, as a metabolic residue of DDT injected intraperitoneally into mice during pregnancy, was found in fetal and maternal blood, brain, liver, and fat (Schmidt and Dedek, 1972).

Metabolism

Metabolism of the 1,2-DCBs was studied by Azouz, et al. (1955) in chinchilla rabbits. Single doses of 500 mg compound/kg body weight were given by stomach tube, the 1,2-DCB suspended in water

and the 1,4-DCB dissolved in olive oil at 25 percent (w/v). Their results showed 1,2-DCB to be mainly metabolized by oxidation to 3,4-dichlorophenol and excreted (primarily in urine) as conjugates of glucuronic and sulphuric acids. Peak excretion of these occurred on the first day after dosing. Minor metabolites also formed and excreted as conjugates included 2,3-dichlorophenol (peak excretion on second day), 4,5-dichlorocatechol, 3,4-dichlorocatechol, and 3,4-dichlorophenylmercapturic acid. Metabolism and urinary excretion of 1,2-DCB was considered relatively slow, being essentially complete five to six days after dosing. During this period an average of 76 percent of the dose was excreted as "total conjugates," of which identified components were 48 percent glucuronide, 21 percent ethereal sulfate, and 5 percent mercapturic acid. 1,4-DCB was metabolized mainly by oxidation to 2,5-dichlorophenol and excreted as only glucuronides and ethereal sulfates. Peak excretions occurred on the second day after dosing, possibly reflecting a slower absorption (however, no 1,4-DCB was detected in the feces during the 6-day test period, indicating that absorption was essentially complete). 2,5-Dichloroquinol was also formed as minor metabolite (about 6 percent of the dose), but in contrast to the case with 1,2-DCB, no mercapturic acid or dichlorocatechol was formed from 1,4-DCB. Total conjugates (64 percent of dose) during the 6-day period after dosing were comprised essentially of glucuronide (36 percent) and ethereal sulfate (27 percent), but excretion of metabolites was not considered complete after six days. Pagnotto and Walkley (1966) indicated that 2,5-dichlorophenol was also the principal metabolite of 1,4-DCB in

humans, and that levels excreted in urine were useful in assessing occupational exposure by inhalation.

Parke and Williams (1955) studied the metabolism and excretion of 1,3-DCB using the rabbit and methods as described by Azouz, et al. (1955), discussed previously. An average of 54 percent of the administered dose of 1,3-DCB was measured as urinary conjugates of the metabolites, primarily glucuronides (36 percent) and ethereal sulfates (7 percent) which reach peak excretion on the first day after dosing. The major metabolite of 1,3-DCB was shown to be 2,3-dichlorophenol (2,3-DCP), accounting for at least 20 percent of the dose. 3,5-Dichlorophenol, 2,4-dichlorophenylmercapturic acid, and 3,5-dichlorocatechol were additional, minor metabolites. Excretion of 1,3-DCB was considered to be relatively slow, as with 1,2- and 1,4-DCB. Metabolites in measurable quantities were not excreted after five days from dosing, at which time about half of the dose was accounted for as total conjugates.

The detailed analytic and metabolic chemistries involved in the above studies are omitted here but are discussed in the original reports (Azouz, et al. 1955; Parke and Williams, 1955).

Daily dosing of rats with DCBs at doses from 450 to 1,000 mg/kg has induced delta-aminolevulinic acid (ALA) synthetase activity in liver and has produced hepatic porphyria characterized by increased levels of porphyrins and porphyrin precursors in liver and urine (Rimington and Ziegler, 1963; Poland, et al. 1971). Dosing with 1,3-DCB at 1,000 mg/kg was prophyrogenic, but at 800 mg/kg a biphasic influence on hepatic metabolic activity was noted. There was an initial stimulation of ALA synthetase activity and

increased urinary excretion of coproporphyrin, peaking at one and three days, respectively, and then declining. There was also a stimulation of drug metabolism by the hepatic microsomal system that peaked at five days. The investigators (Poland, et al. 1971) emphasize that in some cases porphyria could be caused by the 1,3-DCB or its metabolites (primarily 2,4-dichlorophenol in rabbits). However, since 2,3-DCP was not found in significant quantity in the experimental rats, it was concluded that the 1,3-DCB was responsible for the porphyria shown in this experiment. The authors interpreted their decline in porphyria as being a result of 1,3-DCB stimulating its own metabolism. A similar biphasic pattern of coproporphyrin excretion was observed in rats dosed with 2,4-DCP (the major metabolite of 1,3-DCB) and 1,4-DCB at 900 mg/kg/day. Carlson and Tardiff (1976) also reported on the induction of hepatic microsomal xenobiotic metabolism systems by DCB and other chlorinated benzenes. Chronic dosing of 1,4-DCB at low levels (10 to 40 mg/kg/day) in male rats increased detoxication of EPN (o-ethyl o-p-nitrophenyl phenylphosphonothiolate) benzpyrene hydroxylation and azoreductase activity (Ware and West, 1977). Effects persisted for at least 30 days after termination of exposure. The ability of halogenated aromatic compounds such as DCBs to induce enzyme systems associated with the metabolism of foreign compounds may influence the metabolism and effects of endogenous steroids, drugs, and other environmental contaminants (Ware and West, 1977).

Excretion

As noted above, excretion of the metabolic products of the DCBs, primarily through the urine, is rather slow. Five to six

days were required to metabolize and eliminate the metabolites of a single intragastric dose (500 mg/kg) of 1,2-DCB or 1,3-DCB. Elimination of the metabolites of 1,4-DCB (similar dose) were not complete at six days after dosing (Parke and Williams, 1955), although this may have been influenced by a slower or delayed absorption. The excretion of DCB metabolites in rabbits dosed (single, intragastic) at 500 mg/kg body weight, as reported by Parke and Williams (1955) is summarized in Table 4. Peak excretion for some of the metabolites occurred on the first day after dosing and for others, later. Measurements by Pagnotto and Walkley (1966) of urinary dichlorophenol in workers exposed to 1,4-DCB indicated that excretion of metabolites began within the workshift "soon after exposure began," peaked at the end of the working shift, then decreased rapidly at first and then more slowly, continuing for several days.

Ware and West (1977) stated that the portion of halogenated benzenes that escape biotransformation "may be excreted in part unchanged in the urine, feces, or expired air." No information was available to quantify these phenomena. These authors also indicated that halobenzenes which are not extensively metabolized: (1) may be hazardous if they form an arene oxide intermediate; (2) not only tend to accumulate in the body reaching toxic levels but may recirculate for long periods; and (3) may cause repeated tissue insults and increase the likelihood of cellular damage from toxic intermediates (e.g., arene oxides, phenols). Azouz, et al. (1955) and Parke and Williams (1955) did not report any excretion by way of the feces, nor did they report the fate of that portion of administered DCBs unaccounted for in urinary metabolites. Available data

TABLE 4

Excretion of DCB Metabolites by Rabbits*

Metabolite	1,2-DCB	1,3-DCB	1,4-DCB
Glucuronide	48	36	36
Ethereal sulfate	21	7	27
Mercapturic acid	5	11	0
Total conjugates	74	51	63
Monophenols	39	25	35
Catechols	4	3	0
Quinols	0	0	6
Period of excretion, days	6+	5+	6++

Data expressed as percent of dose fed (500 mg/kg).

+Excretion apparently complete.

++Excretion not complete.

*Source: Parke and Williams, 1955.

also did not provide information on the efficiency of detoxication and elimination of the DCBs in humans at lower, more "realistic" environmental levels.

As noted previously, nonmetabolized DCBs accumulate in tissues. Bioconcentration factors in fish (bluegill sunfish) were reported as 89, 66, and 60 for 1,2-, 1,3-, and 1,4-DCB, respectively (U.S. EPA, 1978c). Morita and Ohi (1975) reported levels averaging about 2 mg/kg in adipose tissues of residents of the Tokyo area compared with blood levels averaging only 0.0095 mg/l. When several Rhine River contaminants including 1,2-DCB were fed to rats, tissue accumulation was greater in fat tissue than in liver, kidney, heart, and blood, and there was no evidence of saturation (at dose levels of less than 1 mg/day) (Jacobs, et al. 1974a,b). Residue of DCB in eggs of injected (intramuscularly) hens was measured at much higher levels in the yolk sac than in white (about 0.5 percent of dose vs. virtually none) (Lunde and Ofstad, 1976). Eggs of hens exposed to 1,4-DCB in air at 20 or 38 mg/m^3 developed an unpleasant taste within three days, and two metabolites were detected in the yolks (Langner and Hilliger, 1971). Undesirable odor and taste of pork meat from swine exposed to vapor of 1,4-DCB used for odor control in the stalls were reported by Schmidt (1971).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Prior to the 1940's very little had been reported concerning any harmful properties of DCBs, which had become industrially important in recent years. DCBs were generally regarded as having very low or no toxicity for man (Downing, 1939; Perrin, 1941).

However, clinical data reported beginning in 1939 have substantiated the conclusion that DCBs should no longer be considered harmless (Perrin, 1941).

Most reported cases (16 of 22) of human poisoning by DCBs since 1939 have resulted from long term exposure primarily by inhalation of vapors, but some have also resulted from exposure by ingestion (3 of 22) and skin absorption (3 of 22). Toxic exposures have been occupational in nature in most cases, but have also involved the use or misuse of DCB products in the home. Most case reports (15 of 22) have involved exposure to agents containing primarily 1,4-DCB, and the remainder involved primarily 1,2-DCB. In some of these, DCB mixtures including 1,3-DCB were involved. Target systems or tissues have involved one or more of the following: liver, blood (or reticuloendothelial system, including bone marrow and/or immune components), central nervous system (CNS), respiratory tract, and integument (references noted: Dupont, 1938; Girard, et al 1969; Gadrat, et al. 1962; Downing, 1939; Sumers, et al. 1952; Cotter, 1953; Petit and Champeix, 1948; Perrin, 1941; Weller and Crellin, 1953; Hallowell, 1959; Campbell and Davidson, 1970; Frank and Cohen, 1961; Nalbandian and Pierce, 1965; Ware and West, 1977). Clinical findings in these reports, which are summarized in Table 5, imply broad toxicologic propensities for the DCBs in terms of biological systems and tissues affected.

Riedel (1941) reported that a burning sensation was produced when 1,2-DCB was applied for 15 minutes to the skin of human subjects. The response intensified with continued exposure up to one hour and abated when the liquid was removed. However, hyperemia

TABLE 5

Human Poisoning by Dichlorobenzene

Compound	Subject and Exposure	Effects	Reference
1,2-DCB (vapor)	Sewage workers; occupational; inhalation; effluent from dry cleaning establishment.	Eye and upper respiratory tract irritation, vomiting.	Dupont, 1938
1,2-DCB solvent mixtures: 80% 1,2-DCB; 15% 1,4-DCB; 2% 1,3-DCB	Male, 40 yrs; occupational; use of solvent to clean equipment; chronic daily exposure probably inhalation of vapor, and perhaps dermal absorption from clothing.	Weakness, fatigue; peripheral lymphadenopathy; chronic lymphoid leukemia.	Girard, et al. 1969
1,2-DCB solvent mixture: 95% 1,2-DCB; 5% 1,4-DCB	Female, 18 yrs; occupational; chronic daily inhalation exposure to vapors as pressing-ironing worker.	Severe acute hemolytic anemia; leukocytosis; polynucleosis; fatigue, nausea, headache; icterus; bone marrow hyperplasia; possible inherent predisposing factor.	Gadrat, et al. 1962
1,2-DCB and other chlorobenzene	Male, 60 yrs; occupational; filling barrels with 1,2-DCB and other chlor. benzenes (mono-, tri-); chronic inhalation of vapors (last 3 yrs.), perhaps also skin contact.	Anemia, requiring transfer to other work.	Girard, et al. 1969
1,2-DCB included in mixture	Male, 47 yrs; occupational; handling window sashes dipped in solution; chronic skin contact (also inhalation).	Contact eczematoid dermatitis (itch, eruption) on hands, arms, face, erythema, edema, bullae in response to skin test.	Downing, 1939
1,2-DCB (37% in commerc. soln.)	Female, 15 yrs; non-occupational; chronic repeated dermal contact from compulsive use of cleaning solution on clothing (in place).	Acute myeloblastic leukemia progressing to 100% leukoblastosis, hemorrhage, death.	Girard, et al. 1969
1,2-DCB 80% (in solvent mixtue with 1,4-DCB, 15% and 1,3-DCB, 2%)	Female, 55 yrs; non-occupational; chronic repeated inhal. exposure to vapors from use of solution to clean clothes; 1 to 2 l/yr.	Acute myeloblastic leukemia.	Girard, et al. 1969

TABLE 5 (continued)

Compound	Subject and Exposure	Effects	Reference
1,4-DCB primarily	Female, 30 yrs; occupational; for two years selling mothballs and insecticide products containing 1,4-DCB chiefly; chronic inhalation, perhaps some dermal component.	Weakness, nausea, splenomegaly; "severe hepatocellular derangement and ensuing portal hypertension" with esophageal varices.	Sumers, et al. 1952
1,4-DCB primarily	Female, 34 yrs; occupational; demonstrating 1,4-DCB products in booth in department store; odor strong in area;chronic inhalasure to vapors.	Malaise, then acute nausea, vomiting, headache, icterus, hepatomegaly, splenomegaly, esophageal varices and hemorrhoids; subacute yellow atrophy and cirrhosis of liver.	Cotter, 1953
1,4-DCB	Male, 52 yrs; occupational; used 2 years in fur warehouse (formerly used naphthalene); chronic inhalation exposure to high vapor levels.	Weakness, nausea, hematemesis, jaundice, emaciation, petech, hemorrhages; hepatomegaly, splenomegaly, hemorrhoids; proteinuria, biliribinuria; hematuria; anemia, leukopenia; subacute yellow atrophy of liver.	Cotter, 1953
1,4-DCB primarily	Female, 19 yrs; occupational; crushing, pouring, seiving, filling containers; poor ventilation; chronic inhalation of vapors.	Marked asthenia, dizziness, weight loss; anemia and reactional leucocytosis.	Petit and Champeix, 1948
1,4-DCB	Female, occupational; casting 1,4-DCB in molds; chronic inhalation (skin contribution unknown, if any).	Severe anemia.	Perrin, 1941
1,4-DCB	Male, 20 yrs. and workmates; occupational; 1,4-DCB manufacturing activities; 1 to 7 months exposure; inhalation (presumably).	Weight loss, exhaustion, decreased appetite; methemoglobinemia and other blood pathologies.	Ware and West, 1977
1,4-DCB	Male, 62 yrs; non-occupational; used "moth killer" product in bathroom at home, chronic inhalation of vapors, and wearing of impregnated clothing (possible skin exposure).	Asthenia, dizziness; anemia, hypogranulocytosis. Similar to cases of intoxication by benzene.	Perrin, 1941

TABLE 5 (continued)

Compound	Subject and Exposure	Effects	Reference
1,4-DCB	Female, 36 yrs; non-occupational; use of commericial moth killer in home (presumably inhalation of vapors).	Acute illness with intense headache, profuse rhinitis, periorbital swelling.	Cotter, 1953
1,4-DCB	Male, 60 yrs; non-occupational; 3 to 4 month exposure to "moth gas vapor" in home.	Headache, weight loss, diarrhea numbness, clumsiness, icterus, enlarged liver, anemia, neutropenia; developed ascites, died; acute yellow atrophy of liver.	Cotter, 1953
1,4-DCB	Female, wife of above, non-occupational; prolonged severe exposure to "moth gas vapor."	Gradual loss of strength and weight, then abdominal swelling and jaundice before acute illness; elevated temperature and pulse, dilated vessels, swollen liver, toxic granulocytosis; died 1 year later; acute yellow atrophy (liver), Laennec's cirrhosis, splenomegaly.	Cotter, 1953
1,4-DCB	Female, 53 yrs; non-occupational; used moth eradicator product heavily in home for 12 to 15 years, odor always apparent; chronic inhalation of vapor.	Chronic progressive cough and dyspnea with mucoid sputum, wheezing, fatigue, diminished breath sounds and rales; abnormal lung field on x-ray; fibrotic, rubbery lung with architecture changes on histology of biopsy; diagnosis: pulmonary granulomatosis.	Weller and Crellin, 1953
1,4-DCB	Male, 3 yrs; non-occupational; played with canister of de-mothing crystals, spreading on floor, handling; ingestion, likely acute.	Listlessness, jaundice, oliguria, methemoglobinuria and other urine abnormalities, anemia, hypothermia; diagnosis: acute hemolytic anemia.	Hallowell, 1959

TABLE 5 (Continued)

Compound	Subject and Exposure	Effects	Reference
1,4-DCB	Female, 21 yrs; non-occupational; ingestion during pregnancy of toilet air freshner blocks (pica) at rate of 1 to 2 each week.	Fatigue, anorexia, dizziness, edema of ankles; hypochromic microcytic anemia; bone marrow normoblastic hyperplasia; diagnosis: toxic hemolytic anemia. Recovery complete.	Campbell and Davidson, 1970
1,4-DCB	Female, 19 yrs; non-occupational; ingestion (pica), 4 to 5 moth pellets daily for 2½ years.	Increased skin pigmentation in areas 3 to 7 cm. diameter on limbs; mental sluggishness, tremor, unsteady gait upon withdrawl, along with decrease in pigmentation; 1 diagnosis: fixed drug eruption, conversion hysteria.	Frank and Cohen, 1961
1,4-DCB	Male, 69 yrs; non-occupational; dermal exposure, presumably interrupted; episode precipitated by use of chair treated with 1,4-DCB.	Dyspnea followed by stiff neck; "tightness" in chest, "gas pains" in abdomen; symmetrical petechia and purpura on extremitities, swelling discomfort; stool occult blood positive, blood cells in urine, and incr. BUN; basophil degranul. test positive for 1,4-DCB; diagnosis: allergic (anaphylactoid) purpura acute glomerulonephritis.	Nalbandian and Pierce, 1965

and blisters developed afterward at the site of application and were followed by a brown pigmentation that persisted at least three months (Hollingsworth, et al. 1958). Analyses of workroom air associated with 1,2-DCB manufacture and handling operations at the Dow Chemical Company were reported by Hollingsworth, et al. (1958) as ranging from 6 to 264 mg/m^3, with a 40-sample average of 90 mg/m^3. Medical examinations of workers from time to time, including hemograms and urinalyses, revealed no evidence of organic injury or adverse hematologic effects attributable to 1,2-DCB exposure. Although Patty (1963) and Hollingsworth, et al. (1958) stated that eye and nose irritation are not noticeable at the concentration in air detectable by the average person (300 mg/m^3), the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) mentions that a ceiling limit of 300 mg/m^3 should prevent serious but not all eye and nose irritation. Elkins (1959) reported concentrations approaching 600 mg/m^3 to be irritating but without other effects (ACGIH, 1977).

Hollingsworth, et al. (1956) have reported on surveys of plant conditions associated with the manufacture of 1,4-DCB. Workroom air contamination levels were previously summarized in the section on Exposure. Workers were monitored also under the various conditions of air contamination in the surveys. These data indicated that concentrations of 1,4-DCB greater than 960 mg/m^3 were irrespirable (intolerable) for unacclimated persons, i.e., painful irritation of the eyes and nose occurred at levels of 480 to 960 mg/m^3, odor was strong at 180 to 360 mg/m^3, and a faint odor was noticeable at 90 to 180 mg/m^3. Workers complained under conditions

yielding air sample concentrations ranging from 800 to 1,020 mg/m^3, but conditions yielding samples with concentrations of 90 to 510 mg/m^3 did not elicit complaints. In the data of periodic medical examinations on the workers no evidence was found of organic injury or adverse changes in hematology or eye lenses attributable to 1,4-DCB exposure (Hollingsworth, et al. 1956). Solid particles of 1,4-DCB and heavy vapor or fumes (such as when heated and volatilized in poorly ventilated spaces) are painful to the eyes and nose. The painful effect of vapor is evident to most people at 300 to 480 mg/m^3 and is severe at 960 mg/m^3 or more. Tolerance or acclimatization may occur with repeated exposure, so sensory warning properties may be less protective of more generalized toxicity in these persons (Hollingsworth, et al. 1956).

Solid 1,4-DCB is not regarded as significantly irritating to intact skin unless held in close contact for some time, when it may produce a burning sensation. Warm fumes or strong solutions may be irritating to skin on prolonged and repeated contact, but 1,4-DCB is said to produce no significant hazard from skin irritation or absorption except under extreme conditions (Hollingsworth, et al. 1956).

Although Berliner (1939) reported two cases of human cataracts that he believed to be due to chronic exposure to a 1,4-DCB-containing moth or deodorant product, Hollingsworth, et al. (1956) has interpreted considerable subsequent human data as indicating that 1,4-DCB does not produce human cataracts.

Varshavskaya (1967a) reported that odor and taste thresholds for 1,2-DCB in water were determined to be 0.002 and 0.0001 mg/l,

and for 1,4-DCB, 0.002 and 0.006 mg/l, respectively. The olfactory and gustatory thresholds for DCBs were also separately reported as 0.001 to 0.002 mg/l (Varshavskaya, 1967b). These organoleptic properties have been considered in establishing Russian tolerance levels of 1,2- and 1,4-DCB in drinking water (Stofen, 1973).

The 1,2- and 1,4-DCBs are extensively metabolized. One theory for the mechanism of toxicity of DCBs (i.e., cellular damage) is that reactive metabolites such as arene oxides or epoxides are formed in the process of metabolic transformation of the parent foreign compound through the action of hepatic microsomal enzyme systems involving cytochrome P-450. The enzymes concerned with foreign compounds (including drugs), often referred to as mixed function oxidases (MFO), are located in the endoplasmic reticulum (ER) of liver cells and require nicotinamide adenine dinucleotide phosphate ($NADPH_2$), molecular oxygen, and P-450 (a cytochrome). Biotransformation of drugs and other xenobiotic chemicals occurs in two phases: (1) oxidation, reduction, and hydrolysis reactions, and (2) syntheses or conjugations. Biotransformation enzymes and reactions vary among species and tissues and are influenced by steroids, various intermediate and metabolic byproducts and xenobiotics. P-450 content and the ability to form toxic intermediate metabolites also vary with species. Other factors affecting biotransformation and xenobiotic toxicity are the quantity of enzymes catalyzing conjugation with glutathione, an important detoxification mechanism (glutathione depletion by such a process is associated with toxicity and cellular damage), subsequent formation of mercapturic acids, and the concentration of the enzyme epoxide hydrase (Ware and West, 1977).

Hepatic damage in rats is enhanced when biotransformation of bromobenzenes (a prototype hepatotoxic chemical relative of DCB) is stimulated by pretreatment with phenobarbital (an MFO-inducer or stimulant). Conversely, blocking metabolism of the bromobenzene by use of SKF-525A or piperonyl butoxide (metabolic inhibitors) lessens the toxicity. Studies of halobenzenes have shown that toxicity such as reflected by hepatic necrosis is a result of their conversion to reactive toxic intermediate metabolites (Ware and West, 1977). In the case of bromobenzene, hepatic necrosis results from the reaction of the toxic intermediate, arene oxide, with cellular macromolecules. Severity of hepatic necrosis correlates well with the extent of covalent binding and with the depletion of glutathione from conjugation with toxic metabolites (Ware and West, 1977).

Bromobenzene and 1,2-DCB caused hepatic necrosis in rats, significant covalent binding, mercapturic acid excretion, and glutathione depletion (Ware and West, 1977).

In 1937, Cameron, et al. report early toxicity tests of 1,2-DCB. In the work a mixture containing only 48.8 percent 1,2-DCB was used, so conclusions as to specific toxicity of the pure compound may be questionable. Later, Hollingsworth, et al. (1958) exhaustively investigated the toxicity of 1,2-DCB using inhalation, gastric intubation, and ocular exposure techniques in several species of experimental animals over a range of lower dose levels. In the inhalation studies, groups of 20 rats, eight guinea pigs, four rabbits, and two monkeys were exposed to vapor seven hours per day, five days per week for six to seven months at an

average concentration of 560 mg/m^3. On the basis of the following criteria, none of the following effects were noted in any of the species: gross appearance, behavior, growth, organ weights, hematology (rabbits, monkeys), urinalysis (qualitative, for blood, sugar, albumin, sediment), blood urea nitrogen, gross and microscopic examination of tissues and mortality. A similar test using 20 rats, 16 guinea pigs, and 10 mice exposed to 290 mg/m^3 in the same pattern for six and one-half months was also negative.

Hollingsworth, et al. (1958) conducted single and repeated-oral-dose studies of 1,2-DCB. Intubation of 10 guinea pigs with 1,2-DCB (50 percent in olive oil) in single oral doses of 800 mg/kg resulted in loss of body weight, but was survived by all subjects, whereas 2,000 mg/kg doses were fatal to all subjects. In a test of repeated doses of 1,2-DCB in olive oil emulsified with acacia, groups of white rats were dosed by stomach tube five days a week for a total of 138 days in 192 days at dose levels of 18.8, 188, and 386 mg/kg. Positive toxicologic findings in the high-dose subjects included: increased liver and kidney weights, decreased spleen weight, and slight to moderate cloudy swelling on microscopic examination of the liver. In the intermediate-dose group, liver and kidney weights were slightly increased. No adverse effects were noted at the low-dose level. Two drops of undiluted 1,2-DCB in the rabbits' eyes caused pain and conjuctival irritation which cleared completely within one week. Prompt washing with water reduced pain and irritation.

Varshavskaya (1967a) reported on the hygienic evaluation of dichlorobenzenes in reservoir waters. Median lethal dose

(LD_{50}) values for DCBs given to four animal species in single doses in oil by stomach tube are as follows (in mg/kg body weight):

Species	1,2-DCB	1,4-DCB
White mice	2,000	3,220
White rats	2,138	2,512
Rabbits	1,875	2,812
Guinea pigs	3,375	7,593

The acute poisoning manifestations were similar between compounds and among species which included: hyperemia of mucous membranes; increased lacrimation and salivation; excitation followed by sleepiness, adynamia, ataxia, paraparesis, paraplegia, and dyspnea developing into Kuss-Maul breathing; death from central respiratory paralysis, usually within three days; autopsy findings of a plethora of parenchymatous organs; enlarged liver with necrotic areas; submucosal hemorrhages in stomach; brain edema; histological findings of vascular and necrotic changes in the liver, stomach mucosa, kidneys, and brain edema. In a later experiment, rats were given DCBs at a daily dose level of one-fifth of the LD_{50} dose. 1,2-DCB, in contrast to 1,4-DCB, was concluded to be a cumulative toxin since half of the animals died when they had received a total dose equal to the single LD_{50} dose. 1,4-DCB was, again, less toxic than 1,2-DCB.

In a chronic toxicity test, rats were given 1,2-DCB at daily doses of 0.001, 0.01, and 0.1 mg/kg. Toxicity was evaluated on the basis of multiple criteria, including: weight, serum enzymes and protein fractions, prothrombin index, leukocyte phagocytosis, sulfhydryl groups in blood, urinary 17-ketosteroids, conditioned

reflex activity. Preliminary results reported as of five months into the experiment indicated that 1,2-DCB was toxic and exerted a predominant effect on the hematopoietic system. Effects included: reduced hemoglobin, erythrocytes, and thrombocytes; increased leukocytes and reticulocytes (an apparent shift of the blood formula to the left); increased prothrombin time and activity of alkaline phosphatase and transaminases; altered liver and central nervous system function; altered conditioned reflex activity (Varshavskaya, 1967a).

According to Varshavskaya (1967b), at the completion of the chronic testing, results were interpreted as follows: at the 0.1 mg/kg dose level, 1,2-DCB disturbed higher cortical function in the central nervous system; at the 0.01 mg/kg dose level was "liminal," and at the low dose level (0.001mg/kg) was "subliminal." The highest dose level (0.1 mg/kg) caused inhibition of erythropoiesis (decreased hemoglobin and erythrocytes, anisocytosis, poikilocytosis, increased reticulocytes), thrombocytes, neutropenia, and inhibited bone marrow mitotic activity. Similar, but less pronounced effects were noted at the intermediate level, and the low dose level showed no such effects. At the high dose level, there was a marked increase in urinary 17-ketosteroids with an increase in adrenal weight coefficient and a decrease in adrenal ascorbic acid content. The high level resulted in increased alkaline phosphatase and serum transaminase activity, and decreased glutathione (SH groups) in the blood. Reduced alkaline phosphatase and increased acid phosphatase, and decreased di- and triphosphopyridine-nucleotides occurred in the liver and kidneys; decreased succinate

dehyrogenase, glucose-6-phosphatase, and α-glycerophosphate also occured in liver and kidney. The intermediate exposure had similar effects on blood enzymes and less effect on other enzyme activities. Enzyme-system effects were not noted in the low-dose subjects. Although the 0.1 and 0.01 mg/kg regimens caused decreased alkaline phosphatase, there was no microscopic or histologic evidence of carcinogenic activity. The maximal innocuous concentration of 1,2-DCB in water by toxicological criteria was considered to be 0.02 mg/l (extrapolated from 0.001 mg/kg/day), and 0.2 mg/l by water sanitation criteria; but since the liminal concentration by organoleptic criteria was 0.002 mg/l, the recommended maximum permissible water concentration was set at 0.002 mg/l. Although toxicity of 1,4-DCB was regarded as less than 1,2-DCB, its organoleptic and sanitary properties were similar to those of 1,2-DCB, so its recommended maximum permissible concentration was set at 0.002 mg/l (as for 1,2-DCB) on the organoleptic basis (Varshavskaya, 1967b).

The toxicological observations of Varshavskaya (1967a,b) are in qualitative agreement with the clinical toxicity of DCBs discussed earlier (e.g., anemia and other blood changes, liver damage, central nervous system depression), and with some aspects of other reported animal toxicology, but indicate that adverse effects occur at considerably lower exposure levels than indicated by the other data presented.

The highest no-detected-adverse-effect level for 1,2-DCB reported by Varshavskaya (1967b) was 0.001 mg/kg/day, whereas the comparable subliminal level in the long-term rat study by

Hollingsworth, et al. (1958) was 18.8 mg/kg/day. The reason for this discrepancy of several thousandfold is not clear.

Acute and subacute toxicity of 1,4-DCB was investigated by Ito, et al. (1973) using subcutaneous injections and inhalation test methods. Male mice (22 to 26 g) were injected subcutaneously with 1,4-DCB in olive oil at doses ranging from 3,500 to 7,258 mg/kg and observed for one week. The calculated LD_{50} dose for 1,4-DCB was reported as 5,145 mg/kg (4,760 to 5,530). Tremors occurred within two to three hours and continued over three days. Naphthalene was more potent (LD_{50} = 969 mg/kg), but both were regarded as neurotoxins and death was attributed to respiratory paralysis. Mice were exposed to atmospheres containing 1,4-DCB vapor for one 8-hour period and for two weeks at eight hours per day. The 8-hour exposure caused "inertia" (probably lassitude, weakness, or listnessness) and an increased breathing rate. The repeated subacute exposure resulted in liver damage and a 1,4-DCB concentration in blood of 64.5 mg/l. Vapor concentrations were not clearly identified in the translated report.

Hollingsworth, et al. (1956) reviewed some of the literature concerning toxicity of 1,4-DCB. The report of Landsteiner and Jacobs (1936) stating that the material did not sensitize guinea pig skin should be interpreted with caution in view of the clinical report of allergic purpura by Nalbandian and Pierce (1965). Berliner's report in 1939 of lenticular cataracts in humans exposed to vapors containing 1,4-DCB was not substantiated in subsequent studies with better characterization of vapor or more controlled experimental conditions (Hollingsworth, et al. 1956). Further,

1,4-DCB does not produce mercapturic acid and interfere with lens metabolism (by virtue of inhibition and/or depletion of glutathione, cyteine, and protein), as does napthalene, which is cataractogenic.

Several species of laboratory animals were exposed to 1,4-DCB vapor at each of five concentrations for seven hours per day (eight for the highest dose group), five days per week (Hollingsworth, et al. 1956). Effects in animals (rats, guinea pigs, rabbits) exposed to 4,800 mg/m^3 for up to 69 exposures included: some deaths (up to 25 percent), marked tremors, weakness, collapse, eye irritation, and reversible eyeground changes in rabbits, but no lens changes, weight loss, liver degeneration, and necrosis, cloudy swelling of renal tubular epithelium (rats), lung congestion, and emphysema (rabbits). Effects in rats and guinea pigs exposed at 2,050 mg/m^3 for six months included: growth depression (guinea pigs); increased liver and kidney weights (rats); liver pathology (cloudy swelling, fatty degeneration, focal necrosis, cirrhosis). Effects in animals exposed for as high as 139 exposures over 199 days at 1,040 mg/m^3 were: increased liver, spleen, and kidney weights (guinea pigs); pulmonary edema, congestion, hemorrhage; hepatic centrolobular congestion, and granular degeneration (rats). Effects in animals exposed to 950 mg/m^3 for 157 to 219 days included: growth depression (guinea pigs); increased liver weights (rats, guinea pigs) and increased kidney weights (rats); centrolobular hepatocellular cloudy swelling or granular degeneration (rats). No adverse effects were observed in rats, guinea pigs, rabbits, mice, or a monkey exposed at 580 mg/m^3 for six to seven months.

Results from acute, single high-level exposures to 1,4-DCB in oil by stomach tube are summarized as follows:

Species	No Deaths	100% Killed
Rats	1,000 mg/kg	4,000 mg/kg
Guinea pigs	1,600 mg/kg	2,800 mg/kg

1,4-DCB was dissolved in oil and given to male adult rats at 10, 100, or 500 mg/kg/dose five days per week for four weeks. Centrolobular hepatic necrosis and marked cloudy swelling of renal tubular epithelium with cast formation occurred in animals given 500 mg/kg. No effects were observed at the lower dose levels (Hollingsworth, et al. 1956).

White female rats were fed, 1,4-DCB in oil (emulsified with acacia) by stomach tube five days a week for a total of 138 doses in 192 days (Hollingsworth, et al. 1956). At the high dosage level of 376 mg/kg/dose, increased liver and kidney weights, and hepatic cirrhosis and focal necrosis were observed. No adverse effects were noted at the low dose level (18.8 mg/kg). No cataracts were observed in these exposures. The same investigators fed rabbits with 1,4-DCB in oil by intubation for up to 92 doses in 219 days at a level of 1,000 mg/kg/dose. Another group received a dose level of 500 mg/kg/dose five days a week for a total of 263 doses in 367 days. Effects at the high dose level (1,000 mg/kg) included: weight loss, tremors, weakness, hepatic cloudy swelling and focal necrosis, and deaths. Similar changes, but no deaths, were noted in rabbits on the lower dose regimen. No cataracts were observed. Peking ducks fed 1,4-DCB in their diet at 0.5 percent (5,000 mg/kg diet) for 35 days experienced retarded growth and 30 percent

mortality in 28 days, but no cataracts were observed (Hollingsworth, et al. 1956).

Coppola, et al. (1963) reported an effect on blood coagulation (increase in thromboelastrogram reaction and clotting formation times) in guinea pigs injected intramuscularly with daily doses of 124 mg 1,4-DCB in oil for three weeks. Totaro (1961) reported weight loss and increased serum transaminases in guinea pigs injected intramuscularly with 1,4-DCB (50 percent in oil) for 11 and 20 days at 125 mg per day. The increase in the serum glutamic-oxalacetic transaminase (SGOT) level was greater than the increase in serum glutamic-pyruvic transaminase (SGPT). The level of serum aldolase was not altered. The effect of lipotropic factors on transaminase and weight loss effects of injected 1,4-DCB were later studied by Totaro and Licari (1964). Groups of guinea pigs were injected intramuscularly daily for 20 days with 125 mg 1,4-DCB in oil (group 2), with a mixture of betaine chloride 70 mg:choline chloride 75 mg:vitamin B_1 1 mg:vitamin B_{12} 0.5 μg (group 3), or with 125 mg 1,4-DCB together with the lipotropic mixture (group 4). The control group received no treatment. Weight losses in groups 2 and 4 were 11.4 and 5.5 percent, respectively. SGOT and SGPT increases in group 2 were 312 and 149 percent, respectively, and in group 4 they were 187 and 124 percent, respectively. The authors concluded that the lipotropic factors exerted a protective action on the enzymatic modifications induced by 1,4-DCB. A similar protection action by lipotropic factors against the lowering of clotting factors ascribed to liver damage by 1,4-DCB was demonstrated

by Salamone and Coppola (1960) in an experiment similar to that just described for the transaminases.

Hepatic prophyria was induced in rats fed 1,2- and 1,4-DCB in liquid paraffin by stomach tube at levels increasing over several days to 455 and 770 mg/kg, respectively (Rimington and Ziegler, 1963). The first sign of intoxication was a markedly increased urinary excretion of urinary coproporphyrin III. Urinary excretion of uroporphyrin, porphobilinogen (PBG), and delta-aminolevulinic acid (ALA) increased. Liver content of protoporphyrin and uroporphyrin was also increased. Liver catalase was increased in subjects with necrotic liver changes, which occurred with 1,2-DCB. Clinical observations included: anorexia and weight loss, hemiparesis (one rat on 1,4-DCB), weakness, ataxia, clonic contractions, hepatomegaly, severe liver damage with intense necrosis and fatty change (1,2-DCB) or degeneration and focal necrosis (1,4-DCB) or degeneration and focal necrosis (1,4-DCB). No skin lesions were observed after testing for light sensitivity. 1,4-DCB was more porphyrogenic than 1,3-DCB. Of several chlorinated benzenes tested, those with para-positioning of chlorine atoms were the more porphyrogenic. The authors point out that mechanisms producing porphyrin derangements are different from those leading to hepatic necrosis. Of the two DCBs considered, 1,2-DCB was the more acutely toxic and liver-damaging, apparently reflecting the metabolism and formation of mercapturic acid, a process which depletes resources of sulfur compounds (e.g., glutathione) (Rimington and Ziegler, 1963).

As noted previously, 1,3-DCB also induced hepatic porphyria in rats fed the compound daily by intubation at 800 mg/kg or 900 to

1,000 mg/kg (Poland, et al. 1971). The higher dose level produced porhyria similar to that reported by Rimington and Ziegler (1963), but the lower dose produced an initial porphyric response which then abated, probably as a result of the accompanying stimulation of liver microsomal drug metabolizing mechanisms.

Carlson and Tardiff (1976) studied the ability of several halogenated benzenes to induce enzyme systems associated with the metabolism of foreign compounds. Rats were given daily oral doses of from 10 to 40 mg/kg for 14 days. In this regimen, 1,4-DCB and other benzene derivatives decreased hexabarbital sleeping time during exposure and the effect persisted at least two weeks after treatment. Cytochrome c reductase, cytochrome P-450 content, glucuronyl transferase, benzpyrene hyroxylase, azoreductase, and detoxication of o-ethyl-o-nitrophenyl-phenylphosphonothiolate (EPN) were increased (most of them at the 20 and 40 mg/kg dose levels) (Ware and West, 1977).

Ariyoshi, et al. (1975) and others have reported the induction of liver drug metabolizing enzyme systems in rats acutely fed chlorinated benzenes at 250 mg/kg. The three DCB isomers were highly metabolized, increased ALA synthetase, and were considered a possible producer of epoxide intermediates (Ware and West, 1977).

Rats injected intraperitoneally with 1,2-DCB at 735 mg/kg (5 mmol/kg) showed an increase in bile duct pancreatic flow (Yang and Peterson, 1977). Injection of 1,2-DCB and 1,4-DCB caused a reduction of protein concentration in bile duct pancreatic flow and increased hepatic bile flow.

Selected toxicity data for 1,2- and 1,4-DCB are summarized in Tables 6, 7, 8, and 9.

Synergism and/or Antagonism

There would appear to be many possibilities for synergistic and/or antagonistic actions among halogenated benzene compounds and between them and other compounds or conditions (Ware and West, 1977). DCBs have been shown to induce hepatic xenobiotic drug-metabolism systems and components (Ariyoshi, et al. 1975; Carlson and Tardiff, 1976), and the effects of DCBs have been shown to be modified by other chemical or biological factors (Salamone and Coppola, 1960; Totaro and Licari, 1964; Gadrat, et al. 1962). For example, an individual, with existing liver damage or under the influence of another chemical (or hormone) which enhanced the metabolism of 1,2-DCB into reactive hepatotoxic intermediates would be expected to be more susceptible to DCB toxicity (Thompson, 1955). Conversely, a condition or other chemical, that reduced conversion of DCB to hepatotoxic metabolites or provided essential materials to protect against harmful depletions (e.g., glutathione, lipotropic factors), would tend to ameliorate the direct cellular toxicity of absorbed DCB.

Teratogenicity

Embryotoxicity and teratogenicity of DCBs apparently have not been studied and reported. A pregnant woman who developed mild, chronic erythrotoxic anemia from ingestion of toilet air freshner blocks containing 1,4-DCB recovered after withdrawal and treatment and delivered an infant free of congenital abnormality (Campbell and Davidson, 1970). The potential for transplacental toxicosis or

TABLE 6

Acute Toxicity of 1,2-DCB

Route	Conc. or Dose	Regimen	Subject	Effect	Reference*
Inhalation	5,872 mg/m^3	7 hrs	Rat	Lethal in 4/5	e
	4,808 mg/m^3	24 hrs	G. pig	LC_{Lo}	f
	4,808 mg/m^3	11-50 hrs	Rat	Irritation, eyes, nose; coma; death in 1/10; liver necrosis	e cit. g
	4,249 mg/m^3	7 hrs	Rat	LC_{Lo}	f
	3,239 mg/m^3	7 hrs	Rat	Eye irrit.; CNS depress.; liver, kidney damage	e
	300-4,808 mg/m^3	Few hrs	Animals	Liver damage	c cit. g
Oral	2,000 mg/kg	Single (oil)	G. pig	Lethal to 100%	e
	1,875 mg/kg	"	Rabbit	Lethal to 50% (LD_{50})	l
	800 mg/kg	"	G. pig	Survival, but weight loss.	e
	428 mg/kg	Daily, 3 days	Rat	Cumulative lethal toxicity; 1/5 LD_{50}	l
	324-649 mg/kg	Single	Rabbit	Lethal within 24 hrs.	b cit. g
	250 mg/kg	Daily	Rat	Increased liver metab. enzym. syst.	b cit. p
Intravenous	520 mg/kg	Single	Mouse	LD_{Lo}	f
	330 mg/kg	Single	Rabbit	LD_{Lo}	f
Subcutaneous	Unspecified			Localized edema and necrosis	b cit. h
Dermal	Undil.	Appl. to skin 1/4 - 1 hr	Human	Irritation, abnorm. pigmentation afterward lasting 3 mos.	e cit. h
	Unspecified	Skin appl. 2x/d x 5 applic.	Rat	Absorption of lethal amount	e cit. h
Eye	Undil., 2 drops	Single	Rabbit	Moderate pain; conjunct., irritation, clearing in 7 days	e
Nose	600 mg/m^3	Single	Human	Strong odor; nasal and ocul. irritation; possible adaptation	a,e cit. n
	300 mg/m^3	Single	Human	Odor detectable; no irritation	a, e

*References listed after Table 9.

TABLE 7

Long-term Toxicity of 1,2-DCB

Route	Conc. or Dose	Regimen	Subject	Effect	Reference*
Inhalation	560 mg/m^3	7 h/d, 5d/wk, 6-7 mos.	Rat, g. pig, rabbit	No effect on several param.	e
	290 mg/m^3	7 h/d, 5d/wk, 6.5 mos.	Rat, g. pig,	No effect on several param.	e
	6-264 mg/m^3 (av. 90)	Plant expos., daily	Human	No evidence of organic or hematol. effect on clin. exam.	e
	455 mg/m^3 (tube)	Daily up to 15 days	Rat	Hepatic porphyria	r
Oral	376 mg/kg (tube)	5d/wk, 138 doses	Rat	Liver, kidney weight increase; cloudy swelling in liver	e
	188 mg/kg (tube)	5d/wk, 138 doses	Rat	Increase in liver and kidney weight	e
	18.8 mg/kg (tube)	5d/wk, 138 doses	Rat	No effects noted	e
	0.01-0.1 mg/kg/day	5 mos.	Rat	Hematopoietic syst; altered cond. reflexes; increased prothromb time and altered enzyme activities	l
Dermal	Expos. to liquid mixture	Repeated	Human	Sensitization, dermatitis (case report)	e
Subcut.	Unspecified	Repeated	Rabbit	Blood dyscrasias, (agranulocytosis)	b

Note: See also TABLE 5 pertaining to human poisoning.

*References listed after Table 9.

TABLE 8

Acute Toxicology of 1,4-DCB

Route	Conc. or Dose	Regimen	Subject	Effect	Reference*
Inhalation	10^5 mg/m^3	30 min., daily	Rabbit	CNS depression; ocul. and nasal irrit.	c cit. k
	10^5 mg/m^3	30 min., daily	Rat	Irritation, narcosis	c cit. k
	10^5 mg/m^3	30 min., daily	G. pig	Irritation, CNS depression, deaths	c cit. k
	300-480 mg/m^3	Acute	Human	Painful irrit. to eyes and nose; acclimatization can occur.	a
	90-180 mg/m^3	Single	Human	Odor detection (strong odor at 180-360)	j
Oral	4,000 mg/kg	Single, 20 or 50% solution	Rat	LD_{100}	j
	2,950 mg/kg	Single	Mouse	LD_{50}	c cit. k
	2,812 mg/kg	Single (oil)	Rabbit	LD_{50}	l
	2,800 mg/kg	Single, 50% solution	G. pig	100% lethal	j
	1,600 mg/kg	Single, 50% solution	G. pig	100% survival	j
	500 mg/kg	Single	Rat	LD_{50}	f
	300 mg/kg	Single	Human	Toxic dose	f
Intraperitoneal	2,562 mg/kg	Single	Rat	LD_{50}	c cit. i
Subcutaneous	5,145 mg/l	Single	Mouse	LD_{50}	b cit. m
Skin	Contact with solid	Single	Human	Somewhat irritating. Burning sensation if contact is direct and prolonged. No apprec. abs. through skin	a, j
	Strong fumes	Single or repeated	Human	May irritate in severe expos. conditions; no problem normally	j
Eye	Solid particles, vapor, fumes	Single	Human	Painful (also vapor at 300-480 mg/m^3 and severe at 960 mg/m^3)	j
Injection	5 mg	Single	Rat	Occasionally, slight liver necrosis	c cit. g

*References listed after Table 9.

TABLE 9

Long-term Toxicity of 1,4-DCB

Route	Conc. or Dose	Regimen	Subject	Effect	Reference*
Inhalation	10^5 mg/m^3	0.5 h/d, 5-9 days	Rabbit	Granulocytopenia; irrit.; CNS and lung tox.; death (12/18)	b cit. i
	4,800 mg/m^3	8h/d, 5d/wk., up to 69 expos.	Rat, G. pig, rabbit	Severe irrit,; CNS depress. & collapse; liver, kidney, lung pathol.; deaths	j
	4,600-4,800 mg/m^3	8h/d, 5d/wk	Rabbit	Tremors, weakness, nystagmus; some deaths	j cit. o
	2,050 mg/m^3	7h/d, 5d/wk, 6 mos.	Rat, G. pig	Growth depression, incr. liver, kidney wt.; liver pathol. (necrosis, fatty degen., swelling, fibrosis)	j
	1,040 mg/m^3	7h/d, 5d/wk, 16 days	Rat, G. pig	Incr. liver, kidney wt. (rat); lung, liver pathol.	j
	950 mg/m^3	7h/d, 5d/wk, 157-219 days	Rat, G. pig rabbit, mouse, monkey	Growth depress. (g.p.); incr. liver, kidney weight; histol. liver changes (cloudy swelling, granular degen.) in rats	j
	300-1,020 mg/m^3 (avg. 630)	8/h/d, 5d/wk, chron.	Human	Eye, nose irritation	j
	900 mg/m^3	8h/d, 2 wks	Mouse	Respir. excitation; liver pathol., deaths; at serum conc. 39 mg/l	m
	576 mg/m^3	7h/d, 5d/wk, 6-7 mos.	Rat, G. pig, mice, rabbit, monkey	No adverse effects on several parameters	j
	480-960 mg/m^3	Daily, occupational	Human	Painful irrit. of eyes, nose. Intolerable at more than 960 mg/m^3	j
	180-360 mg/m^3 (avg. 270)	Daily expos.	Human	Strong odor	j
	90-510 mg/m^3	Daily occupational	Human	No complaints or evidence of injury	j

*References listed after Table 9.

TABLE 9 (Continued)

Route	Conc. or Dose	Regimen	Subject	Effect	Reference*
Oral	1,000 mg/kg per dose (tube)	92 doses in 219 days	Rabbit	CNS depression; wt. loss; liver degen. and necrosis; deaths	j
	770 mg/kg/day	Up to 5 days	Rat	Hepatic porphyria	r
	500 mg/kg/day (tube)	5d/wk, 20 doses	Rat	Hepatic centrolobular necrosis; cloudy swelling, renal tubul. epith., and casts	j
	5,000 mg/kg dose	Up to 35 days	Peking duck	Death in 3/10. Retarded growth	j
	500 mg/kg/day (tube)	5d/wk 263 doses in 367 days	Rabbit	CNS depress.; wt. loss; liver pathol.	j
	376 mg/kg/day	5d/wk 138 doses in 192 days	Rat	Incr. liver and kidney wt.; liver cirrhosis and focal necrosis	j
	250 mg/kg/day	3 days	Rat	Induced liver metab. enzyme syst.	b cit. p
	188 mg/kg/day	5d/wk 138 doses in 192 days	Rat	Incr. liver and kidney wt.	j
	20-40 mg/kg/day	2 weeks	Rat	Induced liver metab. enzyme syst.	b. cit. q
	18.8 mg/kg/day	5d/wk 138 doses in 192 days	Rat	no adverse effects detected	j

Note: See also TABLE 5 pertaining to human poisoning.

*References follow this page.

Previous references used in Tables 6, 7, 8, & 9

a. Patty, 1963

b. Ware and West, 1977

c. Am. Conf. Gov. Ind. Hyg., 1977

d. Occup. Safety Health Admin., 1976

e. Hollingsworth, et al. 1958

f. Christenson and Fairchild, 1976

g. Cameron, et al. 1937

h. Riedel, 1941

i. Zupko and Edwards, 1949

j. Hollingsworth, et al. 1956

k. Domenjoz, 1946

l. Varshavskaya, 1967a

m. Irie, et al. 1973

n. Elkins, 1959

o. Pike, 1944

p. Ariyoshi, et al. 1975

q. Carlson and Tardiff, 1976

r. Rimington and Ziegler, 1963

developmental effects may be inferred from evidence that lower chlorinated benzenes pass membrane barriers (including egg and placenta) and affect hormone-metabolizing systems (Ware and West, 1977).

Mutagenicity

The formation of a metabolic arene oxide intermediate has been associated with mutagenesis and carcinogenesis, and halobenzenes have been shown to form reactive intermediates (Ware and West, 1977). Chromosomal and other nuclear derangements in roots of Allium exposed for four hours to 1,4-DCB vapor (resulting from placing 0.5 to 1.5 g in a petri dish) were reported by Carey and McDonough (1943). Abnormal chromosome numbers were found in dividing nuclei; polyploidy was especially apparent in metaphase stages; and lagging chromosomes and dumbbell-shaped nuclei were occasionally noted. The authors warned of the possibility of varietal instability if 1,4-DCB products were allowed to come in contact with buds.

Sharma and Bhattacharyya (1956) reported their experience with the use of 1,4-DCB solution in processing plant tissues for chromosome analyses. They indicated the potential of aqueous solutions causing chromosomal breakage and persistence of fragment-containing cells for several cell generations after treatment. Sharma and Sarkar (1957) reported on effects of 1,4-DCB solution on chromosomes of root tips, flower buds, and pollen grains of Nothoscordum fragans. Saturated aqueous solution caused meta- and anaphase chromosome fragmentation in root tip cells, chromosomal

"stickiness" and non-disjunction in meiotic cells of flower buds, but no irregularities in pollen grain chromosomes.

Various mitotic anomalies were observed in cells and somatic chromosomes of 1,4-DCB-treated root tips of Vicia faba, V. narbonesis, V. hirsuta, Pisum arvense, and Lathyrus sativus (Srivastava, 1966). These deviations from normal mitosis included: shortening and thickening of chromosomes, precocious separation of chromatids, tetraploid cells, binucleate cells, chromosome bridges, and chromosome breakage (generally at heterochromatic regions). The author emphasized the potential of 1,4-DCB as a mutagenic substance.

Treatment of Aspergillus nidulans (a soil mold organism) for one hour in an ether solution of 1,2-, 1,3-, and 1,4-DCB isomers increased the frequency of back-mutations (Prasad, 1970). Chlorination in the para- position appeared to have special genetic significance.

Anderson, et al. (1972) found 1,2-DCB not to be mutagenic in an in vitro point mutation test system using several strains of histidine-requiring mutants of Salmonella typhimurium. Several compounds chemically similar to DCBs were also reported as negative in Salmonella mutagenicity tester strains (Simmon, et al. 1977). These were benzene, bromobenzene, 1,3- and 1,4-bromochlorobenzene, and parachlorotoluene.

Carcinogenicity

DCB (isomer not specified) gave negative results in a skin test of carcinogenicity in mice (Guerin and Cuzin, 1961; Guerin, et al. 1971). Three- to four-month old Swiss mice in lots of four to eight (male and female) were treated topically three times with

0.1 ml of a solution of 10^4 mg DCB/l acetone. After 10 days the mice were euthanized and the treated skin area was examined for atrophy of sebaceous glands and for epithelial hyperplasia. On a scale of 0 to 4 (negative to very strongly positive) DCB was rated 0.9 and 0.7 on the sebaceous gland and hyperplasia criteria, respectively. This was interpreted as a negative result (not carcinogenic).

In a later investigation using an in vitro carcinogenicity test system, Guerin, et al. (1971) reported DCB as being negative again. This test involved treating a culture of rat pulmonary cells with test material and evaluating the inhibition of mitoses in cells fixed on slides after eight days. The test had been demonstrated as being able to detect known carcinogens, the correspondence between test results on mitotic inhibition and carcinogenic versus noncarcinogenic chemicals being significant at the one percent level. The authors also reported a correlation between results of the lung cell mitosis inhibition test and those of the cutaneous test (sebaceous gland atrophy and epithelial hyperplasia) for various chemicals.

Ware and West (1977) have summarized a series of toxicity experiments by Hollingsworth, et al. (1956, 1958) in which toxicities of 1,2- and 1,4-DCB were studied in several animal species exposed by inhalation and gastric intubation at various dose levels over various periods of time. No tumors were reported in combined totals of 146 animals exposed to 1,2-DCB or 189 exposed to 1,4-DCB. These were regarded as negative carcinogenicity results, but it should be pointed out that these studies were toxicity tests and were not designed to assess carcinogenicity. Small group sizes and

relatively short durations render the data from these studies inconclusive and inadequate for the assessment of carcinogenic properties of the DCBs. Further details of these experiments were discussed in the toxicity section.

Varshavskaya (1967b) reported macroscopic, histolgic, and histochemical data in rats exposed for nine months to 1,2-DCB (in oil, by tube) at daily dose levels of 0.1, 0.01, and 0.001 mg/kg. No evidence of carcinogenic activity was revealed. Again, this experiment (previously summarized in greater detail) was clearly not designed for the assessment of carcinogenicity. Although the exposure duration may be sufficient for some test models, the exposure levels were quite low and the group sizes (numbers of animals) were too small for valid detection and quantification of carcinogenesis.

Murphy and Sturm (1943) reported that repeated exposures to a relatively high concentrations of 1,4-DCB vapor caused a reduction in the induced resistance to transplanted leukemia in rats. They tested four toxic agents (including 1,4-DCB) which they characterized as having been found to increase the leukemia rate in a strain of mice having a natural leukemia tendency (but no reference or details for this characterization were given). All four compounds, 1,4-DCB, L.C. sodium pentobarbital, Sovasol (a purified naphtha), and amyl acetate, were positive in the leukemia resistance reduction test. Two other carcinogenic agents, x-ray and coal tar, had been shown to modify induced resistance to transplantable tumors in mice (Murphy and Sturm, 1943). Eighty-four percent of the activity control group (non-immunized) responded with leukemia

(takes) to the injected leukemia cells. Only 20 percent occurred in the immunized but untreated group. The immunized and treated (1,4-DCB vapor-exposed) group had 68 percent takes. About 40 young rats were used in each group. The toxic mechanism of the effect and its general applicability to distinguishing carcinogenic versus noncarcinogenic chemicals had not been determined.

Parsons (1942) reported that injections of 1,4-DCB (commercial, in sesame oil) along with injection of silica have induced early tumor formation in mice. In six irradiated mice a single dose of 0.2 ml of a 0.2 percent solution of 1,4-DCB (2,000 mg/l) in oil was injected subcutaneously, and 0.2 ml of silica in suspension was introduced at the injection site on the fourth day. One irradiated mouse received its injection intraperitoneally. On the tenth day the intraperitoneally treated mouse had ascites, and when euthanized was found to have "widespread sarcomatous growth" throughout the peritoneum. This tumor gave 100 percent takes when grafted. Three of the irradiated mice died by the tenth day. Ten nonirradiated mice were injected subcutaneously with similar 1,4-DCB preparations for nine doses over two months, receiving also silica at two week intervals. Four of these died within 30 days. In one of the survivors a large sarcoma had developed (by the 77th day), with secondary growths in the lymph glands and peritoneum. Small group sizes and lack of further detail, especially concerning control groups, limit the usefulness of this data in assessing 1,4-DCB carcinogenicity.

Of the seven case reports of human poisoning by 1,2-DCB or products containing primarily 1,2-DCB (Table 5) three involved

diagnoses of neoplastic disease (leukemia: two acute myeloblastic, one chronic lymphoid). Although these data suggest the posibility of cancer-related hazard with exposure to 1,2-DCB, they fall very short of proving a cause-effect relationship and do not permit a quantitative risk assessment applicable to the general population.

Veljkovi'c and Lalovi'c (1977) examined the correlation between the quasi-valence number (Z*) and the known carcinogenic activity of a number of chemical compounds tested in animals and evaluated by IARC criteria. The Z* is a derived parameter recognizing valence electrons, atoms, and elements in the compound formula. The authors reported a strong correlation in the array of values examined, those with Z* below 3.20 corresponding to potential carcinogens and those above noncarcinogens. DCB was evaluated as being in the potential carcinogen class with a Z* = 2.50.

No reports of specific carcinogenicity tests of DCBs in animals or of pertinent epidemiologic studies in humans were available.

Although strong direct evidence of carcinogenicity of DCBs is not at hand, there seems to be a sufficient collection of varied data to suggest a prudent regard of the DCBs as suspected carcinogens, pending the availability of better data. Apparently on the basis of the limited sarcoma induction data of Parsons (1942), 1,4-DCB was listed in the National Institute for Occupational Safety and Health Subfile of Suspected Carcinogens (Christensen and Luginbyhl, 1975). The National Academy of Sciences (NAS, 1977) found the lack of information "disturbing, in view of the suspected role of DCB in human leukemia and its apparent ability to undergo

metabolic activation and covalent binding to tissue constitutents." The International Agency for Research on Cancer (IARC, 1974) regarded the data on DCBs as of 1974, i.e., primarily those of Hollingsworth, Parsons, and Girard, as insufficient for assessing carcinogenic risk. Clearly, additional data is needed for a DCB carcinogenic risk evaluation, especially studies involving humans in pertinent exposure categories and animal studies under well-designed protocols. 1,2- and 1,4-DCB have been selected for testing in the bioassay program of the National Cancer Institute (NCI, 1978), and as of January 1978, a study of 1,4-DCB in mice was in progress at the Nagoya City University Medical School in Japan (IARC, 1978).

CRITERION FORMULATION

Existing Guidelines and Standards

The known current standards and guidelines for DCBs in air and water are summarized in Table 10. For air the only official federally regulated limits are by the Occupational Safety and Health Administration (OSHA) (29 CFR 1910) for 1,2-DCB and 1,4-DCB in workroom air at 300 mg/m^3 (ceiling) and 450 mg/m^3 (time-weighted average), respectively. The threshold limit value (TLV) guidelines of the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) are virtually the same as the OSHA standards. These may need downward revision in view of human sensory responses in unacclimated persons. The Russian maximal allowable concentration (MAC) value for both 1,2-DCB and 1,4-DCB is 20 mg/m^3 (IARC, 1974), much lower than U.S. standards. The U.S. EPA (1977) has published multimedia environmental goals (MEGs) for health related Estimated Permissible Concentrations in air (EPC-AH): 1,2-DCB, 0.714 mg/m^3 (0.12 ppm) and 1,4-DCB, 1.07 mg/m^3 (0.18 ppm). The Russian and MEG limits appear to recognize the following detection limits more closely than the OSHA and ACGIH values: 1,2-DCB, 12 to 24 mg/m^3, odor threshold; 60 to 90 mg/m^3, very noticeable odor; 150 to 180 mg/m^3, unpleasant odor and eye irritation; 360 to 600 mg/m^3, painful mucosal irritation; and 960 mg/m^3, painful irritation (Am. Ind. Hyg. Assoc., 1964).

1,4-DCB is listed for inclusion among chemicals to be monitored by the U.S. EPA under the Safe Drinking Water Act (40 CFR 141, Subpart E, PL 93-523).

TABLE 10

Standard, Criteria, or Goal Limits of Contamination for Dichlorobenzenes[a]

Medium	Standard, criterion, etc.	1,2-DCB	1,4-DCB	Reference
Air	OSHA Standard for worker exposure	50 ppm (300 mg/m^3) (ceiling)	75 ppm (450 mg/m^3) (TWA)[b] (Car)[c]	A,B
	ACGIH recommended TLV	50 ppm (300 mg/m^3) (ceiling)	75 ppm (450 mg/m^3) (limit)	C
	EPA, MEG: EPC-AH1[d]	0.12 ppm (0.714 mg/m^3)	0.18 ppm (2.07 mg/m^3)	D
	Russian MAC (max. allow. conc.)	3.3 ppm (20 mg/m^3)	3.3 ppm (20 mg/m^3)	E
Water	EPA, MEG: EPC-WH1[e]	10.7 mg/l	16.1 mg/l	D
	WH2[f]	4.4 mg/l	6.21 mg/l	D
	Russian MPC[g]	0.002 mg/l	0.002 mg/l	F

A: *Occup. Safety Health Admin.* 1976. B: Christensen and Luginbyhl, 1975. C: ACGIH, 1977. D: U.S. EPA, 1977. E: IARC, 1974. F: Stofen, 1973

[a]Current, based on available information. Note: No known regulatory standards exist in U.S. for any DCB isomers (1,2-, 1,3-, or 1,4-DCB) in ambient air or water; 1,3-DCB apparently omitted altogether

[b]Time weighted average, 8 hours

[c]Carcinogenicity notation in ref. B; carc. determination *indefinite* in A

[d]Estimated permissible concentration in air based on a model utilizing TLV

[e]Estim. permiss. conc. in water derived from EPC-ALL extrapolated to water intake

[f]Estim. permiss. conc. in water based on max. safe body conc. and biol. half-life considerations

[g]Maximum permissible concentration recognizing organoleptic effect

The U.S. EPA (1977) has published MEGs for health-related EPCs in water based on different approaches (Table 11): (1) derived from the air-health EPC, extrapolated to water intake assuming the following daily intake and absorption efficiency values: EPC-WH1, 10.7 mg 1,2-DCB/1 and 16.1 mg 1,4-DCB/1; (2) based on considerations of maximum safe body concentration and biological half-life data: EPC-WH2, 4.4 mg 1,2-DCB/1 and 6.21 mg 1,4-DCB/1. The reported maximum permissible concentrations (MPCs) in Russia, recognizing that organoleptic factors (odor, taste) are much more conservative, are: 0.002 mg/1 for both 1,2-DCB and 1,4-DCB (Varshavskaya, 1968; Stofen, 1973).

Apparently 1,3-DCB has been omitted from regulations or guidelines for media contamination, undoubtedly reflecting its insignificant environmental contamination level and potential at this time. Practically speaking, it would seem reasonable to assume that efforts to control the 1,2- and 1,4- isomers of DCB would also effectively control the 1,3-DCB as well, since it generally would accompany its isomers in total DCB contamination and would not have a significant contamination mode of its own.

Under the Federal Food, Drug and Cosmetic Act certain uses of both monochlorobenzene (MCB) and 1,4-DCB are regulated. MCB is a solvent in the manufacture of resins for food contact articles; residues in such resin products must not exceed 500 mg/kg. 1,4-DCB is an intermediate in the manufacture of other resins for coating products in food contact use; in such products 1,4-DCB residues are limited to 0.8 mg/kg (32 FR 14324, Oct. 17, 1967; 34 FR 17332, Oct.

TABLE 11

Estimated Dichlorobenzene Exposure from Drinking Water*

Exposure Level	Exposure, mg			
	Daily uptake		Annual uptake	
	Per person	Per kg	Per person	Per kg
"Minimal" case:				
Median level in drinking water of 0.000005 mg/l (assume 3).	6×10^{-6}	0.086×10^{-6}	2.2×10^{-3}	0.031×10^{-3}
"Moderate" case:				
Assume level of 10^{-4} mg/l (33 x minimal, 1/33 x maximal).	200×10^{-6}	2.86×10^{-6}	73×10^{-3}	1.04×10^{-3}
"Maximal" case:				
Maximal reported level in drinking water of 0.003 mg/l.	$6{,}000 \times 10^{-6}$	86×10^{-6}	$2{,}190 \times 10^{-3}$	31.3 x 10-3

*Assuming human water consumption of 2 l/day, absorption efficiency of 100 percent, and body weight of 70 kg. Values are about equally applicable to any single isomer, but not total of all. See exposure section for data base.

25, 1969; 37 FR 22374, Oct. 19, 1972). No information on regulation of residues or levels in food commodities was available.

The U.S. EPA has regulatory authority over some uses of DCBs under the Federal Environmental Pesticide Control Act of 1972. Registered under this act are 43 uses of 1,2-DCB and 304 uses of 1,4-DCB. The chlorinated benzene pesticides are categorized as Class III toxins (oral LD_{50} values ranging from 500 to 5,000 mg/kg and LC_{50} values ranging from 200 to 20,000 mg/m^3) and as such, have a hazard signal ("caution") and precautionary labeling requirement: "Harmful if swallowed, inhaled or absorbed through skin. Avoid breathing vapors (dust or spray mist). Avoid contact with skin (eyes or clothing). In case of contact immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists" (40 FR 28242, July 3, 1975).

The Department of Transportation (DOT) regulates interstate transport, and there are specific requirements in regard to handling DCBs as combustible materials (for which they are classified due to their toxic and flashpoint properties). The Coast Guard has regulatory authority for overseas transportation and has recognized toxic, aquatic life hazard, and combustible properties of DCBs by requiring notification of health, pollution, and fire authorities in the event of spills. DCBs have been determined to be hazardous to aquatic life in very low concentrations (Ware and West, 1977).

Several states have or intend legislation regulating manufacture, use, disposal, handling, and/or registration and inventory of toxic/hazardous chemicals, often mirroring Federal legislation and promulgations (Ware and West, 1977).

Current Levels of Exposure

Generally, there is a paucity of environmental data on dichlorobenzenes. In the few samples of relatively uncontaminated ground water and of drinking water, the reported DCB levels ranged from on the order of less than 0.001 to 0.003 mg/l. In the National Organics Monitoring Survey (U.S. EPA,, 1978a) median concentrations and frequency of positive samples in drinking water were low, compared to halomethanes. This data by itself would suggest a relatively low exposure level for the general public from drinking municipally treated water.

An attempt to estimate human DCB exposure doses by using available survey contaminant-level data and certain assumptions for water consumption and absorption efficiency is shown in Table 11. A spread of about 1,000 times between "minimal" and "maximal" case exposures resulted. Even so, less than "minimal" exposures may apply for some of the population (e.g., very pure water supply) and more than "maximal" exposure for others (e.g., highly contaminated supplies). Meaningful representative or typical values and limits defy precise definition at this time.

Specific data on ambient air contamination by DCBs was meager. Based on the data of Morita and Ohi (1975) an attempt is made to estimate levels of human exposure via air contamination (Table 12). The extent of the population that may be represented by the table values is simply unknown. Some segments may be subject to less exposure (e.g., remote rural dwelling), and some to more (e.g., highly contaminated urban or industrial area air, especially contaminated air associated with some occupations or perhaps indoor air where

TABLE 12

Estimated Dichlorobenzene Exposure
from Air Contamination*

Exposure Level	Estimated Exposure, mg			
	Daily uptake		Annual uptake	
	Per person	Per kg	Per person	Per kg
"Minimal" case:				
1.5×10^{-3} mg/m^3 (lowest suburban concentration reported)	0.01725	0.000246	0.63	0.09
"Moderate" case:				
0.24 mg/m^3 (mean of all values reported from urban, suburban, and indoor air)	2.76	.0394	1,007	14
"Maximal" case:				
1.7 mg/m^3 (Reported in wardrobe air due to use of 1,4-DCB)	19.55	0.28	7,136	102

+Based on assumptions as follows: daily inspired volume for reference adult male, 23m^3 (NAS, 1978); human body weight, 70 kg (NAS, 1978); absorption efficiency by inhalation, 50 percent.

*Based on data of Morita and Ohi (1975) for 1,4-DCB.

DCB products are used). Comparison of Tables 11 and 12 suggest greater intake doses via air than via water.

No data are available by which specific exposure to DCBs by consumption of food could be estimated. Reports of detectable, even significant levels in fish, meat, eggs, and grains representing direct-contamination residues or products of degradation of other chemicals would suggest the likelihood of at least some intake by ingestion of food (probably mostly from food of lipid nature because of food-chain lipophilic bioaccumulation processes).

Data indicate the possibility of dermal absorption from unusually high-level exposure to vapors or perhaps liquids, but this would likely be significant only in special individual circumstances. There are no data on the level or importance of dermal exposure for the general public, but it seems reasonable to speculate that it would be insignificant in relation to other exposure routes.

Special Groups at Risk

Persons with pre-existing pathology (hepatic, renal, central nervous system, blood) or metabolic disorders, who are taking certain drugs (hormones or otherwise metabolically active), or who are otherwise exposed to DCBs or related (chemically or biologically) chemicals by such means as occupation, or domestic use or abuse (e.g., pica or "sniffing") of DCB products, might well be considered at increased risk from exposure to DCBs.

Basis and Derivation of Criteria

There is not a sufficient weight of evidence from human or animal tests to qualitatively suggest that DCBs are carcinogenic or mutagenic in mammals or to derive a quantitative estimate of acceptable daily intake using cancer risk extrapolation methods. In addition, there are no human data to allow an estimation of the maximum daily oral dose producing no detected adverse effect.

Hollingsworth's data were chosen over the Varsharskaya study for several reasons. Although Varsharskaya reported lower effect levels, the endpoints of this study were not clearly pathologic, nor were sufficient data provided on which to substantiate the author's claims. The acute data from both studies were in agreement while a significant difference was seen in the chronic toxicity data. It is possible that had Hollingsworth been studying chemical endpoints, he might have seen effects at lower levels than he did. However, it is very difficult to make comparisons between data with different endpoints. The Varsharskaya data do provide an organoleptic value but this cannot be used to recommend a criterion for the protection of health.

Therefore, the most usable controlled experimental data on chronic enteric exposure in multiple animal species is that of Hollingsworth, et al. (1956, 1958). The maximum tested dose level producing no detectable adverse effects in these tests was 13.42 mg/kg/day (18.8 x 5/7) over a period of six to seven months, for both 1,2-DCB and 1,4-DCB. Assuming the average weight of adult humans to be 70 kg, and applying an uncertainty factor of 1,000

(NAS, 1977), the acceptable daily intake (ADI) of 1,2- or 1,4-DCB in man is calculated as follows:

$$ADI = \frac{18.8 \times 5/7 \times 70}{1000} = 0.94 \text{ mg/day.}$$

The water quality criterion can be calculated from the ADI as follows:

$$\text{Criterion} = \frac{0.94 \text{ mg/day}}{2 + (0.0065 \times 55.6)} = 0.398 \text{ mg/l or } 400 \text{ µg/l,}$$

where:

0.94 mg/day = ADI
2 = liters of drinking water consumed daily
0.0065 = kg of fish consumed daily
55.6 = bioconcentration factor.

The similarity of toxicities among the DCB isomers indicates the applicability of this value to 1,3-DCB as well.

This calculation assumes that 100 percent of man's exposure is assigned to the ambient water pathway. The only environmental monitoring data available on the DCBs, inadequate as they are, suggest that man's exposure by inhalation of the material in air may be 3,000 to 15,000 times his exposure from water. Although it is desirable to arrive at a criterion level for water based on total exposure analysis, the data base for exposure pathways other than water is not sufficient to support a factoring of the ADI level calculated from ambient water assumptions.

The calculated level of 0.40 mg/l, or 400 µg/l for any DCB isomer should be considered a total, i.e., the total contamination by DCB isomers whether occurring singly or in combination should not exceed the criterion level. Pending the availability of better data on relative exposure by various routes and on carcinogenic

risk, this level should be adequate to prevent adverse health effects from long-term ambient water exposures.

In summary, based upon the use of chronic toxicologic test data in animals, and an uncertainty factor of 1,000, the criterion level for DCBs (total) corresponding to the calculated total acceptable daily intake of 0.94 mg/day is 400 µg/l. Drinking water contributes 85 percent of the assumed exposure, while eating contaminated fish products accounts for 15 percent.

The criterion level for DCB can alternatively be expressed as 2.6 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

REFERENCES

American Conference of Governmental Industrial Hygienists. 1977. Documentation of the threshold limit values for substances in workroom air (with supplements for those substances added or changed since 1971). 3rd ed. Cincinnati, Ohio.

American Industrial Hygiene Association. 1964. o-Dichlorobenzene and p-dichlorobenzene. Am. Ind. Hyg. Assoc. Jour. 25: 330.

Anderson, K.J., et al. 1972. Evaluation of herbicides for possible mutagenic properties. Jour. Agric. Food Chem. 20: 649.

Ariyoshi, T., et al. 1975. Relationship between chemical structure and activity. II. Influences of isomers in dichlorobenzene, trichlorobenzene and tetrachlorobenzene on the activities of drug-metabolizing enzymes. Chem. Pharm. Bull. 23: 824.

Azouz, W.M., et al. 1953. Studies in detoxication. 51: The determination of catechols in urine, and the formation of catechols in rabbits receiving halogenobenzenes and other compounds. Dihydroxylation in vivo. Biochem. Jour. 55: 146.

Azouz, W.M., et al. 1955. Studies in detoxication. 62: The metabolism of halogenobenzenes. Ortho- and paradichlorobenzenes. Biochem. Jour. 59: 410.

Balba, M.H. and J.G. Saha. 1974. Metabolism of lindane-^{14}C by wheat plants grown from treated seed. Environ. Lett. 7: 181. (Abst.).

Berliner, M.L. 1939. Cataract following the inhalation of paradichlorobenzene vapor. Arch. Ophth. 22: 1023.

Cameron, G.R., et al. 1937. The toxicity of certain chlorine derivatives of benzene with special reference to o-dichlorobenzene. Jour. Pathol. Bact. 44: 281.

Campbell, D.M. and R.J.L. Davidson. 1970. Toxic haemolytic anemia in pregnancy due to a pica for paradichlorobenzene. Jour. Obstet. Gynaec. Br. Cmnwlth. 77: 657.

Carey, M.A. and E.S. McDonough. 1943. On the production of polyploidy in Allium with paradichlorobenzene. Jour. of Heredity. 34: 238.

Carlson, G.P. and R.G. Tardiff. 1976. Effect of chlorinated benzenes on the metabolism of foreign organic compounds. Toxicol. Appl. Pharmacol. 36: 383.

Christensen, H.E. and E.J. Fairchild (eds.) 1976. Registry of toxic effects of chemical substances. Natl. Inst. Occup. Safety Health, U.S. Dep. Health Edu. Welfare, Rockville, Maryland.

Christensen, H.E. and T.T. Luginbyhl (eds.) 1975. Suspected carcinogens. A subfile of the NIOSH toxic substances list. Natl. Inst. Occup. Safety Health, U.S. Dep. Health Edu. Welfare, Rockville, Maryland.

Coppola, A., et al. 1963. Thromboelastographic changes in subacute poisoning with paradicholorobenzene. Folia Med. 4b: 1104. (Abst.)

Cotter, L.H. 1953. Paradichlorobenzene poisoning from insecticides. N.Y. Jour. Med. 53: 1690.

Domenjoz, R. 1946. Arch. Int. Pharmacol. 73. (Cited by Am. Conf. Gov. Ind. Hyg., 1977.)

Downing, J.G. 1939. Dermatitis from orthodichlorobenzene. Jour. Am. Med. Assoc. 112: 1457.

Dupont, R. 1938. Origin of a discomfort experienced by workers during the cleaning of a sewer. Arch. Malad. Profess. 1: 312.

Elkins, H.B. 1959. The Chemistry of Industrial Toxicology. John Wiley and Sons, Inc., New York.

Frank, S.B. and H.J. Cohen. 1961. Fixed drug eruption due to paradichlorobenzene. N.Y. Jour. Med. 61: 4079.

Gadrat, J., et al. 1962. Acute hemolytic anemia in a female worker of a dyeing and dry-cleaning shop exposed to inhalation of chlorobenzenes. Arch. des Malad. Prof. Med. due Travail et Secur. Sociale. 23: 710. (Fre.)

Gaffney, P.E. 1976. Carpet and rug industry case study. I. water and wastewater treatment plant operation. Jour. Water Pollut. Control Fed. 48: 2590.

Girard, R., et al. 1969. Serious blood disorders and exposure to chlorine derivatives of benzene (a report of seven cases). Jour. Med. Lyon. 50: 771. (Fre.) (Transl.)

Glaze, W.H., et al. 1976. Analysis of New Chlorinated Organic Compounds Formed by Chlorination of Municipal Wastewater. In: Proc. Conf. Envir. Impact Water Chlorination. Iss. Conf. 751096, p. 153. (Abst.)

Guerin, M. and J. Cuzin. 1961. Skin tests on mice for determining the carcinogenic activity of cigarette tobacco smoke tar. Bull. de l'Assoc. Francaise pour I'Etude du Cancer. 48: 112. (Fre.) (Abst.) (Transl.)

Guerin, M., et al. 1971. Inhibitory action of chemical carcinogens on mitosis of rat lung cultures. 2. Comparative study of carcinogenic and noncarcinogenic substances. C.R. Seances. Soc. Biol. Filiales. 165: 2255. (Transl.)

Hallowell, M. 1959. Acute haemolytic anemia following the ingestion of paradichlorobenzene. Arch. Dis. Child. 34: 74.

Hollingsworth, R.L., et al. 1956. Toxicity of paradichlorobenzene. Determinations on experimental animals and human subjects. AMA Arch. Ind. Health. 14: 138.

Hollingsworth, R.L., et al. 1958. Toxicity of o-dichlorobenzene. Studies on animals and industrial experience. AMA Arch. Ind. Health. 17: 180.

International Agency for Research on Cancer. 1974. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Vol. 7: Some antithyroid and related substances, nitrofurans and industrial chemicals: Ortho- and para-dichlorobenzene.

International Agency for Research on Cancer. 1978. Information bulletin on the survey of chemicals being tested for carcinogenicity. No. 7. Lyon, France.

Irie, D., et al. 1973. Acute toxicity, inhalation toxicity and skin irritation of cyclododecane, tricyclododecane, naphthalene, and p-dichlorobenzene (parazol.) Toho Igakkai Zasshi. 20: 772. (Jap.) (Abst.)

Ito, D., et al. 1973. Acute toxicities of cyclodocecane (CD), tricyclododecane (TCD), naphthalene (NP) and para-dichlorobenzene (PZ). Jour. Med. Soc. Toho Univ. 20: 772. (Jap.) (Transl.)

Jacobs, A., et al. 1974a. Accumulation of noxious chlorinated substances form Rhine River water in the fatty tissue of rats. Vom Wasser. 43: 259. (Ger.) (Abst.)

Jacobs, A., et al. 1974b. Accumulation of organic compounds, identified as harmful substances in Rhine water, in the fatty tissue of rats. Dernforschungszentrum Karlsruhe. KFK 1969 UF, p. 1. (Abst.)

Johnson, K. 1980. Memorandum to D.W. Kuehl. U.S. EPA. March 10.

Kazama, M., et al. 1972. Chemical hygiene studies on organic halogen compounds. I. Transfer of chlorobenzenes into hen eggs. Tokyo Toitsu Fisei Kenkyusho Kenkyu Nempo. 23: 93. (Jap.) (Abst.)

Kohli, J., et al. 1976. Contributions to ecological chemistry. CVII. Fate of lindane-^{14}C in lettuce, endives, and soil under outdoor conditions. Jour. Environ. Sci. Health. B11: 23. (Abst.)

Kopperman, H.L., et al. 1976. Chlorinated Compounds Found in Waste-treatment Effluents and Their Capacity to Bioaccumulate. In: Proc. Conf. Environ. Impact Water Chlorination. Iss. Conf. 751096. p. 327. (Abst.)

Landsteiner, K. and J. Jacobs. 1936. Studies on the sensitization of animals with sample chemical compounds -- II. Jour. Exp. Med. 64: 25.

Langner, H.J. and H.G. Hillinger. 1971. Taste variation of the egg caused by the deodorant p-dichlorobenzene. Analytical proof. Berlin. Muenchen Tierairztl. 84: 851. (Ger.)

Lunde, G. and E. Ofstad. 1976. Determination of fat-soluble chlorinated compounds in fish. Fresenius' Z. Anal. Chem. 282: 395. (Abst.)

Mathur, S.P. and J.G. Saha. 1977. Degradation of lindane ^{14}C in a mineral soil and in an organic soil. Bull. Environ. Contam. Toxicol. 17: 424. (Abst.)

Morita, M. and G. Ohi. 1975. Para-dichlorobenzene in human tissue and atmosphere in Tokyo metropolitan area. Environ. Pollut. 8: 269.

Morita, M., et al. 1975. A systematic determination of chlorinated benzenes in human adipose tissue. Environ. Pollut. 9: 175. (Abst.)

Mostafa, I.Y. and P.N. Moza. 1973. Degradation of gamma-pentachloro-1-cyclohexane (gamma-PCCH) in corn and pea seedlings. Egypt. Jour. Chem. Iss. Spec.: 235. (Abst.)

Murphy, J.B. and E. Sturm. 1943. The effect of sodium pentobarbital, paradichlorobenzene, amyl acetate, and sovasol on induced resistance to a transplanted leukemia of the rat. Cancer Res. 3: 173.

Nalbandian, R.M. and J.F. Pierce. 1965. Allergic purpura induced by exposure to p-dichlorobenzene. Jour. Am. Med. Assoc. 194: 828.

National Academy of Sciences. 1977. Drinking Water and Health. Contract No. 68-01-3169. U.S. Environ. Prot. Agency, Washington, D.C.

National Academy of Sciences. 1978. Nonfluorinated halomethanes in the environment. Environ. Studies Board, Natl. Res. Counc. Washington, D.C.

National Cancer Institute. 1978. Report of testing status of chemicals. Div. Cancer Cause and Prev., Natl. Cancer Inst., Natl. Inst. Health, U.S. Dep. Health Edu. Welfare, Bethesda, Maryland.

Novokovskaya, M.I., et al. 1976. Study of the composition of gas emissions in the production of silicone medical tubing. Kauch. Rezina. 6: 48. (Rus.) (Abst.)

Occupational Safety and Health Administration. 1976. General industry standards. 29 CFR 1910, July 1, 1975; OSHA 2206, revised Jan. 1976. U.S. Dep. Labor, Washington, D.C.

Pagnotto, L.D. and J.E. Walkley. 1966. Urinary dichlorophenol as an index of paradichlorobenzene exposure. Ind. Hyg. Assoc. Jour. 26: 137. (Rev. in Food Cosmet. Toxicol. 4: 109.) (Abst.)

Parke, D.V. and R.T. Williams. 1955. Studies in detoxication: The metabolism of halogenobenzenes. (a) Metadichlorobenzene. (b) Further observations on the metabolism of chlorobenzenes. Biochem. Jour. 59: 415.

Parsons, L.D. 1942. On early tumor formation in pure line mice treated with carcinogenic compounds and the associated blood and tissue changes. Jour. Pathol. Bact. 54: 321.

Patty, F.A. (ed.) 1963. Industrial Hygiene and Toxicology. Vol II: Toxicology. 2nd ed. John Wiley and Sons, Inc., New York.

Perrin, M. 1941. Possible harmfulness of paradichlorobenzene used as a moth killer. Bull. de l' Acad. de Med. 125: 302. (Fre.) (Transl.)

Petit, G. and J. Champeix. 1948. Does an intoxication caused by paradichlorobenzene exist? Arch. des Malad. Prof. de Med. 9: 311. (Fre.) (Transl.)

Pike, M.H. 1944. Ocular pathology due to organic compounds. Jour. Mich. Med. Soc. 43: 581.

Poland, A., et al. 1971. A reciprocal relationship between the induction of aminolevulinic acid synthetase and drug metabolism produced by m-dicholrobenzene. Biochem. Pharmacol. 20: 1281.

Prasad, I. 1970. Mutagenic effects of the herbicides 3',4'-dichloropropionanilide and its degradation products. Can. Jour. Microbiol. 16: 369.

Riedel, H. 1941. Einge beobachtungen uber orthodichlorobenzol. Arch. Gewerbepath. Gewerbehyg. 10: 546. (Ger.)

Rimington, C. and G. Ziegler. 1963. Experimental porphyria in rats induced by chlorinated benzene. Biochem. Pharmacol. 12: 1387.

Salamone, L. and A. Coppola. 1960. Changes in blood coagulation in experimental subacute poisoning with p-dichlorobenzene. Influence of some lipotropic factors. Folia Med. 43: 259. (Abst.)

Schmidt, G.E. 1971. Abnormal odor and taste due to p-dichlorobenzene. Arch. Lebensmittelhyg. 22: 43. (Ger.) (Abst.)

Schmidt, R. and W. Dedek. 1972. Transport, distribution, and metabolism of (^{3}H)- and (^{14}C)-DDT in the pregnant mouse under starvation conditions. Experientia. 28: 56. (Abst.)

Sharma, A.K. and N.K. Bhattacharyya. 1956. Chromosome breakage through paradichlorobenzene treatment. Cytologia. 21: 353.

Sharma, A.K. and S.K. Sarkar. 1957. A study on the comparative effect of chemicals on chromosomes of roots, pollen mother cells and pollen grains. Proc. Indian Acad. Sci. Sect. B. 45: 288.

Simmon, V.F., et al. 1977. Mutagenic activity of chemicals identified in drinking water. 2nd Int. Conf. Environ. Mutagens, Edinburgh, Scotland, July 1977.

Srivastava, L.M. 1966. Induction of mitotic abnormalities in certain genera of tribe Vicieae by paradichlorobenzene. Cytologia. 31: 166.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3, 1980.

Stofen, D. 1973. Tolerance levels for toxic substances in drinking water. Stadthyg. 24: 109. (Transl., Oak Ridge Natl. Lab., ORNL-Tr-2975).

Sumers, J., et al. 1952. Hepatitis with concomitant esophageal varices following exposure to moth ball vapors. N.Y. Jour. Med. 52: 1048.

Thompson, J.H. 1955. Some aspects of liver disease caused by industrial poisoning. Am. Med. Assoc. Arch. Ind. Health. 12: 522.

Totaro, S. 1961. Serum transaminase and aldolase activity in subacute experimental intoxication with p-dichlorobenzene. Folia Med. 44: 586. (Abst.)

Totaro, S. and C. Licari. 1964. Serum transaminases in subacute poisoning with p-dichlorobenzene. Influence of some lipotropic factors. Folia Med. 5: 507. (Abst.)

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water: Rep. to Congress. NTIS PB-250-961. Natl. Tech. Inf. Serv., Springfield, Virginia.

U.S. EPA. 1977. Multimedia environmental assessment. EPA 600/7-77-136a,b. Off. Res. Dev., U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1978a. The National organic monitoring survey. Rep. of the Tech. Supp. Div., Off. Water Supply., U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1978b. Statement of basis and purpose for an amendment to the National interim primary drinking water regulations on trihalomethanes. Off. Water Supply, U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1978c. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, California. Final Report, Task 11. Contract No. 68-01-3887.

Varshavskaya, S.P. 1967a. The hygienic standardization of mono- and dichlorobenzenes in reservoir waters. Nauch. Tr. Aspir. i Ordin. Pervyi Mosk. Med. Institut. 175. (Rus.) (Transl.)

Varshavskaya, S.P. 1967b. Comparative toxicological characteristics of chlorobenzene and dichlorobenzene (ortho- and para- isomers) in relation to the sanitary protection of water bodies. Gig. Sanit. 33: 17. (Rus.)

Varshavskaya, S.P. 1968. The comparitive sanitary and toxicological characteristics of chlorobenzene and dichlorobenzene (ortho- and para- isomers) from the point of view of sanitation of water reservoirs. Gig. Sanit. 33: 15. (Rus.) (Abst.)

Veljkovi'c, V. and D.I. Lalovi'c. 1977. Simple theoretical criterion of chemical carcinogenicity. Experimentia. 33: 1228.

Ware, S. and W.L. West. 1977. Investigation of selected potential environmental contaminants: Halogenated benzenes. EPA 560/2-77-004. Rep. EPA Contract No. 68-01-4183. Off. Toxic Subst. U.S. Environ. Prot. Agency, Washington, D.C.

Weller, R.W. and A.J. Crellin. 1953. Pulmonary granulomatosis following extensive use of paradichlorobenzene. Arch. Intern. Med. 91: 408.

Yang, K.H. and R.E. Peterson. 1977. Differential effects of halogenated aromatic hydrocarbon on pancreatic excretory function in rats. Fed. Proc. Fed. Am. Soc. Exp. Biol. 36: 356. (Abst.)

Young, D.R., et al. 1976. Synoptic survey of chlorinated hydrocarbon inputs to the Southern California Bight. Natl. Environ. Res. Center, U.S. Environ. Prot. Agency, Corvallis, Oregon. (Draft)

Zupko, A.G. and L.D. Edwards. 1949. Toxicological study of p-dichlorobnezene. Jour. Am. Pharm. Assoc. (Sci. Ed.) 38: 124.

U S GOVERNMENT PRINTING OFFICE 1980 720-016/4363