NICNAS

National Industrial Chemicals Notification and Assessment Scheme

ortho-Dichlorobenzene

Priority Existing Chemical Assessment Report No. 14

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with Environment Australia and the Therapeutic Goods Administration, which carry out the environmental and public health assessments, respectively.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals.

This Priority Existing Chemical report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with the Act. Under the Act manufacturers and importers of Priority Existing Chemicals are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the *Commonwealth Chemical Gazette.*

In accordance with the Act, publication of this report revokes the declaration of this chemical as a Priority Existing Chemical, therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of Assessment Reports for New and Existing Chemical assessments may be inspected by the public at the library of the National Occupational Health and Safety Commission (NOHSC). Summary Reports are published in the *Commonwealth Chemical Gazette*, which are also available to the public at the NOHSC library.

Copies of this and other Priority Exising Chemical reports are available on the NICNAS website. Hardcopies are available from NICNAS either by using the prescribed application form at the back of this report, or directly from the following address:

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Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on PEC and New Chemical assessment programs;
- safety information sheets on chemicals that have been assessed as PECs;
- subscription details for the NICNAS Handbook for Notifiers; and
- subscription details for the Commonwealth Chemical Gazette.

More information on NICNAS can be found at the NICNAS Web site:

http://www.nicnas.gov.au

Other information on the management of workplace chemicals can be found at the website of the National Occupational Health and Safety Commission:

http://www.nohsc.gov.au

Overview

ortho-Dichlorobenzene (*o*-DCB; CAS No. 95-50-1) was declared a Priority Existing Chemical on the 7 April 1998. The declaration of *o*-DCB was in response to health and environmental concerns due to its widespread use as a degreasing agent.

Industrial uses in Australia include formulations as paint removers, as a degreaser (for grease traps, drains and automotive parts) and as a decarboniser in the automotive and marine industries.

The manufacture of *o*-DCB does not occur in Australia, consequently, all of the material used is imported. Current imports amount to less than 100 metric tonnes per annum. Approximately 10 tonnes are for industrial uses and the remainder for agricultural/veterinary uses which are not assessed in this report.

o-DCB is well absorbed by inhalation and oral routes. The target tissues and organs are adipose tissue, liver, kidneys and plasma proteins. Metabolism of *o*-DCB is by aromatic hydroxylation to give dichlorophenol. Further metabolism by conjugation with glutathione, sulfate or glucuronate can occur. The parent compound and its derivatives are rapidly excreted in the urine with minor amounts lost in faeces. Due to its volatile nature, traces of *o*-DCB may be found in expired air.

In humans, acute exposure to *o*-DCB can result in headache, malaise, nausea, vomiting and vertigo. Dermal exposure to *o*-DCB can result in painful irritation with reddening and blistering of the skin while the vapour may cause eye irritation. In animals, acute high dose exposure may induce central nervous system depression resulting in respiratory distress and death. Liver damage can result from chronic exposure to *o*-DCB.

In several microbial assays *o*-DCB has been found to be without mutagenic or clastogenic effects. Similarly, in mammalian test systems *o*-DCB has shown no evidence of genotoxicity. Long-term studies with animals have shown no evidence of carcinogenicity.

Based on the assessment of health effects, *o*-DCB should be classified in accordance with the NOHSC *Approved Criteria for Classifying Workplace Hazardous Substances* (NOHSC, 1999a), as 'Harmful if swallowed' (risk phrase R22) and 'Irritating to the eyes, respiratory system and skin' (risk phrases R36/37/38).

Occupational exposure to *o*-DCB in Australia can occur during product formulation or end-use of such products. However, exposure to *o*-DCB is expected to be low due to the enclosed nature of some operations, limited exposure duration and the relatively small quantities of material used.

The occupational risk assessment for *o*-DCB concluded that, for known Australian work situations, potential atmospheric concentrations of *o*-DCB are unlikely to reach levels that may cause acute effects. In addition, it is unlikely that workers in these situations will be at risk from chronic adverse health effects related to *o*-DCB exposure, as margins of exposure are likely to be high after taking into account the intermittent nature of the exposure, the small quantities involved and the dilute nature of the products.

The chemical is biodegradable under aerobic conditions and relatively soluble in water. Its removal from aqueous systems occurs significantly from volatilisation, and at equilibrium, around 98% of the chemical would be expected to partition to the atmosphere where it will break down through reaction with hydroxyl radicals. Large discharges to relatively small water volumes could constitute a hazard to the aquatic environment. However, concentrations likely to occur in aquatic systems are expected to be generally of low concern, and this expectation is supported by monitoring data from Australia and overseas. A relatively low aquatic risk is predicted.

The relatively short atmospheric lifetime of *o*-DCB indicates concentrations will not occur at levels harmful to the atmosphere. While widespread transport within the troposphere is likely, the chemical is not expected to reach the stratosphere and therefore not expected to have an influence on global warming or ozone depletion.

Under present conditions of use, there are no significant risks to the public from the appropriate use *o*-DCB or products containing *o*-DCB.

It is recommended that, for the protection of the environment, *o*-DCB should be sent to licenced liquid waste disposal contractors where possible.

It is further recommended that the exposure standard for *o*-DCB be reviewed by the National Occupational Health and Safety Commission.

Contents

LIST OF FIGURES

LIST OF TABLES

Acronyms and Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADG	Australian Dangerous Goods
AICS	Australian Inventory of Chemical Substances
ALT	alanine aminotransferase
APHA	American Public Health Association
AST	aspartate aminotransferase
ASTM	American Standard Test Method
BCF	bioconcentration factor
BrdU	5-bromo-2'-deoxyuridine
BUA	Beratergremium für Umweltrelevante Altstoffe
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstracts Service
cDNA	complementary deoxyribonucleic acid
CHO	Chinese hamster ovary
C.I.	confidence interval
CNS	central nervous system
CO_2	carbon dioxide
CYP	cytochrome P450
DCB	dichlorobenzene
DCBQ	dichlorobenzoquinone
DCP	dichlorophenol
DNA	deoxyribonucleic acid
dw	dry weight
EA	Environment Australia
EASE	Estimation and Assessment of Substance Exposure
EC_{50}	median effective concentration
ECD	electron capture detection
EH	epoxide hydrolase
EINECS	European Inventory of Existing Commercial Chemical Substances
EPA	Environmental Protection Agency (USA)
EU	European Union
FID	flame ionisation detection
GC	gas chromatography
GLU-T	glucuronyl transferase
γ-GT	γ-glutamyl transferase
GSH	glutathione (reduced)
GS-T	glutathione S-transferase
HGPRT	hypoxanthine guanine phosphoribosyl transferase
HPLC	high performance liquid chromatography
IARC	International Agency for Research on Cancer
IC	Inhibitory concentration
IUPAC	International Union of Pure and Applied Chemistry
i.p.	intraperitoneal
i.v.	intravenous

Koc	organic carbon partition coefficient
LC	lethal concentration
LC_{50}	median lethal concentration
LD	lethal dose
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
m	metre
m-DCB	*meta*-dichlorobenzene (1,3-dichlorobenzene)
µg	microgram
MLD	minimum lethal dose
MOE	margin of exposure
MS	mass spectroscopy
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Cooperation and Development
o-DCB	*ortho*-dichlorobenzene (1,2-dichlorobenzene)
p-DCB	*para*-dichlorobenzene (1,4-dichlorobenzene)
Pa	pascals
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
PID	photoionization detection
POP	persistent organic pollutant
PPE	personal protective equipment
ppm	parts per million
ppb	parts per billion
RD_{50}	the dose at which the respiratory frequency is reduced by 50% due to a reflex pause in the expiratory phase of respiration
RTECS	Registry of Toxic Effects of Chemical Substances
SCE	sister chromatid exchange
S-D	Sprague-Dawley
SDH	sorbitol dehydrogenase
STEL	short-term exposure limit
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TWA	time-weighted average
UDS	unscheduled DNA synthesis
UN	United Nations

1. Introduction

1.1 Declaration

The chemical *ortho*-dichlorobenzene (*o*-DCB), Chemical Abstracts Service (CAS) number 95-50-1, was declared a Priority Existing Chemical for full assessment by the Minister for Workplace Relations and Small Business under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), as amended, by notice in the *Chemical Gazette* on 7 April 1998.

The declaration was made on the basis that there were reasonable grounds for believing that the handling and use of *o*-DCB may give rise to a risk of adverse health and environmental effects. In summary, these grounds were:

- the potential for occupational and environmental exposure and potential adverse effects;
- lack of published information on the health and environmental effects of *o*-DCB; and
- a need for characterisation of exposure and associated health and environmental risks.

In accordance with the Act, persons who wished to manufacture or import *o*-DCB into Australia were required to apply for assessment whilst *o*-DCB remained a Priority Existing Chemical. As *o*-DCB is not manufactured in Australia, applications were limited to importers.

The declaration of *o*-DCB as a Priority Existing Chemical (*Chemical Gazette 7 April 1998*) indicated that it was to be assessed with *para*-dichlorobenzene. While under investigation it became apparent that the use and toxicological profiles of these two chemicals were substantially different. Consequently, the two chemicals have been published separately. The *para*-dichlorobenzene report [*para*-Dichlorobenzene, *Priority Existing Chemical No. 13 – Full Public Report*] may be obtained from NICNAS.

1.2 Objectives

The objectives of this assessment were to:

- characterise the hazards of *o*-DCB to human health and the environment;
- characterise current and potential occupational, public and environmental exposure to *o*-DCB;
- characterise the risk of adverse effects resulting from exposure to workers, the general public, and the environment; and
- make appropriate recommendations to control exposures and/or reduce potential health and environmental risks.

1.3 Australian perspective

Industrial uses of *o*-DCB in Australia are as a paint remover and as a degreaser/decarboniser in the automotive and marine industries. It has also found limited use as an industrial deodorant for refuse containers. However, the predominant use is in agricultural applications (as a sheep branding fluid). A small quantity of *o*-DCB is also used as a pharmaceutical. This assessment focuses on the industrial uses of *o*-DCB and does not consider agricultural or pharmaceutical uses.

1.4 International perspective

Historically, *o*-DCB has been manufactured on a large scale for several decades. The chemical is co-produced during the manufacture of *para*-dichlorobenzene and the two isomers are separated at a later stage.

o-DCB has found many uses in industry including use as an intermediate in the synthesis of several organic compounds, principally 3,4-dichloroaniline and dyes. According to published literature, it is used as an industrial solvent for organic compounds and for oxides of non-ferrous metals, as a degreasing agent and engine cleaner, in metal polishes, as a heat-exchange medium and as an insecticide and fumigant for the control of peach tree borers, bark beetles and for termite control. It has some limited use in industrial odour control (Lewis, 1997).

1.5 Sources of information

As there were no recent international assessments upon which to base the metabolism, toxicity and health effects sections of this assessment, a comprehensive literature search for the chemical was undertaken and the required documents obtained and evaluated.

Reviews of the environmental effects of *o*-DCB by international organisations have been carried out by the GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA, 1990) and Environment Canada (1993). These reviews formed the basis of the environmental sections of this report unless otherwise noted.

In addition, surveys were conducted by NICNAS. Questionnaires were sent to importers, formulators, and end users of *o*-DCB to obtain information on amounts of *o*-DCB imported, uses, formulation process, Material Safety Data Sheets (MSDS), labels, worker and environmental exposure, and current control measures.

1.6 Peer-review

During all stages of preparation, this report has been subject to internal peer review by NICNAS, Environment Australia (EA) and the Therapeutic Goods Administration (TGA).

2. Applicants

Following the declaration of *o*-DCB as a Priority Existing Chemical, seven companies applied for assessment of the chemical. The applicants supplied information on the properties, import quantities and uses of the chemical. In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, NICNAS provided the applicants with a draft copy of the report for comment during the corrections/variation phase of this assessment.

The applicants were as follows:

Australian Manufacturing Workers Union
3/440 Elizabeth Street
Melbourne
VIC 3000

Bio-Scientific Pty Ltd
PO Box 78
Gymea
NSW 2227

Clarient (Australia) Pty Ltd
606 St Kilda Road
Melbourne
VIC 3004

Crown Scientific Pty Ltd
144 Moorebank Avenue
Private Mail Bag 4
Moorebank
NSW 2170

Merck Pty Ltd
207 Colchester Road
Kilsyth
VIC 3137

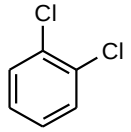
Recochem Inc
PO Box 478
Wynnum
QLD 4178

Redox Chemicals Pty Ltd
30-32 Redfern Street
Locked Bag No. 60
Wetherill Park
NSW 2164

3. Chemical Identity and Composition

3.1 Chemical identity

Table 1 - Chemical identity

Chemical name (IUPAC)	1,2-Dichlorobenzene
Other names	*ortho*-Dichlorobenzene *o*-Dichlorobenzene 1,2-DCB o-DCB
CAS Number	95-50-1
EINECS Number	202-425-9
RTECS Number	CZ4500000
Empirical formula	$C_6H_4Cl_2$
Structural formula	
Molecular weight	147.00

Trade and product names are listed at Appendix 1.

3.2 Chemical composition (including additives and impurities)

Commercially available *o*-DCB in Australia (industrial or technical grade) is typically 65 to 85% pure and the remainder comprises isomers of *para*- and *meta*-dichlorobenzene with lesser amounts of chlorobenzene and trichlorobenzene.

4. Physical and Chemical Properties

4.1 Physical properties

o-DCB is a clear liquid at ambient temperature and pressure (Merck, 1989). The odour threshold in air is 1.8 mg/m^3 and the odour threshold in water is 24 µg/L (Amoore and Hautala, 1983).

Conversion factors

1 ppm = 6.01 mg/m^3 and 1 mg/m^3 = 0.17 ppm (at 20°C and 1013 hPa; Verschueren, 1996).

The physical properties of *o*-DCB are given in Table 2.

Table 2 - Physical properties

Property	Value	References
Melting point	-16.7°C	Carswell, 1928
Boiling point	180.3°C	Carswell, 1928
Flash point (closed cup)	66°C	Sax, 1996
Ignition Temperature	648°C	Sax, 1996
Density (25°C)	1.3007 g/cm^3	Curry and Gilkerson, 1957
Vapour density (20°C)	5.05 g/cm^3	Sax, 1996
Vapour pressure (25°C)	1.96 hPa	Mackay and Shiu, 1981
Water solubility (25°C)	155.8 mg/l	Banerjee *et al*., 1980
Solubility in organic solvents	Miscible with most organic solvents	Sax, 1996
Henry's Law constant (25°C)	193 Pa.m^3/mol	Mackay and Shiu, 1981
Partition coefficient (25°C)	Log P_{ow} = 3.4	Banerjee *et al*., 1980 Miller *et al*., 1985

4.2 Chemical properties

Hydrolysis: Hydrolysis of *o*-DCB to *o*-chlorophenol and catechol proceeds only under drastic conditions (days at > 200°C).

Combustion products: Oxides of carbon, hydrogen chloride gas and some phosgene may form on combustion of *o*-DCB.

Reactivity: *o*-DCB can react vigorously with oxidising materials. *o*-DCB can slowly react with aluminium on storage to form an explosion hazard if in a sealed container.

Polymerisation: *o*-DCB does not polymerise.

Explosivity: The explosion limits in air are 2.2 vol. % (lower) to 9.2 vol. % (upper) (Sax, 1996).

5. Methods of Detection and Analysis

5.1 Identification

The isomers of dichlorobenzene are quantitatively determined by gas chromatography (GC) and, if required for definitive analysis, gas chromatography/mass spectroscopy (GC-MS). Sample preparation is based on concentration techniques utilising adsorption onto porous resins or activated charcoal with thermal or extractive desorption techniques followed by electron capture (ECD), flame-ionisation (FID) or photoionization (PID) detection. The use of capillary columns has been found to provide better resolution and sensitivity than packed columns (Washall and Wampler, 1988).

The analytical accuracy for *o*-DCB can be influenced by several factors such as sampling flow rates, temperature and humidity. These factors can influence the adsorption of *o*-DCB onto various sorbants (APHA, 1995). Separation of all isomers of dichlorobenzene can be achieved using Carbowax 20M coated glass capillary columns with isothermal or temperature gradient methods (Korhonen, 1983).

5.2 Atmospheric monitoring

The determination of atmospheric levels of *o*-DCB (NIOSH, 1994; Method 1003) entails the passage of 10 litres of sample volume over activated charcoal at a rate of 50 to 200 mL/min. Desorption is achieved with carbon disulfide followed by GC-FID. The detection limit is 0.1 mg/m^3.

The determination of dichlorobenzenes in ambient air can be achieved by either passive or active means. Passive sampling involves adsorption onto activated charcoal with desorption by carbon disulfide followed by capillary GC. Active methods include adsorption onto Tenax (a porous polymer) using an air flow rate of 23 L/hr. Analysis is undertaken by thermal desorption at 200° to 250°C followed by GC/MS (Wallace, 1987). The limit of detection is within the ng/m^3 range.

5.3 Water monitoring

Determination of dichlorobenzenes in water samples can be achieved using several methods. Older methods utilise liquid/liquid partitioning. The United Kingdom Department of the Environment (1986) method requires a 2-litre sample of water to be extracted with hexane and an aliquot subjected to capillary column analysis with GC-ECD or GC-FID. If wastewater is to be analysed, clean up of the sample will be required. The detection limit for *o*-DCB is stated to be in the range of 9 ng/ml for surface water and 420 ng/ml for wastewater.

Recent techniques depend on purging the sample with an inert gas, usually helium or nitrogen, which is then passed through a sorbent. Final analysis is achieved by thermal desorption followed by GC or GC/MS techniques. The detection limit varies depending on the quality of water sampled and can range from 0.1 to 100 ng/ml. For wastewater, an intermediate clean-up procedure is required.

5.4 Monitoring of soil and sediments

The determination of *o*-DCB in soil or sediment samples according to the method of Oliver and Bothen (1982) involves the extraction of 30 g wet weight (or 10 to 15 g dry weight) of sample with hexane/acetone. GC-ECD is proceeded by extraction and column chromatography. The detection limit is given as 5 μg/kg.

5.5 Biological monitoring

The presence of dichlorobenzenes in biological samples including urine, blood, tissues, milk and breath can be detected by various techniques, however, many of the techniques have not been validated. Generally, extraction of dichlorobenzenes from biological samples requires liquid/liquid partitioning or, for blood, urine and human milk, purge techniques using an inert gas.

6. Manufacture, Importation and Use

6.1 Manufacture and importation

6.1.1 Manufacture

The manufacture of *o*-DCB does not occur in Australia. Overseas, the manufacture of *o*-DCB is accomplished by the fluid phase chlorination of benzene in the presence of a catalyst. The resulting *o*-DCB, as a technical grade, is approximately 80% *o*-DCB with less than 19% of 1,4- and 1,3-dichlorobenzene, less than 1% trichlorobenzenes and less than 0.05% monochlorobenzene although this may vary depending on production methods. A purified grade is produced containing 98% *o*-DCB with less than 0.2% 1,2,4-trichlorobenzene and 0.05% monochlorobenzene. Technical grade *o*-DCB can contain from 15% to 30% of *p*-DCB (BUA, 1990).

6.1.2 Importation

In 1998, 6 companies imported *o*-DCB with 2 companies accounting for 99% of all imports. The bulk of imported material was of the technical grade with a small amount of purified *o*-DCB imported for research use. The total imports of *o*-DCB for 1998 amounted to less than 100 tonnes. Similar volumes were also imported in 1997 and 1996. Of this, approximately 10 tonnes were used for industrial purposes. The imported material was packaged in steel drums each containing 250 or 275 kg net weight of *o*-DCB. The purity of the imported material was stated to range from 65 to 85%, the remainder comprising mixed isomers (*p*-DCB and *m*-DCB). *o*-DCB is also known to be present as an impurity in other imported materials such as pigments for plastics, ink and paint production. The total amount is difficult to estimate but is believed to be less than 5 kg per annum based on information provided by one company.

6.2 Uses

The following areas and sectors of industry, in which *o*-DCB is used, were identified:

- Automotive/Transport/Marine;
- Engineering (general);
- Industrial cleaning; and
- Agriculture.

Information obtained from an industry survey indicated that imported *o*-DCB is formulated into solvents for several types of use. Of the uses identified, approximately 86% was in the agricultural sector as wool branding products followed by industrial uses as degreasers/decarbonisers/paint strippers (approximately 12%) and industrial deodorant (0.3%) with the remainder being for pharmaceutical use (0.3%). Therefore, approximately 10 tonnes/year are used for industrial purposes.

Material for pharmaceutical use as an ear drop medication is formulated overseas and imported as a pre-packaged product containing 14% *o*-DCB.

The agricultural/veterinary and pharmaceutical uses of *o*-DCB, while accounting for the bulk of imports, are outside the scope of this report.

With the exception of the one pharmaceutical product, no retail sales for the domestic use of *o*-DCB (or of products containing *o*-DCB) were identified.

6.3 Formulation of products

All of the *o*-DCB imported into Australia for industrial use (approximately 10 tonnes) undergoes formulation into products. Six companies were identified as formulators of industrial products containing *o*-DCB.

The process of formulating products containing *o*-DCB typically involves blending the chemical with other components in a blending tank, at ambient temperature, from which the finished product is transferred to appropriate sized containers for marketing. The *o*-DCB, supplied in steel drums (250 or 275 kg capacity), is transferred to the blending tank by means of a pump. All operations take place under closed or partially closed conditions. Other chemicals with which *o*-DCB may be blended with include methanol, methylene chloride, cresylic acid, dimethylformamide, phenols, formic acid, liquid hydrocarbons or mineral turpentine.

The percentage of *o*-DCB in finished products for a particular application is variable. For use as a diesel engine air-system cleaner the range is from approximately 20 to 60% (w/v) *o*-DCB. Paint removers contain from 2.5% to 70% (w/v) *o*-DCB while degreasers range from 40% to 70% (w/v) *o*-DCB (see Appendix 1).

6.4 Methods of use

Degreasing/Paint Stripping

For most degreasing or paint stripping operations, items for treatment are immersed in a tank of the solvent for the required time (until degreasing is accomplished or paint blistering occurs). Brushing or swabbing the article with the solvent is used as an alternative to immersion in some cases. When cleaned, the item is rinsed with water to remove debris and residual solvent. While most products can be used at ambient temperature, a number of products are designed for use at temperatures of between 50 to 60^{o}C. Most of the products are designed to be used as supplied although some can be used diluted with another suitable solvent such as diesolene, mineral turpentine or kerosene. The dilution factor is variable and dependent upon the application.

Some application instructions recommend the use of a water seal over the tank to prevent the escape of vapour during the cleaning process.

Of the products identified as paint strippers only one was required to be painted or sprayed onto the surface to be stripped. After application, the paint stripper is left for 5 minutes to allow penetration followed by cleaning with a high-pressure water jet. The *o*-DCB content of this product was stated to be <10% (w/v).

Decarbonising

Diesel or petrol engine components operating at high temperatures and exposed to fuel frequently become encrusted with carbon deposits. Components that require decarbonising can be cleaned by immersion in a tank of decarbonising solvent in a similar manner as for degreasing described above. Alternatively, diesel engine intercoolers can be cleaned *in situ* which involves injecting the solvent into the trunking before the intercooler. Products for use as in-line cleaners of diesel turbocharger intercoolers are diluted with water prior to use.

Deodoriser

Only one product was identified for use as an industrial deodoriser. The product is used for the control of odours in sewage plants, septic systems and effluent streams (e.g. from abattoirs and canning plants). The product (containing 42% *o*-DCB w/v) is used by adding 2 to 4 mL/1000 L of effluent. According to the product information sheet, a dilute solution can be sprayed onto industrial garbage bins to control odours.

6.5 Export

A small quantity of formulated product-containing *o*-DCB for use as a degreaser/decarboniser is exported each year.

7. Environmental Exposure

No studies with respect to environmental fate and toxicity were provided by applicants. Only a few published studies were available, and these were for environmental fate. Therefore, this assessment has relied extensively upon international reports, particularly the German BUA Report (1990) and the Canadian Environmental Protection Act report (Government of Canada, 1993). Some of these data also appear in the IUCLID data sheet (International Uniform Chemical Information Database) (1996), which was used during preparation of the present report. Results from this data sheet are non-confidential data supplied to the European Commission by European industry. The *o*-DCB data sheet has not undergone any evaluation or validation by the European Commission.

Other references relied upon for this section include Howard (1989) and Howard *et al.* (1991). Literature papers are also included where available.

7.1 Release

Approximately 10 tonnes of *o*-DCB were imported for industrial use in 1998, with similar quantities imported in 1997 and 1996. It is likely that over 50% of the compound is released to the environment through evaporation to the atmosphere, and discharge of used products to wastewater etc.

7.1.1 Formulation

The formulation of *o*-DCB into final products is described in Section 6.3. There are no actual figures on release estimates during these processes, but due to the use of engineering controls during formulation, releases to air and water are expected to be minimal. Generally, it would be expected that release to water will be small, but since little information is available estimates of release to air and water were made using the Technical Guidance Document of the European Commission (European Commission, 1996). This document indicates that for a chemical such as *o*-DCB, around 1% will be released to air, and 2% released to water during formulation activities. A negligible quantity (0.01%) is anticipated to be released to the soil compartment. With around 10 tonnes of *o*-DCB used each year in formulating industrial products such as degreasers and paint strippers, annual release to air is estimated as up to 100 kg, and 200 kg released to water. Based on information provided by industry, it has been assumed that formulation processes are conducted on only 5 days of the year, and this results in estimated release to the atmosphere of 20 kg per day of use, and 40 kg per day to water. The data are summarised in Table 3 below.

7.1.2 End use

In 1998, 10 tonnes of *o*-DCB underwent formulation into industrial degreasing/decarbonising solvents and paint strippers. In these applications, if used by medium to large industrial concerns (e.g. aero-engineering companies) disposal of used solvent through specialised solvent disposal companies would be expected. The recovery

of *o*-DCB from spent solvent is unlikely, and most probably the material would be incinerated. In any case, inappropriate disposal to the water compartment is unlikely.

However, little information with respect to this end use pattern is available, and it is possible that much of the degreaser and paint stripper may be used in open systems by small operators. In this scenario inappropriate disposal of used product is more likely, and the resulting release quantities may be estimated using the methodology of Technical Guidance Document of the European Commission (European Commission, 1996). This document indicates that for a compound with solubility between 100 and 1000 mg/L and vapour pressure between 100 and 1000 Pa (for *o*-DCB these parameters are 143 mg/L and 196 Pa respectively), some 10% would be released to air, 40% to water and 5% to soil during end use activities as a solvent or paint stripper. If it is assumed that as a worst case the full 10 tonnes of the chemical are used in these products each year, and that these are used for 200 days each year, the daily release of *o*-DCB to each of the compartments may be estimated. The relevant estimates are summarised in Table 3.

Total annual release of *o*-DCB is estimated as 58% (5,800 kg) with the greater part released to the water compartment (4200 kg). It should be appreciated that almost all the *o*-DCB imported and used within Australia is technical grade material containing a substantial quantity of *p*-DCB and lesser quantities of other chlorinated benzenes (see Section 6.1.2). Consequently, these will be released with, and in the same manner as the *o*-DCB.

Table 3 - Estimated release of *o*-DCB

	Release to Air (kg)		Release to Water (kg)		Release to Soil kg)	
ACTIVITY *	**Annual**	**Daily**	**Annual**	**Daily**	**Annual**	**Daily**
Formulation (5 days per year)	100	20	200	40	1	0.2
End Use in Solvents and Paint Strippers (200 days per year)	1000	5	4000	20	500	2.5
Total Releases	**1100**	**5-25**	**4200**	**20-60**	**501**	**2.5-2.7**

*Annual usage in industry = 10 tonne, based on an annual industrial use of 10%

7.2 Fate

Calculations based on Mackay Level 1 models for the partitioning of released *o*-DCB into the various environmental compartments from the ASTER data-base of the US EPA indicates that at equilibrium, in the order of 97.7% of this chemical will partition to air, with 1.6% and 0.4% partitioning to water and soil respectively (US EPA, 1999). Around 0.3% may partition into sediments, while none is predicted to partition to biota.

7.2.1 Atmospheric fate

o-DCB is expected to partition predominantly to the atmosphere at equilibrium. The chemical absorbs radiation weakly at wavelengths greater than 300 nm, so direct

photolysis in the atmosphere is not likely (Bunce *et al*., 1987). However, reaction with photochemically produced hydroxyl radicals in the atmosphere will occur. Howard *et al*. (1991) has estimated the photo-oxidation half-life to be around 24 days. Wahner and Zetzsch (1983) calculated a rate constant for the reaction between hydroxyl radicals and *o*-DCB in the atmosphere at room temperature of 4.2×10^{-13} cm^3/molecule/sec. When allowance is made for the mean global hydroxyl radical concentration in the troposphere of 5×10^5 molecules/cm^3 (Calamari, 1993), the half-life computes to 38 ± 2 days.

The presence of *o*-DCB in rainwater indicates that it persists long enough to be returned to the earth's surface by atmospheric wash out (Ligocki *et al*., 1985).

7.2.2 Aquatic fate

The Henry's Law Constant at 25°C is 193 Pa.m^3/mol., and according to the scale of Mensink (1995), these results suggest *o*-DCB is readily volatile from aqueous solution. Slimak *et al*. (1980) state that volatilisation is expected to be the dominant mechanism for removal of *o*-DCB from surface water and soil. Smith *et al*. (1980) and Thomas (1982) also indicate that evaporation of *o*-DCB from the hydrosphere constitutes a significant transport mechanism for the chemical.

Howard (1989) reports an estimated half-life of 4.4 hours from a model river one metre deep flowing at 1 m/sec with a wind velocity of 3 m/sec at 20^0C. Other volatilisation half-lives ranging between less than 1 hour for a shallow stream, and up to 60 days for a deep slow moving river have been reported (US EPA, 1987).

Bouwer *et al*. (1981) monitored the decrease in concentration of *o*-DCB from secondary treated wastewater during flow-through infiltration basins. These workers found 40% decrease in *o*-DCB concentration after passage of the water through the basins in which the residence time was 8 hours.

These data indicate that if *o*-DCB is released to an agitated body of water, then it is expected to be volatilised fairly rapidly, and would then be slowly destroyed through reaction with photochemically produced hydroxyl radicals as indicated above. However, if the water body is not agitated the released chemical may become associated with the organic component of suspended particulate matter, and then become assimilated into benthic sediments. When associated with sediments, a large body of data – particularly from North America – indicates that it may be very persistent in this environment. Monitoring data conducted in the Great Lakes area of North America indicate that adsorption to sediment is a major environmental fate process. Its detection in Lake Ontario sediment cores by Oliver and Nicol (1982) indicates that the chemical has persisted in these sediments for decades. Adsorption to sediment in water will attenuate volatilisation.

Photolytic degradation in water is also possible, again through the agency of hydroxyl radicals. Russi *et al*. (1982) have estimated the half-life for photochemical oxidation in water (the river Goldach in Germany) as 12.8 days. According to Mansour *et al*. (1989), mineralisation proceeds fully to production of carbon dioxide and hydrochloric acid. It is unlikely that hydrolytic degradation would be a significant mechanism for degradation in the aquatic environment.

o-DCB may biodegrade in aerobic water after microbial adaptation (see Section 7.2.4). However, it is not expected to biodegrade under anaerobic conditions which may exist in lake sediments or various ground waters (Howard, 1989). Monitoring data tabulated in BUA (1990) shows sediment readings from rivers in Germany and lakes and rivers in North America. Sediment measurements tended to greatly exceed those found in the surface waters, with concentrations in sediments ranging from 1 μg/kg dry weight (dw) in (relatively pristine) Lake Superior to values in excess of 40 μg/kg dw for samples taken from Lake Ontario and river sediments in Germany. However, it should be noted that the high sediment readings were taken from rivers and lakes which historically have received large quantities of pollution from the chemical industry.

o-DCB was reported to be persistent and slightly mobile during field studies of groundwater contaminated by sewage effluent and minicipal and industrial wastes (Govt. of Canada, 1993), with Zoeteman *et al*. (1980) estimating that the half-life in ground water ranged between 30 to 300 days.

7.2.3 Terrestrial fate

Several results for the soil adsorption/desorption coefficient (Koc) are available for a range of soils and sediments, with Koc values ranging from 316 in a silt loam with 1.9% organic carbon (Chiou *et al.*, 1983) to 4654 in a sandy aquifer material described as having only 0.02% organic matter (Mackay *et al.*, 1986; Curtis *et al.*, 1986). The corresponding range for Log Koc is 2.45 to 3.67. This may indicate that the chemical has higher affinity for silicate material and the mineral component of soils and sediments rather than for organic material. This is supported by the study of Stauffer and MacIntyre (1986) who found that adsorption to soils and oxide minerals was very dependent on the ambient pH, with adsorption strongly suppressed under basic conditions. However, in a recent study of adsorption/desorption of *o*-DCB to peat soils, Deitsch and Smith (1999) found that after an adsorption time greater than 2 days, subsequent desorption of the compound was incomplete, and some of the chemical appeared to be irreversibly sorbed to the soil, and could consequently persist in this media. This result was interpreted in terms of interaction of the *o*-DCB with the humic (organic) component of the soils.

On the basis of the measured values for Koc, the compound demonstrates medium to slight mobility in soils according to the McCall scale (McCall *et al.*, 1980), with increased mobility in soils of higher organic carbon and less silicate matter. Medium mobility is supported by the laboratory results of Bouwer *et al*. (1981) which indicated that water percolating through a column of soil previously contaminated with *o*-DCB removed the chemical. Further evidence for mobility is provided by the field results of Demirjian *et al*. (1987) who found that four months after applying sludge contaminated with *o*-DCB to the upper layer of a sandy soil (depth 0 to 15 cm), the chemical was detected in the lower layers at depths between 15 and 48 cm.

The mobility of the chemical in soil and the relative ease with which it is desorbed indicate that re-suspension of contaminated benthic sediments would lead to release of *o*-DCB back into the water column.

Leaching from hazardous waste disposal areas in Niagara Falls to adjacent surface waters has been reported and the detection of *o*-DCB in ground water indicates that leaching can occur (Howard, 1989).

Volatilisation from soil surfaces may be an important transport mechanism; however, this may be mitigated by adsorption or leaching.

Wang and Jones (1994) investigated the behaviour and fate of a series of chloro substituted benzenes when spiked into soil (both "standard" soil and sewage sludge amended soil) using kinetic techniques over a 259 day test period. These authors found that, in general, the decrease in the chlorobenzene content of the soil (temperature between 20 and 30°C) could be described by a two step first order kinetic model, indicating two elimination mechanisms. In the case of *o*-DCB, when this compound was spiked into "standard soil" at a level of 26.8 μg/kg, around 80% was removed after 35 days with a process half-life of 8.6 days, while only an additional 4.3% was removed in the ensuing 224 days (half-life estimated at 191 days). The corresponding data for *o*-DCB (initial level 126 μg/kg) in sewage sludge amended soil were 80% removal over the first 19 days (half-life = 13.2 days) followed by an additional 14 % removal over 240 days (half-life = 892 days). While the half-life for the second stage of the elimination process is significantly longer than that of the first stage, the second stage elimination is pertinent to only a fraction of the initial *o*-DCB load in the soil (around 25%), and the overall half-lives in "standard" soil and sewage amended material were 10.5 and 14.4 days respectively. The authors concluded that volatilisation was the major elimination process, both from the "standard" soil and the sludge amended material, and that biodegradation and other removal processes were of significantly less importance. As mentioned above, Deitsch and Smith (1999) noted that some *o*-DCB appears to become "irreversibly" sorbed to soil, and it is likely that this observation is connected with the relatively slow release of *o*-DCB during the second stage of the elimination process found by Wang and Jones (1994).

In a separate study of 8 archived samples of sewage sludge amended soil collected between 1942 and 1991 Wang *et al*. (1995) found the level of *o*-DCB in the amended soil varied between 0.18 and 0.55 μg/kg compared with 0.15 to 0.36 μg/kg for control samples taken from a neighbouring plot which had not been treated with sludge. Although levels in the sludge amended samples were elevated over those of the control, there was no obvious trend in these figures (i.e. no apparent significant increase with time). This result also supports relatively rapid elimination of *o*-DCB from soils[1].

It is possible that the chemical may be slowly biodegraded in soil under aerobic conditions (see Section 7.2.4.2). Chemical transformation processes such as hydrolysis, oxidation, or direct photolysis on soil surfaces are not expected to occur (Howard, 1989).

[1] It is of interest that the levels of *p*-DCB (1,4-dichlorobenzene) in the same soil samples were roughly an order of magnitude higher than those for *o*-DCB, and this was particularly marked in the samples taken during the 1960's and later. This possibly reflects the extensive use of this compound as a deodoriser in public toilet facilities, and/or indicates *p*-DCB is a breakdown product of pesticides and other agricultural products.

7.2.4 Biodegradation

A variety of data on biodegradation of *o*-DCB are summarised by Howard (1989) and in BUA (1990), with the original test report for only one anaerobic study being available for this assessment.

There is a great deal of variation in the reported results, with some studies indicating almost zero biodegradation, while others report almost complete degradation. In particular, many of the summarised degradation studies using standard OECD or the Japanese MITI test methods reported very low degrees of biodegradation. For example, Canton *et al*. (1985) observed no degradation in a repetitive die-away test. Alternatively, Hoechst (1985) reported results for a closed bottle test (OECD 301 D) where *o*-DCB, initially present at a concentration of 4 mg/L and inoculated with bacteria from a municipal sewer plant, was progressively degraded by 18, 35, 77 and 93% after 5, 14, 21 and 28 days respectively. In the IUCLID data sheet it is indicated that according to the modified MITI test for ready biodegradation (OECD 301 C) no degradation was observed after 28 days. The IUCLID also indicated that in a Closed Bottle Test (OECD 301 D) the compound was degraded 58% after 20 days by domestic sewerage bacteria.

A large number of biodegradation results are summarised in the BUA Report (1990), and an important observation from the majority of tests is that under aerobic conditions the degree of biodegradation is very small unless the bacteria of the inoculum have first been acclimatised to the compound. Also, the absence of appropriate bacterial strains in the inoculation cultures probably accounts for much of the variation in observed degrees of biodegradation. The test result indicating 58% degradation after 20 days quoted in IUCLID was apparently conducted using adapted bacteria.

It has been found (Cobb *et al*., 1974) that strains of *Pseudomonas* bacteria can be selected from "native" populations in activated sludge to fully utilise *o*-DCB. Similarly, Springer and Rast (1988) isolated acclimatised genera of *Pseudomonas*, *Acinerbacter* and *Moraxella* from Rhine River water. These authors also studied the metabolic pathway for degradation and concluded that the aromatic ring is opened through intermediate peroxide formation, followed by elimination of chloride. The end product of primary degradation was stated as being 1,4-dicarboxy butan-2-one. Haigler *et al*. (1988) also studied the breakdown pathway in *Pseudomonas*, and concluded a similar, though not identical pathway which indicated (chloroacetyl)-acrylic acid, an important intermediate product. These authors indicated that *o*-DCB was mineralised to carbon dioxide and chloride ions. In further studies involving pure *Pseudomonas* cultures as well as isolated mixed cultures, metabolites were revealed to be 3,4- and 4,5-dichlorocatechol (III and IV), and after 100 hours incubation, 2,4-dichlorophenol (IV) and 3,5-dichlorocatechol (V) (Ballschmiter and Scholz, 1980).

Accordingly, this report will concentrate on describing the methodology and results obtained for studies which allowed for bacterial acclimatisation.

Although some results for biodegradation in soils are available, it is unclear whether these were conducted using standard methodology.

Aerobic Degradation

Worne (1972) recorded 100% degradation of *o*-DCB after 72 hours from concentrations up to 200 mg/L using adapted *Pseudomonas* in activated sludge. In these experiments the temperature was 30°C and the oxygen consumption measured manometrically.

Kincannon *et al*. (1983a) found that after exposure of a solution of *o*-DCB (concentration 10 μg/L) to activated sludge which had been adapted for three weeks, the compound could not be detected in the effluent after a contact time of 8 to 12 hours.

In another study, Kincannon and co-workers (1983b), using a simulated continuous activated sludge system (presumably fully adapted), observed almost 100% removal of influent *o*-DCB, and of this 24% was attributed to stripping by air and 75% to biodegradation. Elimination through adsorption to the activated sludge was apparently not significant.

Weber *et al*. (1987) found analogous, though not entirely similar results – again in a simulated activated sludge system. The hydraulic retention time was 5.5 hours, the activated sludge retention time 6 days and the influent *o*-DCB concentration 50 to 150 μg/L. These authors found 94% elimination of the *o*-DCB with 59% attributed to air stripping, 35% to biodegradation and 6% remaining in the plant effluent. Again adsorption onto the sludge biomass was stated as negligible.

According to Goltz *et al*. (1983), a pilot plant scale biological waste water treatment plant removed > 97% of influent *o*-DCB (concentration 38.6 to 405 μg/L) after the biota had been stabilised. Stover and Kincannon (1982, 1983) using a similar continuous pilot plant (operated over a 60 day period), whose biota had been allowed to adjust, reported > 99% removal of *o*-DCB after 8 hours contact time from an influent concentration of 83 mg/L. Approximately 75% of the removal was attributed to biodegradation, with the remainder due to evaporation.

Bouwer *et al*. (1982) ran influent contaminated with *o*-DCB (concentration 9.8 ± 2.4 μg/L) through a column of glass beads onto which a biofilm had been allowed to grow. The biofilm was derived from primary sewage, and allowed to adapt to *o*-DCB for approximately 20 days. The liquid flow rate through the column was such that the empty bed contact time was 60 minutes, and the column was run over a two year period during which the degradation rate of the *o*-DCB was 96 ± 2%.

Piwoni *et al*. (1986) obtained results for the removal of *o*-DCB from contaminated soil. These authors apparently demonstrated that when wastewater contaminated with *o*-DCB at concentration 0.35 ± 0.15 mg/L infiltrates soil over an extended period (28 to 36 weeks), around 79 ± 12% was degraded while 21 ± 12 % was lost through evaporation.

Kuhn *et al*. (1985) used soil percolation columns to simulate conditions under which river water infiltrates ground water, and found at most only 25% degradation. However, the contact times or the degree to which the soil bacteria had become adjusted to the presence of *o*-DCB was not described in the summary from the BUA Report (1990).

A two year field trial reported by Roberts *et al*. (1986) concluded that *o*-DCB undergoes almost complete degradation in sandy ground water aquifers. After approximately 60 days, the concentration of *o*-DCB in ground water had dropped from 332 μg/L to around 33 μg/L.

A second field study by Wilson *et al*. (1987) also found evidence of bacterial adaption to the presence of *o*-DCB in soils, and evidence of steady biodegradation after an initial adaption period of several weeks.

A summary table of the most relevant aqueous aerobic biodegradation data is given in Table 4.

Table 4 - Aqueous aerobic biodegradation data

TEST	RESULT	SOURCE/REFERENCE; NOTES
MITI – OECD 301 C	0% after 28 days	IUCLID
Closed Bottle - OECD 301 D	58% after 20 days	IUCLID – *o*-DCB initially present at 4 mg/L; adapted bacteria.
Die away test	No degradation	Canton *et al*., (1985)
Not Specified	100%	Worne, (1972); Adapted *Pseudomonas* in sewage
Simulated Activate Sludge Plant	> 97%	Goltz *et al*., (1983); Adapted bacteria
Simulated Activated Sludge Plant	100% removal (75% attributed to biodeg.)	Kincannon *et al*., (1983b)
Simulated Activated Sludge Plant	> 99% removal (75% attributed to biodeg.)	Stover and Kincannon, (1982, 1983b); Test run over 60 days.
Simulated Activated Sludge Plant	94% removal (35% attributed to biodeg.)	Weber *et al*., (1987)
Biofilm on glass beads	96 ± 2%.	Bouwer and McCarty, (1985); Test duration 2 years.

Conclusion

Tests reported with respect to aerobic degradation generally appeared to follow non-standard conditions, but the available data strongly indicate that fast biodegradation is only observed when the bacteria have been allowed to acclimatise to the presence of *o*-DCB. Bacteria, including strains of *Pseudomonas*, are capable of aerobic degradation of the compound, and several authors have studied the metabolic pathways for bacterial degradation and mineralisation.

Anaerobic/Anoxic Degradation

In their studies of degradation of *o*-DCB in soil columns, Kuhn *et al*. (1985) found no evidence of biodegradation under anaerobic conditions. Similarly, Bouwer (1985) reported no evidence of anaerobic degradation in a reactor filled with glass beads on which biofilms had been allowed to form.

Kirk *et al*. (1989) found that 66% of *o*-DCB (present initially at 710 μg/L) was eliminated after 32 days incubation with digested sludge under anaerobic conditions. However, this elimination was attributed to a chemical conversion or physical removal process other than sorption, rather than biodegradation, since similar elimination rates were observed in a system in which all biological activity had been suppressed through addition of sodium azide. Similarly, Garrison (1969) recorded 20% removal of *o*-DCB in 7 days using digested sludge from a municipal sewage plant, but the sludge was not analysed for adsorbed chemical.

Conclusion

Although the data are not as extensive as for aerobic degradation, it may be concluded that *o*-DCB is unlikely to be extensively degraded under anaerobic conditions in the environmental water compartment. The persistence over several decades of *o*-DCB in the sediments of the North American Great Lakes supports this conclusion (Oliver and Nicol, 1982).

7.2.5 Bioaccumulation

Only two results are summarised in the IUCLID datasheet, but BUA (1990) and Howard (1989) summarise a great number of investigations on the bioaccumulation of *o*-DCB. Bioconcentration data in aquatic organisms are summarised in Table 5.

Oliver and Niimi (1983) exposed rainbow trout in a flow through system to a concentration of *o*-DCB of 0.047 ± 0.017 μg/L for a period of 119 days, and found a Bioconcentration Factor (BCF) of 270 ± 21 based on whole fish weight. A parallel experiment using concentrations of 0.94 ± 0.16 μg/L run over 105 days gave a BCF of 560 ± 130. The equilibrium between absorption and depuration had been established within 7 to 8 days at both concentrations. Based on the content of fatty tissue in the fish, the BCF values for the lower and higher concentrations were 3200 and 6600 respectively.

Periera *et al*. (1988) conducted a field study of four different organisms in a Louisiana estuary contaminated with *o*-DCB at a concentration of around 9 ng/L, and found BCF values of the same order of magnitude as Oliver and Niimi (1983).

Other studies indicate similar bioconcentrations in fish (BUA, 1990). These BCF values are modest as could be expected (Connell, 1990) for compounds having relatively low values for the n-octanol/water partition coefficient and relatively high water solubility (see Section 4). Additionally, elimination is expected to be rapid based on research from Barrows *et al*., (1978) and Veith *et al*., (1980) where a half-life for elimination from the tissues of bluegill sunfish was less than one day.

Davis *et al*. (1983) found a BCF of 6212 in cyanobacteria and green algae after 40 hours exposure to *o*-DCB in wastewater treatment stabilisation ponds. This enrichment factor was based on the wet weight of the algal biomass. Casserly *et al*. (1983) investigated bioconcentration of *o*-DCB by the green algae *Selenastrum capricornutum* and found an enrichment factor of 19700. Again this factor is based on the wet weight of biomass, and it was unclear whether the *o*-DCB had been assimilated into the algal cells, or was adsorbed onto the surface of the cells.

Oliver (1984) investigated the bioavailability of *o*-DCB incorporated in lake sediments (Lake Ontario, at level of 27 μg/kg) to benthic worms including *Limnodrilis hoffmeisteri* and *Tubifex tubifex*. In this study no uptake of *o*-DCB by these organisms was observed, but when the contaminant loading of the sediment was increased by a factor of 10 in a later experiment (Oliver, 1987) uptake by the worms was detected. However, although uptake was observed, once transferred to an uncontaminated environment, the *o*-DCB was quickly eliminated and could not be detected in the worms after 5 days.

Table 5 - Bioaccumulation of *o*-DCB in aquatic organisms

ORGANISM	BCF (Whole Organism)	BCF (Lipid Content)	Reference
FISH			
Rainbow Trout (*Salmo gairdneri)*	270 ± 21 [*o*-DCB]=0.047 μg/L	3200	Oliver and Niimi, (1983)
Rainbow Trout (*Salmo gairdneri)*	670 ± 99 [*o*-DCB]=0.940 μg/L	6600	Oliver and Niimi, (1983)
Spotted Sea Trout (*Cynoscion nebulosis*)	142	6166	Periera *et al*., (1988)
Blue Cat Fish (*Ictalurus furcatus*)	218	6607	Periera *et al*., (1988)
Atlantic Croaker (*Micropogonias undulatus*)	192	8710	Periera *et al*., (1988)
Blue Crab (*Callinectus sapidas*)	144	28840	Periera *et al*., (1988)
OTHER ORGANISMS			
Cyanobacteria/Green Algae	6212		Davis *et al*., (1983)
Green Algae *Selenastrum capricornutum*	19700		Casserly *et al*., (1983)

Knezovich and Harrison (1988) showed that *o*-DCB sorbed on sediments was bioavailable to midge larvae (*Chironomus decorus*) which inhabit the sediments, when exposed through flow-through conditions. Using C^{14} labelled *o*-DCB in a lake sediment, which was composed of 51% sand, 47% silt, 2% clay, organic matter of 14.5% and pH of 4.4, these workers found bioconcentration factors in the wet larvae corresponding to 0.23, 49 and 29 in sediment, overlying water and interstitial water respectively. When the sediment was modified to lower the organic matter (3.6%), the increase in bioavailability was significant in overlying water, with corresponding BCFs of 1.08, 1,071 and 31 in sediment, overlying water and interstitial water respectively. These results indicate sediment characteristics have a profound effect on the bioavailability of sediment sorbed chemicals in aquatic ecosystems. Specifically, a sediment's organic carbon content is likely to be the main determinant of chemical bioavailability for neutral organic compounds.

Conclusion

The conclusion from these data is that *o*-DCB has some tendency for bioaccumulation, and the BCFs in fatty tissue of aquatic species may be quite high. However, once the exposed organisms are transferred to a clean environment, the chemical is eliminated fairly rapidly.

7.2.6 Summary of environmental fate

o-DCB is expected to predominantly partition to the atmospheric compartment of the environment. Reaction with photochemically produced hydroxyl radicals in the atmosphere will occur, and the estimated half-life in the atmosphere ranges between 24 and 38 days.

Photochemical oxidation in the aquatic compartment (again initiated through reaction with hydroxyl radicals) is also possible, and a half-life of 12.8 days has been estimated in one instance.

The Henry's Law Constants for *o*-DCB suggest it is readily volatile from aqueous solution. Estimates of the aqueous half-life range from <1 to 60 days depending on the flow velocity and level of agitation of the water.

Where *o*-DCB becomes associated with soils or sediment, it can be expected to exhibit moderate mobility. However, monitoring data from North America indicates that adsorption to sediment is a major environmental fate process with significantly higher concentrations found in sediments than surface waters.

Tests reported with respect to biodegradation generally appeared to follow non-standard procedures, and there is a large amount of variation in reported degrees of degradation. However, provided the ambient bacterial populations (in water, soil or sludge) have been exposed to the compound for a sufficiently long period for selective adjustment to occur, aerobic biodegradation appears to be relatively rapid. The compound is not degraded under anaerobic conditions.

The chemical has a low potential for bioaccumulation, and although capable of being assimilated from water into the fatty tissue of fish, the measured bioconcentration factors are typically between 100 and 500. However, depuration is rapid, and once transferred to uncontaminated waters the *o*-DCB is eliminated fairly quickly. Similarly, transfer of *o*-DCB from contaminated sediments to benthic dwelling organisms is possible, but again elimination through depuration appears rapid.

7.3 Predicted environmental concentrations

7.3.1 Local PEC in air

While much of the *o*-DCB used in Australia is expected to be released to the atmosphere (approx. 11% - see Table 3), the use patterns are such that the release will be diffuse, and at low levels. The only large point sources for atmospheric release are likely to be those facilities involved in formulating products containing the chemical.

The concentration in air at 100 m from a point source can be estimated as:

C_{air} = Emission. $Cstd_{air}$

where:

C_{air} = concentration in air at 100 m from a point source (mg/m^3)

Emission = emission rate to air (kg/day)

$Cstd_{air}$ = Standard concentration in air at source strength of 1 kg/day = 2.78 x 10^{-4}mg/m^3.

Assuming as a worst case that all formulation occurs at the one plant, 20 kg can be expected to be released to the atmosphere per day (see Section 7.1.1). This results in a concentration of around 55.2 x 10^{-4} mg/m^3 of *o*-DCB at points 100 m distant from the source. This is equivalent to an air concentration of 5.52 µg/m^3, (approximately 0.9 ppb). Equivalent calculations for releases to air from end users would result in lower concentrations than estimated above, but since no reliable data on end user numbers, locations and work practices are available, the results from such calculations would have little significance.

7.3.2 Local PEC in water

A maximum of 40 kg of *o*-DCB is expected to be released daily to the water compartment, again during formulation activities. This is anticipated to occur on 5 days of each year. Lesser quantities (up to 20 kg/day) will be released during use of products containing the chemical, although this would take place far more frequently. In order to calculate a worst-case PEC for the chemical in the water compartment, it will be assumed that all formulation takes place at one location, and that the effluent from this plant enters a sewer system serving a population of 50,000 persons[2]. If it is further assumed that each person generates 150 L of sewage each day, the local PEC of *o*-DCB in the sewer is estimated as 40 x 10^6 mg/(50000 x 150 L) = 5.5 mg/L. Since formulation has been assumed to occur on only 5 days each year, raw sewage levels of this magnitude would only be expected on those days.

In the sewage treatment plant much of the compound could be expected to be stripped from the sewage during the aeration stages of sewage treatment, and would enter the atmosphere. Some may also be destroyed through aerobic biodegradation, and other portions removed through sorption to sludge. The Simple Treat Model developed by the European Commission (European Commission, 1996) indicates that during sewage treatment, for a compound with Log Pow = 3.4 and Henrys Law Constant 190 Pa.m^3/mol (Log H = 1.9), approximately 40% would be stripped to the atmosphere, around 20% would become associated with the sludge, leaving 40% in the treated sewage effluent. This would indicate that the maximum concentration of *o*-DCB in the treated sewage which originates from releases during product formulation would be 2.2 mg/L. After discharge of treated sewage to the receiving waters it is appropriate to assume a dilution factor of at least 10:1, and so the final PEC in the receiving waters would be unlikely to exceed 0.22 mg/L, and the concentration would probably be significantly lower.

[2] This corresponds to an area such as Warriewood in Sydney where at least one formulation company is located.

It is also appropriate to make some estimates of the levels of *o*-DCB in sewage sludge. According to the Simple Treat Model, around 20% of the material discharged to sewer may become associated with the sludge, and in the present worst-case scenario where 40 kg are released daily, this amounts to a total of 8 kg per day entering the sludge. It is often assumed that on a dry weight basis (dw) each person serviced by a sewage system contributes around 50 grams of sludge per day. So for a system servicing 50,000 people, the daily sludge production would be around 2.5 tonnes (dw). The worst-case level of *o*-DCB in the sludge would then be around 0.3% (i.e. $8 \times 10^3 \times 10^2 / 2.5 \times 10^6$ %) which is a significant loading. However, this estimate is very much a worst-case scenario and based on very localised release. Further, such large releases are expected to occur on only a few days each year, and also much of the assimilated compound could be expected to be re-released to the atmosphere through volatilisation. In any case, prior to being applied to soil as a conditioner, the "contaminated" sludge would be substantially diluted with other material which would lower the overall levels of the compound in the sludge and soil.

7.3.3 Local PEC in soil

It is estimated (see Section 7.1) that around 500 kg of *o*-DCB (5% of all chemical used in the industrial sector) will be released directly to the soil compartment each year, with a maximum daily release of 2.7 kg, primarily as a result of product end use. Release to this compartment is likely to be localised to landfills, but without further information it is not possible to calculate local soil PECs.

The estimate above has not considered the contribution of *o*-DCB from soil amended by sewage sludge. If it is assumed that on average 20 kg are released to the sewer each day as a result of product use (see Section 7.1), and that 20% of this becomes associated with sewer sludge which is subsequently applied to soil, then an additional 4 kg per day enters the soil compartment.

However, the compound is volatile, and also expected to be mobile in soil, and consequently most of the *o*-DCB released to this media is expected to be dispersed into air and water. In respect of this the previously mentioned articles (see Section 7.2.3) by Bouwer *et al*. (1981), Demirjian *et al*.(1987) and Wang and Jones (1994) dealing with the fate of *o*-DCB in soil media are of relevance. It is also relevant that Wang *et al*.(1995) found *o*-DCB levels between 0.18 and 0.55 µg/kg in soils which had been repeatedly treated with sewage sludge over several years.

7.3.4 Measured concentrations – Australian and overseas data

As mentioned previously the use patterns of the chemical within Australia indicate that almost all is likely to be released to the atmosphere. Little monitoring data for environmental concentrations of *o*-DCB in Australia are available, but for reference a summary of overseas monitoring data are also included below. It should be noted that this data was collected from countries such as Germany and the US which either manufacture and/or use large volumes of *o*-DCB in a variety of industrial processes (e.g. in production of dyes, or toluene diisocyanate), and from which concomitant release is expected to be relatively high. Consequently, while these data are of interest, they are likely to be far in excess of levels in the respective environmental compartments in Australia.

Effluent

Within Australia, in 1994/95, 208 effluent samples taken from 10 sewage treatment plants discharging effluent to coastal areas of Sydney and the Illawarra in NSW found measurable levels of *o*-DCB in excess of the detection limit of 5 ppb in five samples and ranged from 11 to 64 μg/L (Sydney Water, 1996).

The BUA Report (1990) has given measured levels of *o*-DCB within sewage treatment plant effluents in the USA and Canada. The highest reading was 9.1 μg/L (Los Angeles in 1977), while in 1980 the measured levels in effluent from four Canadian biological wastewater treatment plants was between 0.006 and 0.022 μg/L.

Surface water

Within Australia, no *o*-DCB was detected in the receiving waters (detection limit 0.5 ppb) when effluent was discharged from 16 sewage treatment plants to the Hawkesbury-Nepean River system in NSW (Sydney Water, 1996).

The BUA report (1990) has given measured levels of *o*-DCB in a number of lake and river environments. Several water measurements in the North American Great Lakes recorded concentrations from below the detection limit to 0.007 μg/L (Oliver and Nicol, 1982).

In Europe the highest documented concentration in river waters was recorded for the Rhine in Germany near Hitorf as up to 15 μg/L in 1976, although the IUCLID data sheet indicates that concentrations as high as 27 μg/L have been measured in polluted areas of Germany. However, more recent measurements over the German and Dutch portions of the river provide much lower levels, rarely exceeding 0.5 μg/L. In North America the highest measured level for *o*-DCB was 0.056 μg/L recorded in 1980 in the Niagra river just below the outfall from a chemical manufacturing company. Typically, measured concentrations in North American rivers are at least an order of magnitude lower than this level, and more recent measurements in the Niagra river indicate a concentration of 0.002 μg/L (Govt. Canada, 1993).

Sediment

Surficial sediment studies near the mouth of the Niagra river in Lake Ontario indicated sediment loadings between 27 and 35 μg/kg, with the origin of this contamination being industrial concerns. As noted previously, the chemical is not susceptible to biodegradation in anoxic environments, and is likely to be persistent in sediments.

Air

The IUCLID data sheet indicates that the median value for *o*-DCB in the air throughout urban areas of the United States was found to be 0.066 μg/m^3. However, levels as high as 0.61 μg/m^3 have been recorded in highly industrialised areas in New Jersey (Bozzilli *et al.*, 1982). Similarly, air in the vicinity of refuse dumps may contain elevated levels of the chemical, and concentrations as high as 658 μg/m^3 have been recorded in gases evolved from a dump in Berlin (Hofler *et al.*, 1986).

Rain samples in 1984 in Portland, Oregon showed a mean concentration of 0.120 μg/m^3 in air and 0.0048 μg/L in rain. As noted in Section 7.2.1, *o*-DCB has been detected in rainwater in Canada, although levels are not provided.

Soil

Wegman *et al.* (1981) reported *o*-DCB levels as high as 325 μg/kg in soils adjacent to a domestic dump in Amsterdam. However, this dump had been used for disposal of the organochlorine pesticide Lindane, and it is likely that the high *o*-DCB levels resulted from breakdown of Lindane in the dump. Other soil monitoring data is summarised in the BUA Report.

Wang *et al.* (1995) found the level of *o*-DCB in archived samples of soil which had been repeatedly treated with sewage sludge between 1942 and 1991 were between 0.18 and 0.55 μg/kg. These levels were marginally higher than those recorded for control samples which had not been treated with sludge (i.e. 0.18 to 0.36 μg/kg). While there was a degree of variation in the results between the samples, neither the amended soil or control samples showed any obvious general increase of *o*-DCB levels with time.

8. Occupational Exposure

8.1 Routes of exposure

The major routes for occupational exposure to *o*-DCB are by inhalation and dermal contact. Exposure to *o*-DCB vapour or liquid can occur during its formulation into products or the end-use of such products.

8.2 Methodology for estimating exposure

Ideally, the assessment of occupational exposure is based on workplace monitoring data. Where such data is inadequate or unavailable, reliance must be placed on knowledge-based mathematical models that can estimate exposure when the various patterns of use and the physical properties of the substance under investigation are known. Due to a lack of monitoring data for *o*-DCB, exposure estimates were made using the UK EASE (Estimation and Assessment of Substance Exposure) model, developed by the UK Health and Safety Executive. The estimates presented are considered to be feasible worst-case scenarios in that they determine exposure at the high-end or maximum concentration of the substance likely to be encountered in the workplace. They do not take into consideration exposures due to accidents, spills or other unusual situations. The information input into the EASE model was derived from industry through survey results.

8.3 Exposure during formulation

Within Australia, *o*-DCB is formulated into a limited number of products for industrial use. These primarily include degreasing/decarbonising agents and paint-stripper/paint removal products. The percentage of *o*-DCB in these products can vary from 2.5 to 70 % (w/v). In 1998, the amount of *o*-DCB undergoing formulation for industrial products amounted to approximately 10 tonnes of material. The activities involved in the formulation of *o*-DCB products are generally limited to blending and packaging operations.

Duration of exposure

From a survey, 6 companies were identified as formulators of industrial products containing *o*-DCB. Due to the limited applications available for products containing *o*-DCB and the small market size, production tends to be intermittent and generally occurs for less than one working week per year. The number of workers involved in blending/packaging processes consequently tends to be small, typically 1 to 2 operators per company. The formulation of products containing *o*-DCB is typically a semi-closed process involving the pumping of *o*-DCB into a blending tank where it is combined with other chemicals at ambient temperature. The filling of product containers is also semi-enclosed and automated, further reducing the extent of exposure. Consequently, it is assumed that dermal exposure is unlikely to contribute significantly to body burden during formulation processes. Respondents to the survey indicated that local exhaust

ventilation is used during formulation. Exposure durations for workers in Australia engaged in the major activities (obtained by survey) are shown in Table 6.

Table 6 - Handling of *o*-DCB in Australia during formulation

Activity	Number of Workers/Company (range)	Hours/day (range)	Days/year (range)
Blending	1 - 2	0.25 - 4	1 - 5
Packaging	1 - 2	1 (maximum)	1 - 5

Levels of exposure

Due to a lack of monitoring data for *o*-DCB exposure in Australia, exposure data were estimated by use of the UK EASE model which gave exposure values of 0.5 to 3 ppm (8 hour TWA) at 20°C and assuming a non-dispersive pattern of use with local exhaust ventilation present. As stated above, dermal exposure is unlikely to contribute significantly. Using the formulae given in Appendix 2, the exposures of 0.5 and 3 ppm are equivalent to body burden values of 0.3 and 2.0 mg/kg bw per day respectively. These estimates do not take into account the pattern of use (i.e. up to 5 days per year); and therefore are gross overestimates of exposures.

8.4 Exposure during end-use

Due to lack of information, it is difficult to determine the level of exposure likely to be encountered during the end-use of *o*-DCB products. However, it is expected that exposure is likely to be intermittent, to take place under open conditions, and small quantities used per event (as evidenced by the size of the containers *o*-DCB products are sold in, typically 5 to 25 L). There is the potential for dermal exposure while handling items involved in the cleaning process.

Levels of exposure

As no monitoring data were available, exposure data were estimated by use of the UK EASE model. Exposure values of 10 to 50 ppm (8 hour TWA) at 25°C were obtained, assuming a non-dispersive pattern of use and no aerosol formation. Using the formulae given in Appendix 2, body burden values, due to inhalation, derived from these data are 6.7 and 33.6 mg/kg bw per day respectively (Appendix 2).

Dermal exposure is likely to be incidental during an 8-hour day. Therefore the body burden value, using the formulae in Appendix 2, is estimated to be 0.47 mg/kg bw per day (Appendix 2). Total body burden (inhalation and dermal) is estimated to range from 7.2 to 34.1 mg/kg per day. Products labelled as corrosive were not considered as it has been assumed that suitable precautions would be taken to prevent dermal contact.

9. Public Exposure

No retail sales for the domestic use of *o*-DCB (or of products containing *o*-DCB) were identified other than for one pharmaceutical product.

It is expected that during transport, storage and industrial use, exposure of the general public to the notified chemical will be minimal, except in the event of an accidental spill. Due to the low volume of material used and the intermittent nature of the use of *o*-DCB and products containing *o*-DCB, public exposure to industrial wastes are likely to be low.

10. Toxicokinetics and Metabolism

10.1 Absorption

The concentration of *o*-DCB in the plasma of rats (strain Wistar) was assessed after the oral administration of radiolabeled *o*-[^{14}C]-DCB (5, 50 or 250 mg/kg bw). At 5 mg/kg bw, the maximal concentration of the parent compound (C_{max}[DCB]) was detected in the blood during the first 2 hours (detection limit 0.05 μmol/l) while the maximal concentration of radioactivity (C_{max}[Ra]) in the blood occurred at 6 hours. At 50 mg/kg bw, C_{max}[DCB]) occurred at 3 hours and C_{max}[Ra] was reached at 8 hours. At the highest dose C_{max}[DCB]) was constant for the first 6 hours prior to decreasing and C_{max}[Ra] occurred after 24 hours. The recovery of total radiolabel from the whole animal was complete for the low and mid dose groups but was incomplete (83%) from the high dose group. The high dose data indicated that absorption was incomplete and that partial excretion of *o*-DCB may have occurred in the faeces. However, the failure to detect significant amounts of *o*-DCB in the faeces was attributed to its volatile nature (Hissink *et al.*, 1996a).

There are no data for the dermal and inhalation absorption of *o*-DCB in animals or absorption of *o*-DCB via any route in humans.

10.2 Distribution

The distribution of radiolabeled *o*-DCB was examined 24 hours after administering a single dose of *o*-[^{14}C]-DCB (300 mg/kg bw) to male rats (strain F344) by gavage. While adipose tissue accounted for a substantial amount of radiolabel after treatment (5575 nmol/g), the liver and kidneys retained 812 and 883 nmol/g respectively. Dialysis, with or without the inclusion of sodium dodecyl sulfate (0.1%), of isolated macromolecules from plasma, liver and kidney indicated that significant covalent binding of *o*-DCB had occurred. Significant covalent binding of *o*-DCB equivalents to the $\alpha_{2\mu}$-globulin fraction from the kidneys was noted (Charbonneau *et al.*, 1989).

Administration of *o*-[^{14}C]-DCB (132 mg/kg bw) by the i.p. route to male rats (strain F344) followed by analysis of the radiolabel content of the liver at 30 min and at 1, 2, 4, 8 and 12 hours revealed that the highest concentration of radiolabel occurred within the first 4 hours with less than 35% of the radiolabel remaining by 12 hours (Stine *et al.*, 1991).

The tissue distribution of *o*-DCB was examined using male Wistar rats which were orally dosed with *o*-[^{14}C]-DCB (10 mg/kg bw). The distribution of radiolabel was examined at 6, 15, 30 and 75 hours. The highest concentrations of radiolabel were found at 6 hours in the kidney, urinary bladder, perirenal fat, liver, small intestine, and skin (including subcutaneous fat). Tissue concentrations had declined substantially by 15 hours with the exception of the colon and caecum (Hissink *et al.*, 1996a).

The amount of *o*-DCB in the blood, liver and kidneys of male rats (strain Wistar) was determined at 1, 2, 4, 6, 12, 24, 48 and 72 hours after intraperitoneal injection (i.p.) of 1.36 mmol/kg of the compound. Maximal amounts were recorded at 1 hour after administration and declined rapidly over the next 12 hours at near exponential rates. The estimated half-life of *o*-DCB was 0.08, 0.04 and 0.02 hours for blood, liver and kidney respectively. The amount of *o*-DCB in adipose tissue peaked at 2 hours post-injection and was present at significantly higher levels than in other tissues (Kato and Kimura, 1997).

There have been no detailed studies of the distribution of *o*-DCB in humans.

10.3 Metabolism

The major site for the biotransformation of dichlorobenzenes is the liver. The metabolism of *o*-DCB by humans, rats, mice and rabbits proceeds predominately by cytochrome P450-mediated aromatic hydroxylation to dichlorophenol derivatives. Studies indicate that cytochrome P450 isoforms give rise to different metabolites of *o*-DCB, some of which exhibit greater bio-reactivity than others.

10.3.1 Studies in animals

The oral administration *o*-DCB to rabbits (0.5 g/kg) resulted in the formation of a major metabolite, 3,4-dichlorophenol (30% of dose), and lesser amounts of 2,3-dichlorophenol (9% of dose), 4,5-dichlorocatechol and 3,4-dichlorocatechol (3.9% of dose). The major urinary metabolites were composed of glucuronide and sulfate conjugates (approximately 70%). In addition, 3,4-dichlorophenylmercapturic acid was present as a minor metabolite (5% of dose) (Azouz *et al*., 1955).

Analysis of hepatic aqueous soluble metabolites after administration of *o*-[^{14}C]-DCB (0.9 mmol/kg bw; 132 mg/kg bw) to rats (strain F344) by the i.p. route indicated that soluble metabolites of *o*-DCB accounted for 83% of the total radiolabel at 8 hours. The presence of aqueous soluble metabolites correlated with the covalent binding of radiolabel to hepatic proteins, which amounted to 213 to 304 pmol radiolabel bound/mg protein over a 12 to 24 hour period. The role of glutathione was determined by estimating total hepatic non-protein sulfhydryl content over a period of 5 hours after i.p. injection of 1.8 mmol/kg (265 mg/kg bw) of *o*-DCB. Treatment with *o*-DCB resulted in a substantial loss in hepatic glutathione content at 1.5 hours, which continued to decline at 5 hours (Stine *et al*., 1991).

The *in vivo* role of P450 cytochromes in the metabolism of *o*-DCB by male rats (strain F344) was investigated by comparing a control group with animals in which specific cytochromes were induced. Phenobarbital was used to induce CYP2A1, CYP2A2 and CYP2B, β-napthoflavone to induce CYP1A1 and pyridine to induce CYP2E1. The administration of *o*-DCB (2 or 3 mmol/kg) by i.p. injection resulted in a significant increase in plasma alanine aminotransferase (ALT) and blood urea nitrogen (BUN) levels associated with increases in CYP2E1 and CYP2B activity, respectively (Valentovic *et al*., 1993).

The *in vivo* metabolism of *o*-DCB by male Wistar rats was investigated by the oral administration of *o*-[^{14}C]-DCB (5, 50, or 250 mg/kg bw). Urinary metabolites (from 1 animal) were identified as 2,3-dichlorophenol, 3,4-dichlorophenol, and their sulfate and

mercapturic acid derivatives, *N*-acetylcysteinyl-2,3-dichlorobenzene and *N*-acetyl-cysteinyl-3,4-dichlorobenzene. No significant differences were observed in metabolic profiles for different doses of *o*-DCB and no hydroquinone or quinone metabolites were detected. Significant amounts of radiolabel were excreted in the bile after administration of *o*-[^{14}C]-DCB (10 mg/kg bw); analysis of the metabolites showed them to be glutathione conjugates of the epoxides derived from *o*-DCB (Hissink *et al.*, 1996a).

Analysis of urine from male rats (strain Wistar) administered *o*-DCB (500 mg/kg bw) by the oral route every second day for ten days showed the presence of 2,3- and 3,4-dichlorophenyl methyl sulfoxides and 2,3- and 3,4-dichlorophenyl methyl sulfones. These metabolites were also present in the blood (Kato and Kimura, 1997).

The metabolism of *o*-DCB by rat hepatic microsomes (from male Wistars) produced 2,3-dichlorophenol and 3,4-dichlorophenol as the major metabolites. The dichlorophenols were further metabolised to their respective dichlorohydroquinone derivatives. Minor conversion products of *o*-DCB were 3,4-dichlorocatechol and 4,5-dichlorocatechol. Subsequent oxidation of the dichlorohydroquinones produced reactive dichloro-benzoquinone species that were capable of protein binding but exhibited low affinity for DNA. The formation of polar dihydrodiols constituted a major metabolic pathway (Den Besten *et al*., 1992).

The comparative metabolism of *o*-[^{14}C]-DCB (1 mM) by rat liver slices (from strains Sprague-Dawley and F344) was examined. After 2 and 6 hours of incubation, F344 tissue metabolised *o*-DCB faster (1.4 and 3.0 nmol/mg protein respectively) than Sprague-Dawley tissue (0.59 and 1.2 nmol/mg protein respectively). Similarly, differences in covalent binding of reactive *o*-DCB metabolites to liver slices were observed between F344 tissue (0.948 nmol bound/mg protein) and Sprague-Dawley tissue (0.221 nmol bound/mg protein) (Fisher *et al*., 1995).

Metabolism of *o*-[^{14}C]DCB by rat hepatic microsomes (from strains F344, Wistar and Sprague-Dawley) was examined by Hissink *et al*. (1996b). The major metabolites produced included 2,3-dichlorophenol, 3,4-dichlorophenol and dihydrodiol and glutathione-epoxide conjugates (Table 7). The rate of conversion of *o*-DCB was similar between Wistar and F344 strains (0.09 and 0.099 nmol/min/mg protein respectively) with Sprague-Dawley microsomes the least active (0.04 nmol/min/mg protein). Covalent binding was investigated and the results expressed as the percentage of total metabolites bound. Microsomes from Wistar and F344 rats produced similar amounts of binding with 16 and 17% respectively while Sprague-Dawley microsomes resulted in 31% binding. The addition of glutathione resulted in increased formation of glutathione-epoxide conjugates, a decrease in dihydrodiol formation and a subsequent decrease in covalent binding. Glutathione conjugation was found to be non-enzymatic for the rat. Inhibition of epoxide hydrolase resulted in a decrease in dihydrodiols and increased covalent binding. Microsomes from F344 rats possessed a lower level of epoxide hydrolase activity compared to the other rat strains. These data indicate that epoxides are important species contributing to covalent binding. A contribution to covalent binding was also made by reactive quinone species produced by Sprague-Dawley microsomes; diminished binding occurred in the presence of ascorbic acid but did not affect covalent binding for other strains of rat microsomes. Rat microsomes produced predominately one glutathione-epoxide conjugate and the amount produced was enhanced by phenobarbital induction

indicating that CYP2B1/2 enzymes are primarily involved in the metabolism of *o*-DCB by this species.

Table 7 - Metabolites formed by hepatic microsomal metabolism of *o*-DCB

Species (strain)	Conversion (nmol/min/mg protein)	Metabolite (% of total conversion)		
		GS-epoxide[1]	dihydrodiol	2,3- + 3,4-DCP
Rat (F344)	0.099	56.3	23.8	21.1
Rat (S-D)	0.038	58.7	69.31	< LOD
Rat (Wistar)	0.090	72.0	49.9	21.9
Human	0.141	8.5	38.9	38.7

[1] determined in the presence of exogenous GSH. LOD, limit of detection; S-D, Sprague-Dawley; GS, glutathione conjugate; DCP, dichlorophenol (After Hissink *et al*., 1996b).

Further studies of the metabolism of *o*-DCB were undertaken using hepatic microsomes derived from male and female rats (strain Wistar) and mice (strain $B6C3F_1$) with or without induction of CYP3A or CYP2E1. The formation of water-soluble metabolites after the addition of *o*-[^{14}C]-DCB (0.1 mM) to microsomal preparations showed substantial species and sex differences. Microsomes from female rats metabolised *o*-DCB faster than their male equivalents. In contrast, microsomes from male mice were more efficient with respect to *o*-DCB metabolism than microsomes from female mice. Microsomal metabolism of *o*-DCB was 7-fold faster by mice compared to rats. Similarly, covalent binding of metabolites was higher in mice of both sexes compared to rats. Induction of CYP2E1 by benzene inhalation resulted in increased metabolism of *o*-DCB in rats but induction of CYP3A by pregnenolone 16α-carbonitrile did not increase metabolism except in female rats where a 6-fold increase was recorded (Nedelcheva *et al*., 1998).

10.3.2 Studies in humans

Incubation of human liver slices (from 10 individuals; 5 male, 5 female; 7 from head injury victims and 3 from resections with metastatic colon cancer) with *o*-DCB (1 or 2 mM) for up to 6 hours resulted in a decrease in protein synthesis and an increase in leakage of the cytosolic enzyme, lactate dehydrogenase (LDH) though only at the higher concentration. The effect was time-dependent with statistically significant results occurring at 6 hours for protein synthesis and at 4 hours for LDH release (Fisher *et al*., 1991).

The metabolism of *o*-DCB by humans has been investigated by Kumagi and Matsunaga (1995). Urine samples were collected at the end of a work shift from 3 male employees exposed to 1 to 4 ppm of *o*-DCB solvent at a chemical plant. Analysis by GC/MS revealed the presence of 2,3-dichlorophenol, 3,4-dichlorophenol, 3,4-dichlorocatechol

and 4,5-dichlorocatechol. Acid hydrolysis of urine samples gave increased amounts of each metabolite indicating all were present, to some extent, as conjugates.

Studies with microsomes prepared from cell lines transfected with cDNA expressing specific human cytochrome P450 isoforms revealed that *o*-DCB is metabolised principally by CYP2E1 to 2,3-dichlorophenol (69.0%) and 3,4-dichlorophenol (31.0%). CYP1A2 possessed 7.7% of the CYP2E1 activity with little contribution to metabolite formation made by CYP1A1, CYP3A4 or CYP2D6 (Bogaards *et al*., 1995).

The metabolism of *o*-[^{14}C]-DCB (1 mM) by human liver slices (from 7 individuals) was examined. After 2 and 6 hours of incubation total metabolites amounted to 2.2 and 4.6 nmol/mg protein respectively. Covalent binding of reactive metabolites at 2 and 6 hours was observed with human liver slices and amounted to 0.394 and 1.14 nmol bound/mg protein respectively (Fisher *et al*., 1995).

The metabolism of *o*-[^{14}C]DCB by human hepatic microsomes (pooled from 5 individuals) was examined by Hissink *et al*. (1996b). Metabolites produced included 2,3-dichlorophenol, 3,4-dichlorophenol and dihydrodiol and glutathione-epoxide conjugates (Table 8.3). The dihydrodiols arise from the action of epoxide hydrolases on the 3,4-epoxide. In contrast to the rat, glutathione conjugation was found to be catalysed by glutathione-*S*-transferases for human microsomes. The rate of conversion of *o*-DCB by human microsomes was 0.14 nmol/min/mg protein, which is substantially faster than the rates derived for microsomes from various rat strains. Covalent binding amounted to 4.6% of total metabolites. The addition of glutathione to the microsomal preparations resulted in increased formation of glutathione-epoxide conjugates and a decrease in dihydrodiol formation. Similarly, inhibition of epoxide hydrolase resulted in a decrease in dihydrodiols and increased covalent binding. The presence of ascorbic acid did not affect covalent binding to human microsomes. Further experiments with human cell lines transfected with cDNA expressing specific P450 cytochromes demonstrated that CYP2E1 produces equal amounts of 2,3- and 3,4-dichlorophenol and comparable amounts of glutathione-epoxide conjugates. Similar results were obtained with human hepatic microsomes indicating that CYP2E1 is the major human cytochrome involved the metabolism of *o*-DCB.

Nedelcheva *et al*. (1998) found, using human microsomes derived from the livers of male brain injury victims and utilising immunoblotting techniques, that the metabolism of *o*-[^{14}C]-DCB correlated well with CYP2E1 levels but not with other cytochromes tested (1A2, 2A6, 2B6, 2C9 or 3A4). The microsomal metabolism of *o*-DCB was inhibited by approximately 90% in the presence of the CYP2E1 inhibitor, diethyldithiocarbamate.

In a brief report, the analysis of urine from eight human volunteers exposed to the vapour of *o*-DCB (30 to 300 mg/m^3, 5.1 to 51 ppm) twice for 4 hour periods with a 45 minute interval to simulate a working day revealed the presence of 2,3-dichlorophenylmercapturic acid and 3,4-dichlorophenylmercapturic acid (Zenser *et al*., 1997).

The major metabolic routes for the metabolism of *o*-DCB by hepatic microsomes derived from humans, rats and mice and the proposed bio-reactive metabolites are shown in Figure 1.

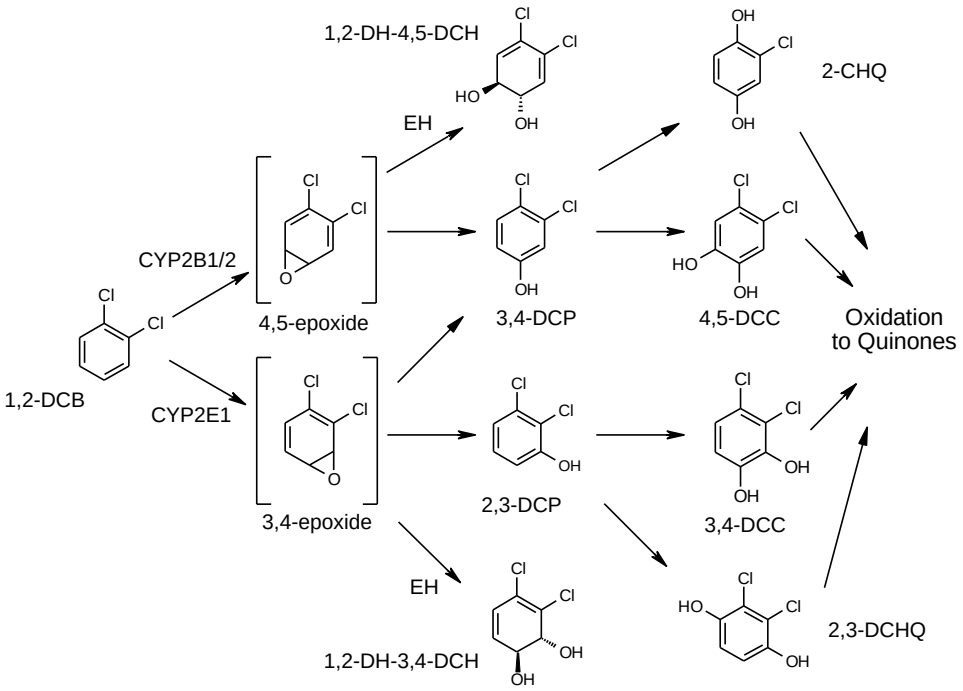


Figure 1 Metabolism of 1,2-dichlorobenzene (*o*-DCB) by human and rat hepatic microsomes. CHQ, chlorohydroquinone; DCB, dichlorobenzene; DCC, dichlorocatechol; 1,2-DH-3,4-DCH, 1,2-dihydroxy-3,4-dichloro-3,5-cyclohexadiene; 1,2-DH-4,5-DCH, 1,2-dihydroxy-4,5-dichloro-3,5-cyclo-hexadiene; DCHQ, dichlorohydroquinone; DCP, dichlorophenol; EH, epoxide hydrolase (After Den Besten *et al*., 1992 and Hissink *et al*., 1996a).

10.3.3 PB-PK modelling

A physiologically based pharmacokinetic (PB-PK) model was developed for *o*-DCB based on the rat and extended for human use. The model was adapted from the inhalation model developed by Ramsey and Andersen (1984) to that of the oral route by assuming first order kinetics for the gastrointestinal uptake of *o*-DCB with direct deposition in the liver, the sole site of metabolism. The model incorporates the Michaelis-Menten parameters (V_{max} and K_m) for the rat with scaling for human use based on microsomal metabolism of *o*-DCB to reactive metabolites and takes account of hepatic glutathione depletion during metabolism of the chemical. The model was used to predict hepatic concentrations of reactive metabolites in the rat *in vivo* after a toxic dose (250 mg/kg bw) using the *in vitro* parameters and the results used to predict the dose required for the same toxic concentration of metabolites in humans. It was found that, due to saturation of the metabolic pathway and partitioning of *o*-DCB into adipose tissue, the concentration could not be reached. The model was also used to predict the time for depletion of GSH from the human liver after a dose of *p*-DCB (250 mg/kg bw), which was estimated to be 10 hours (Hissink *et al*., 1997).

10.4 Elimination and excretion

10.4.1 Studies in animals

In rabbits, the excretion of *o*-DCB metabolites was predominantly in the urine. Administration of *o*-DCB (1.5 g/animal) by gavage resulted in peak levels of metabolites being detected at day 1 which declined to undetectable levels by day 6 after administration (Azouz *et al.*, 1955).

The elimination of *o*-DCB by male rats (strain Wistar) was investigated by the administration of *o*-[^{14}C]-DCB followed by unlabeled *o*-DCB (5, 50, or 250 mg/kg bw) by gavage. Excretion was essentially complete within 24 hours at the lower doses and by 48 hours for the high dose. Elimination was predominantly in urine (75 to 85%) and faeces (19% low dose and 7% high dose). Examination of biliary excretion after a dose of *o*-[^{14}C]-DCB (10 mg/kg bw) revealed the concentration of radiolabel reached a peak in the bile at 6 hours and accounted for 60% of the dose with 25% excreted by the urine and less than 4% in faeces. Less than 1% of the radioactivity was eliminated by exhalation (Hissink *et al.*, 1996a).

10.4.2 Studies in humans

Humans exposed to *o*-DCB (1 to 4 ppm) excreted several metabolites in the urine predominantly as the 2,3-dichlorophenol, 3,4-dichlorophenol, 3,4-dichlorocatechol and 4,5-dichlorocatechol metabolites and as their conjugated derivatives (Kumagi and Matsunaga, 1995).

Eight human volunteers were exposed to *o*-DCB vapour (30 to 300 mg/m^3, 5.1 to 51 ppm) for two 4-hour periods with a 45-minute interval to simulate a working day. Urine was collected for the following 36 hours and analysed for the presence of isomers of dichlorophenylmercapturic acids. A linear relationship was found between *o*-DCB exposure and the excretion of the dichlorophenylmercapturic acids. The excretion kinetics were found to be first order with a half-life for 2,3-dichlorophenylmercapturic acid of 5.3 ± 3.0 hours and a half-life for 3,4-dichlorophenylmercapturic acid of 5.9 ± 1.7 hours (Zenser *et al.*, 1997).

11. Effects on Laboratory Mammals and Other Test Systems

Toxicological studies were identified after extensive literature searches and have been evaluated and are summarised in this section. Use was also made of international reports for *o*-DCB (EPA, 1985; BUA, 1990 and EHC, 1991). In some cases studies cited in such reports, but not accessible for evaluation for this assessment, were utilised and have been acknowledged as such in the appropriate place. As technical grade *o*-DCB can contain from 15% to 30% *p*-DCB as an impurity (see Section 6.1.1), the reader is referred to the report, *para*-Dichlorobenzene, *Priority Existing Chemical No. 13 – Full Public Report* for information relation to the health effects of this impurity.

11.1 Acute toxicity

11.1.1 Lethality

Lethality studies have demonstrated that *o*-DCB presents a low level of toxicity by the oral and inhalation routes. Where available, the LD_{50} and LC_{50} values obtained from several studies are presented in Table 8. No lethality studies were identified addressing dermal exposure to *o*-DCB.

Table 8 - Summary of *o*-DCB acute lethality studies

Route	Species	Result	Reference
Oral	Guinea pig	$LD_{100} \leq 2000$ mg/kg bw	Hollingsworth *et al*., 1958
	Rat	$LD_{50} = 2138$ mg/kg bw	Dura *et a*l., 1985
	Rat	$LD_{50} = 1516$ mg/kg bw	Murakami & Fukami, 1986
Inhalation	Guinea pig	$LC_{100} \leq 1000$ ppm (6.01 mg/L); 20 hrs[1]	Browning, 1937 (cited in Hollingsworth *et al*., 1958)
	Rat	$LC_{100} \leq 977$ ppm (5.9 mg/L); 10 hrs[1]	Hollingsworth *et al*., 1958
Intraperitoneal	Mouse	$LD_{50} = 1228$ mg/kg bw	Mohtashamipur *et al.*, 1987
	Rat	$LD_{50} = 840$ mg/kg bw	RTECS, 1989
	Rat	$LD_{50} =$ 1.66 to 1.76 ml/kg	Kulkarni *et al*., 1996

[1] Exposure time.

Other values are reported by Hollingsworth *et al*. (1958) for the rat. For example, a 4 hour inhalation exposure to *o*-DCB (941 ppm; 5.7 mg/L) resulted in mortality for 1 in 20 animals.

11.1.2 Systemic effects

Rats, mice and guinea pigs exposed to the vapour of *o*-DCB (50 to 800 ppm) for periods of 0.5 to 50 hours exhibited changes in hepatic morphology, characterised by cloudy swelling of cells to focal necrosis and slight fatty changes. Maximal changes typically occurred between 24 to 48 hours after exposure. Leukocytic infiltrates were associated with necrotic areas (Cameron *et al.*, 1937).

Male rats (strain not specified) exposed to *o*-DCB vapour (0, 539, 821, 941 or 977 ppm for 1 to 10 hours) exhibited drowsiness, unsteadiness, eye irritation, difficulty breathing and anaesthesia. Exposure of animals to 821 ppm and above for 7 hours or longer resulted in the death of some animals. Increases in the average weights of livers and kidneys were found and histopathology revealed marked centrilobular necrosis of the livers and cloudy swelling of the kidney tubular epithelium at 539 ppm after 3 hours exposure to *o*-DCB vapour (Hollingsworth *et al.*, 1958).

Charbonneau *et al*. (1989) investigated kidney protein droplet formation 24 hours after a single oral dose of *o*-DCB (3.4 mmol/kg bw; 500 mg/kg bw) to male and female rats (strain F344). The results showed that *o*-DCB treated animals did not develop protein droplets under the conditions employed.

The hepatotoxicity of *o*-DCB (0 to 1784 mg/kg bw) for male rats (strain F344) was evaluated 24 hours after a single oral dose (one animal/dose) by determining serum ALT and aspartate aminotransferase (AST) activities and histopathology. The relative liver weights increased for all doses. Serum ALT and AST levels were elevated at doses of 172 mg/kg bw or greater. Examination of the livers revealed centrilobular hepatic necrosis developing at 172 mg/kg bw and centrilobular vacuolar degeneration at a dose of 98 mg/kg bw or greater. Hepatic cytochrome P450 levels decreased by ≥ 20% in response to 75 mg/kg bw or greater compared to control animals (Allis *et al*., 1992).

In a study by Stine *et al*. (1991), the acute hepatotoxicity of *o*-DCB was assessed for male rats (strains F344) by i.p. administration of *o*-DCB (0, 132, 265, 397, 529, 662 or 794 mg/kg bw). Serum levels of ALT were assessed 24 hours after injection as a determinant of hepatotoxicity. A highly significant increase in ALT levels was observed for *o*-DCB doses of 265 mg/kg bw or greater. The biochemical results were supported by histological examination of the livers that revealed severe centrilobular hepatic damage. Hepatotoxicity was associated with hepatic cytochrome P450 activity as prior treatment of animals with phenobarbital, a P450 inducer, increased the hepatotoxicity of *o*-DCB, as determined 24 hours later, (control animals, 140 units/ml of ALT; phenobarbital-treated animals, 11,500 units/ml of ALT). Conversely, the hepatotoxic effect of *o*-DCB could be prevented by prior treatment with 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF-525A), a P450 inhibitor. The role of hepatic glutathione in modulating *o*-DCB-mediated hepatotoxicity was determined by estimating total hepatic non-protein sulfhydryl content over a period of 5 hours after i.p. injection of *o*-DCB (265 mg/kg bw). Treatment with *o*-DCB resulted in a substantial loss in hepatic glutathione

content at 1.5 hours, which continued to decline at 5 hours. Depletion of hepatic glutathione by pre-treatment of the animals with phorone resulted in a significant increase in plasma ALT levels 24 hours after the administration of *o*-DCB demonstrating a role for glutathione in mediating the hepatotoxicity of *o*-DCB. In addition, the hepatotoxicity of *o*-DCB was compared in F344 and S-D rats at 24 hours (1.8 and 5.4 mmol/kg bw; 265 and 794mg/kg bw). There was a highly significant differential hepatotoxicity between the F344 and S-D strains to *o*-DCB, with the F344 strain more sensitive as judged by a large increase in plasma ALT levels at 24 hours compared with no increase in S-D rats.

Serum ALT levels, determined at 24, 48 and 72 hours, were significantly elevated after a single i.p. injection of *o*-DCB at 1, 2 or 4 mmol/kg (147, 294 or 588 mg/kg bw) to male Wistar rats. Examination of the livers and kidneys at 72 hours for histopathological changes showed significant increased liver weight and hepatic centrilobular hypertrophy at all dose levels and was accompanied by hepatocellular degeneration and fibrosis; there were no pathological changes to the kidneys. Determination of hepatic tissue glutathione content 8 hours after a single i.p. injection of 4 mmol/kg bw of *o*-DCB showed a significant decrease in glutathione content (Den Besten *et al*., 1991).

The contribution of P450 activity to the acute hepatic and renal toxicity of *o*-DCB was assessed by Valentovic *et al*. (1993). Male rats (strain F344) were pre-treated with phenobarbital (to induce CYP2A1, CYP2A2 and CYP2B), β-napthoflavone (to induce CYP1A1) or pyridine (to induce CYP2E1). Twenty-four hours after cytochrome induction the rats were given a single i.p. injection of *o*-DCB (2 or 3 mmol/kg bw; 294 or 441 mg/kg bw respectively) and the animals underwent necropsy 24 h later. Hepatotoxicity was evident in the non-induced rats treated with *o*-DCB at 2 or 3 mmol/kg bw as determined by a dose-dependent increase in plasma alanine amino-transaminase (ALT/GPT) activity. Treatment with phenobarbital or β-napthoflavone resulted in a small increase in ALT/GPT levels and a very much greater increase was observed with pyridine for both dose levels. Liver weights increased in all three treatment groups for both dose levels although the β-napthoflavone group at 2 mmol/kg did not reach significance. The biochemical changes were reflected by changes in the histopathology of the liver with centrilobular damage occurring at 2 mmol/kg and greater damage occurring at 3 mmol/kg. With respect to renal effects, treatment at 2 mmol/kg resulted in no change to urinary output or kidney weight although organic anion and cation uptake by renal slices (determined by *p*-aminohippurate and tetraethylammonium uptake respectively) were decreased. At 3 mmol/kg, urinary output increased approximately 3-fold while *p*-aminohippurate uptake decreased. Kidney weight and tetraethylammonium uptake were not significantly different from controls at the higher dose. Prior treatment with phenobarbital and pyridine, but not β-napthoflavone, resulted in renal toxicity as determined by an increase in BUN. Kidney weights increased after treatment with *o*-DCB for each of the three inducing agents.

Hepatic injury in male rats (strains F344 and Sprague-Dawley) was assessed by determining serum levels of ALT and sorbitol dehydrogenase (SDH) and histopathology after a single i.p. administration of *o*-DCB (0, 0.2, 0.6 or 1.2 ml/kg bw). Comparison was made between hepatic injury and hepatic tissue repair responses (as determined by [^{3}H]-thymidine incorporation). Greater hepatotoxicity was seen in F344 rats compared to Sprague-Dawley rats as judged by elevated serum ALT and SDH activity. Incorporation

of [^{3}H]-thymidine was significantly greater in F344 rats compared to the Sprague-Dawley strain (Kulkarni *et al*., 1996).

The presence of hepatotoxicity in male mice due to a single oral administration of *o*-DCB was demonstrated by Umemura *et al*. (1996), as determined by an increase in serum ALT levels at 200 mg/kg bw *o*-DCB. At 300 mg/kg bw an increase in the hepatic labelling index, a measure of cell proliferation (assessed by incorporation of 5-bromo-2'-deoxyuridine (BrdU)), was observed and histopathological findings showed areas of centrilobular hepatocyte swelling and necrosis. In further experiments, in response to a single dose of *o*-DCB, serum ALT levels were maximal at day 1 and decreased thereafter to basal levels at day 4 while the labelling index which was absent at day 1 was maximal at day 3 and declined to basal levels at day 7. Histopathology revealed hepatic injury at day 1 that was maximal at day 2 and which subsequently declined to undetectable levels at day 7. The authors concluded that *o*-DCB induced hepatocellular proliferation only in response to hepatic injury.

Gunawardhana *et al.* (1995) demonstrated that resident Kupffer cells may play a role in promoting *o*-DCB-mediated hepatotoxicity. Administration of *o*-DCB (3.6 mmol/kg bw; 529 mg/kg bw) to male rats (strain F344) by i.p. injection was followed by examination 24 hours later for evidence of hepatic injury as assessed by serum ALT activity and liver histopathology. Plasma ALT levels were significantly elevated over control values in animals receiving *o*-DCB alone while pre-treatment with methyl palmitate (an inhibitor of Kupffer cell activity) before administration of *o*-DCB resulted in an 80% decrease in plasma ALT activity. A significant decrease of 70% in serum ALT activity was also noted in animals pre-treated with the superoxide scavenger, superoxide dismutase (as the polyethylene glycol conjugate), prior to *o*-DCB administration. The protective effect of methyl palmitate and superoxide dismutase was confirmed by histopathology. However, neither methyl palmitate nor superoxide dismutase conferred protection if the animals were pre-treated with the P450 inducer, phenobarbital.

Further studies examining the role of Kupffer cells and oxidative stress in the modulation of *o*-DCB-mediated hepatotoxicity were conducted by Hoglen *et al.* (1998). Rats (strain F344) were administered *o*-DCB (3.6 mmol/kg bw; 529 mg/kg bw) by i.p. injection and examined at 3, 12, 16, 24 and 48 hours later for evidence of lipid peroxidation products, serum ALT activity and changes in liver histopathology. Liver and serum levels of lipid peroxidation products increased in a time-dependent manner and were detected at 3 hours in the liver and at 12 hours in serum. Similarly, serum ALT activity increased in a time-dependent manner. The maximal response for lipid peroxidation and ALT activity was detected at 24 hours and was absent in the liver or diminished in the serum by 48 hours. Immunohistochemical staining for lipid peroxidation-protein adducts in the liver revealed extensive staining of centrilobular regions at 24 hours but not of periportal regions. Pre-treatment of rats with gadolinium chloride, an inhibitor of Kupffer cell activity, prior to the administration of *o*-DCB protected the animals from hepatotoxicity. *o*-DCB-induced serum ALT activity was reduced by 89% and histopathological examination of the livers showed an absence of necrosis. Prior treatment of rats with desferioxamine, a chelator of ferric ions, before challenge with *o*-DCB resulted in a 48% reduction in serum ALT activity suggesting a role for the iron-mediated Haber-Weiss reaction. A comparison of Kupffer cells isolated from *o*-DCB-treated and untreated rats at 24 hours showed a 3-fold increase in basal superoxide production from Kupffer cells of treated animals. Similarly,

stimulation of Kupffer cells from *o*-DCB-treated animals with phorbol myristate acetate resulted in 72% more superoxide compared to Kupffer cells from untreated controls.

Male mice (strain Swiss) administered *o*-DCB (0, 300, 500 or 600 mg/kg bw) by gavage were examined for hepato- and renal toxicity after 6, 16, 24, 48 and 72 hours. There was no evidence of renal toxicity, determined by alkaline phosphatase staining of histological sections, at any dose. Hepatotoxicity, determined by glucose-6-phosphatase activity in liver sections, was maximal at 48 hours for each dose (Ban *et al*., 1998).

11.2 Irritation and corrosivity

The effect of direct contact of *o*-DCB with the eye was examined by instilling two drops of the undiluted liquid into the eyes of two rabbits. One eye was flushed with water thirty seconds after applying the *o*-DCB. The presence of *o*-DCB resulted in some observed pain and the development of conjunctival irritation that was resolved within one week. Immediate washing of the eye with water appeared to reduce to amount of observed pain and the degree of conjunctival irritation (Hollingsworth *et al*., 1958).

De Ceaurriz *et al*. (1981) reported that *o*-DCB at 182 ppm (1110 mg/m^3) reduced the respiratory rate of mice (strain Swiss OF_1) by 50% (RD_{50}) and was considered indicative of upper respiratory tract irritation due to a reflex drop in respiratory frequency.

In a poorly described study, the RD_{50}, based on breathing frequency, for *o*-DCB using male mice (strain Swiss OF_1) exposed to at least four different vapour concentrations (concentrations not stated) was determined to be 163 ppm (980 mg/m^3) (Zissu, 1995).

o-DCB has not been reported as being corrosive.

11.3 Sensitisation

No studies were located which address the issue of sensitisation due to *o*-DCB.

11.4 Immunotoxicity

There have been few studies of the immunological effects of *o*-DCB. Human lymphocytes exposed for 4 hours to *o*-DCB (100 µM to 10 mM) remained viable as judged by the trypan blue dye exclusion assay indicating that *o*-DCB is not toxic to lymphocytes under the test conditions (Perocco *et al*., 1983).

Rats were exposed to *o*-DCB vapour (0, 5, 10, 16 or 29 ppm) for 4 hours and haematological parameters examined. While the red blood cell and the leukocyte differential counts remained unchanged, a statistical significant ($p < 0.05$) leucopenia was observed at 10 ppm and above. The leukopenia could be prevented by adrenalectomy indicating the involvement of a stress response (Brondeau *et al*., 1990).

Changes in plasma levels of total thyroxine (T4) and total triiodothyronine (T3) at 24 hours after treatment of male rats (strain Wistar) with *o*-DCB (1 or 2 mmol/kg bw; 147 or 294 mg/kg bw) after a single intraperitoneal injection were examined. *o*-DCB produced a significant reduction ($p<0.05$) in T4 and in T3 levels at all doses (Den Besten *et al*., 1991).

Mice administered *o*-DCB (0, 300, 500 or 600 mg/kg bw) by gavage were examined for increases in serum tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels and serum effects on antibody-forming cell (AFC) and natural killer cell (NK) activity after 6, 16, 24, 48 and 72 hours. While no alteration in serum IL-6 levels was observed at any dose, TNF-α levels increased at 6 hours in response to treatment at 500 and 600 mg/kg bw but was undetectable at other time points. A persistent serum-borne immunosuppressive effect was detected at 300 mg/kg bw which depressed AFC and NK cell activity by a maximum of 77% and 29% compared to control levels at respectively (Ban *et al*., 1998).

11.5 Repeated dose toxicity

11.5.1 Oral administration

The results of repeated dose studies (NOAELs, LOAELs and associated effects) are summarised in Table 9.

Charbonneau *et al*. (1989) studied renal protein droplet formation and cell proliferation in a short-term repeat dose study. Treatment of male rats (strain F344) by gavage daily for 7 days with *o*-DCB (0.8 or 2.0 mmol/kg bw; 118 and 294 mg/kg bw) did not lead to an increase in protein droplet formation. Similarly, when treated for 6 days in a similar manner there was no evidence of increased cell proliferation (assessed by incorporation of [^{3}H]-thymidine) compared to controls.

To examine the oral toxicity of *o*-DCB, male and female rats (strain Sprague-Dawley) were administered 0, 37.5, 75, 150 or 300 mg/kg bw per day for 10 days. At 300 mg/kg bw/day a decrease in male total body weight gain and absolute organ weight (heart, kidneys, spleen, testes and thymus) were observed. A significant increase ($p \leq 0.05$) in absolute and relative liver weights and the development of hepatocellular necrosis was evident. Plasma ALT levels were significantly elevated after treatment with 300 mg/kg bw for both sexes while for females, cholesterol levels were elevated at all doses compared with controls. Leukocytosis was present in males at 150 and 300 mg/kg bw while the absolute and relative weights of female livers increased at these doses. Spleen weights decreased only at 300 mg/kg bw. Histopathological findings were the presence of hepatocellular lesions (40% of males treated with 300 mg/kg bw) which were judged by the authors to be slight in severity (Robinson *et al*., 1991).

In a 14-day study of rats (strain F344), *o*-DCB was administered orally at 0, 60, 125, 250, 500 or 1000 mg/kg bw. The highest dose resulted in 100% mortality by day 5 while 500 mg/kg bw resulted in reduced body weight gain (-12%) (NTP, 1985).

In a 14-day study of mice (strain B6C3F$_1$), *o*-DCB was administered orally at 0, 250, 500, 1,000, 2,000 or 4,000 mg/kg bw. Only one mouse (250 mg/kg bw) survived the treatment and one control animal died. Hepatic necrosis was observed in 3/3 males dosed at 500 mg/kg bw and 1/3 females at 250 mg/kg bw when examined for histological lesions. Hepatocellular degeneration was observed in 1/3 males at 250 mg/kg bw (NTP, 1985).

In a second 14-day study of mice (strain B6C3F$_1$), *o*-DCB was administered orally at 0, 30, 60, 125, 250 or 500 mg/kg bw. Two mice died during the course of the study, one male in the 500 mg/kg bw group and one female in the 125 mg/kg group. There were no

changes in body weight. Hepatocellular necrosis (described as mild) was observed in 2/4 males at 500 mg/kg bw while moderate focal hepatic necrosis was observed in 1/4 females at 500 mg/kg bw, mild multifocal hepatitis in 1/4, mild cytomegaly and karyomegaly in 2/4 and hepatocellular degeneration in 1/4 (NTP, 1985).

The toxicity of *o*-DCB was examined during a 13-week study of male and female rats (F344) and mice (strain $B6C3F_1$) administered *o*-DCB (0, 30, 60, 125, 250 or 500 mg/kg bw) 5 days/week by gavage. A decreased survival time for both sexes of mice and female rats at 500 mg/kg bw was observed with pathological findings of hepatic centrilobular necrosis and hepatocellular degeneration, depletion of lymphocytes in the thymus and spleen of both species. High-dose male rats showed renal tubular degeneration while mice exhibited multifocal mineralisation of myocardial fibres and skeletal muscle. A dose of 250 mg/kg bw induced necrosis of individual hepatocytes in both sexes of rats and male mice. Mice were unaffected by 125 mg/kg bw while rats displayed minimal hepatocellular necrosis. Haematological changes were observed at 500 mg/kg bw in rats, which included a slight decrease in haematocrit and haemoglobin, and in the erythrocyte count for male rats (NTP, 1985).

In a two-year study, rats (strain F344) were administered *o*-DCB (0, 60 or 120 mg/kg bw) for 5 days/week. At the highest dose, males exhibited a significant decrease ($p < 0.001$) in survival, however, three of these deaths were accidental and several others were attributed to handling/gavage errors. High-dose males also exhibited a slightly reduced body weight gain while females experienced an increase in weight gain at the same dose level. Histological examination revealed no non-neoplastic lesions. Treatment of mice ($B6C3F_1$) under the same conditions produced no change in body weight compared to control animals and survival rates were similar. A dose-dependent increase in renal tubular regeneration was observed in males (NTP, 1985). The analysis of neoplastic lesions resulting from these studies are summarised in Section 11.9.

The oral toxicity of *o*-DCB for male and female rats (strain Sprague-Dawley) was assessed by administering 0, 25, 100 or 400 mg/kg bw per day for 90 days by gavage. At 400 mg/kg bw per day a significant decrease ($p \leq 0.05$) in total body weight gain was observed for males but not females. Significant increases ($p \leq 0.05$) in absolute and relative liver weights occurred for both sexes at 100 and 400 mg/kg bw and absolute and relative kidney weights were increased at 400 mg/kg bw for both sexes and absolute kidney weights increased for females at 100 mg/kg bw. Plasma ALT levels were elevated at 100 and 400 mg/kg bw in the male but the female levels did not reach significance. In both sexes, an increase in bilirubin occurred at the highest dose. There was no evidence of leukocytosis or other haematological changes for either sex. Histopathological findings included centrilobular degeneration, centrilobular hypertrophy and evidence of apoptosis at 400 mg/kg bw for both genders (Robinson *et al.*, 1991).

Hollingsworth *et al*. (1958) investigated the effect of *o*-DCB (0, 18.8, 188 and 376 mg/kg bw) on female rats (strain not specified) administered by gavage five days/week over 192 days (a total of 138 doses). No treatment-related effects were observed with respect to growth or mortality. At 188 and 376 mg/kg bw significant increases in average liver and kidney weights were observed. No changes in haematological parameters were found. Exposure to 18.8 mg/kg bw produced no adverse effects.

11.5.2 Inhalation

Male mice (strain Swiss OF_1) were exposed to *o*-DCB vapour at 64 and 163 ppm (385 and 980 mg/m^3 respectively) for 4, 9 and 14 days (6 hours/day 5 days/week) and their respiratory tracts examined. Lesions to the olfactory epithelium were observed at 64 ppm after 4 days and were classified as very severe. On increasing the exposure time the severity of the lesions diminished so that on day 9 epithelial damage was classified as severe and on day 14 as moderate. The author concluded that epithelial regeneration may occur in order to replace the damaged epithelium. The respiratory epithelium remained unaffected, as did the trachea and lungs (Zissu, 1995).

In a study of the effects of *o*-DCB (49 ppm; 295 mg/m^3), rats and guinea pigs (strains not specified) were exposed for 7 hours/day, 5 days/week for 6.5 months. No adverse effects were observed based on gross appearance, behaviour, growth, mortality, organ-weight studies and gross and histopathological examination of unspecified tissues. Further studies were conducted at (93 ppm; 577 mg/m^3) for 7 hours/day, 5 days/week for 6 to 7 months with rats, guinea pigs, rabbits and monkeys (strains not specified). Under these conditions, the final average body weight of male rats was significantly lower ($p \leq 0.05$) compared to control males. No significant difference was observed in the final body weights of female rats or both sexes of guinea pigs. The average organ weights (lung, heart, liver, kidneys, spleen and testes) of rats and guinea pigs did not differ with treatment with the exception of the spleens of male guinea pigs which were significantly lower ($p \leq 0.01$) than control animals. However, histopathological examination revealed no splenic abnormalities. No other adverse effects, as determined by gross appearance, behaviour, growth, mortality, organ-weight studies, haematology or urinalysis, were observed in the species tested. Gross and histopathological examination of unspecified tissues proved negative (Hollingsworth *et al.*, 1958). The value of this study is limited due to inadequate reporting of the experimental conditions and results obtained.

Table 9 - Summary of NOAEL and LOAEL values for *o*-DCB in Repeated Dose Studies (non-carcinogenic)

Species (strain)	Sex	Study type and duration	NOAEL (mg/kg bw per day)	LOAEL and associated pathologies	Reference
Rat (SD)	Male	Oral 10 days	75	150 mg/kg bw; leukocytosis and decreased haematocrit[a].	Robinson *et al.*, 1991
	Female			150 mg/kg bw; increased absolute and relative liver weight[a].	
Rat (SD)	Male	Oral 90 days	25	100 mg/kg bw; increased absolute and relative liver weight[a]. Increased absolute kidney weights for females[a]. Increased plasma ALT levels in males[a].	
	Female				
Rat (F344)	Male	Oral 13 week	60	125 mg/kg bw; hepatocellular necrosis.	NTP, 1985
	Female				
Mice ($B6C3F_1$)	Male	Oral 13 week	125	250 mg/kg bw; multifocal mineralisation of myocardial fibres and skeletal muscle.	
	Female		NI	30 mg/kg bw; decreased spleen weight to body weight ratio.	
Rat (strain not specified)	Female	Oral 192 days	18.8	188 mg/kg bw; increase in average liver[c] and kidney weights[d].	Hollingsworth *et al.*, 1958
Rat (F344)	Male	Oral 2 years	120	No treatment-related pathologies observed.	NTP, 1985
	Female				
Mice ($B6C3F_1$)	Male	Oral 2 years	60	120 mg/kg bw; increased renal tubular regeneration.	
	Female		120	No treatment-related pathologies observed.	
Rat (strain not specified)	Male	Inhalation 26 weeks	49 ppm	93 ppm; decreased male body weight[a].	Hollingsworth *et al.*, 1958
	Female		93 ppm	No treatment-related pathologies observed.	
Guinea pig	Male	Inhalation 26 weeks	49 ppm	93 ppm; decreased male spleen weight[b].	Hollingsworth *et al.*, 1958
	Female		93 ppm	No treatment-related pathologies observed.	

[a], $p \leq 0.05$; [b], $p \leq 0.01$; [c], $p = 0.003$; [d], $p = 0.002$; NI = not identified (i.e. effects seen at the lowest dose).

11.6 Reproductive toxicity

No studies of the effects of *o*-DCB on reproductive toxicity were located during the course of this assessment.

11.7 Developmental toxicity

The developmental effects of *o*-DCB for rabbits and rats has been investigated. Inseminated rabbits were exposed to *o*-DCB (0, 100, 200 or 400 ppm) for 6 hr/day on days 6 to 18 of gestation. Maternal toxicity was observed, described as slight, and based on a decrease in body weight gain during the first three days of exposure at all dose levels. At doses up to 400 ppm (2404 mg/m^3) *o*-DCB did not prove to be embryotoxic, fetotoxic or teratogenic in the rabbit based on observations of the number of pregnancies, litter size, resorption rate, foetal body measurements or foetal malformations. Rats treated with *o*-DCB (0, 100, 200 or 400 ppm) for 6 hr/d on days 6 to 15 of gestation showed maternal toxicity at all dose levels as judged by a significant decrease in body weight gain from gestation days 6 through to 20. A significant increase in maternal liver weights occurred with rats exposed to 400 ppm. The only developmental treatment-related effect was a significant increase in the occurrence of delayed ossification of cervical vertebral centra in the highest dose group. However, these effects occurred at maternally toxic doses (Hayes, 1985). For the rabbit and rat, a NOAEL of 400 ppm was determined for developmental effects.

11.8 Genotoxicity

11.8.1 *In vitro* testing

Genotoxicity testing with several microbial test organisms (including several strains of *Salmonella typhimurium*) have generally yielded negative results, with or without metabolic activation. The results of microbial *in vitro* tests with *o*-DCB are summarised in Table 10.

Similarly, genotoxicity testing of *o*-DCB with *in vitro* mammalian systems have produced predominantly negative results, which are summarised in Table 11. However, *o*-DCB did induce sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells and an increase in the mutation frequency in mouse lymphoma cells, both in the presence of metabolic activation. *o*-DCB caused unscheduled DNA synthesis in human lymphocytes without metabolic activation at cytotoxic doses.

Table 10 - Genotoxicity of *o*-DCB *in vitro*: Microbial systems

Genus and species (strains)	Test	Result		Reference
		With activation	Without activation	
S. typhimurium (8 strains, not specified)	Gene mutation	ND	-	Andersen *et al*., 1972
S. typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA1538)	Gene mutation	-	-	Litton Bionetics, 1976 (cited in BUA, 1990)
S. typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538)	Gene mutation	-	-	Lawlor *et al*., 1979
S. typhimurium (TA 100)	Gene mutation	-	-	Rohm & Hass Co, 1979 (cited in IUCLID)
S. typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538)	Gene mutation	-	-	Waters *et al*., 1982
S. typhimurium (TA 98, TA 100, TA 1535, TA 1537)	Gene mutation	-	-	Haworth *et al*., 1983 (cited in IUCLID)
S. typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538)	Gene mutation	-	-	Shimizu *et al*., 1983
S. typhimurium (TA 98, TA 100, UTH 8414, UTH 8413)	Gene mutation	-	-	Connor *et al*., 1985
S. typhimurium (TA 97, TA 98, TA 100, TA 102, TA 1535, TA 1537, TA 1538)	Gene mutation	-	-	Koch *et al*., 1985 (cited in IUCLID)
S. typhimurium (TA 98, TA 100, TA 2637)	Gene mutation	-	-	Nohmi *et al*., 1985 (cited in BUA)
S. typhimurium (TA 98, TA 100, TA 1535, TA 1537)	Gene mutation	- -	- -	NTP, 1985 & Tennant *et al*., 1986
S. typhimurium (TA 1535/pSK1002)	DNA damage	-	-	Nakamura *et al*., 1987
S. typhimurium (TA 1535/pSK1002)	DNA damage	-	-	Ono *et al*., 1992 (cited in IUCLID)
Bacillus subtilis	Recombination assay	-	+	Matsui *et al*., 1989 (cited in IUCLID)
Bacillus subtilis	Recombination assay	ND	-	Waters *et al*., 1982
Escherichia coli	DNA damage & repair	-	-	DeMarini and Brooks, 1992
Escherichia coli	Differential toxicity	ND	+	Waters *et al*., 1982
Escherichia coli	Reverse mutation	-	-	Waters *et al*., 1982

ND = not done; - = negative; + = positive.

Table 10 (continued) Genotoxicity of *o*-DCB *in vitro*: Microbial systems

Genus and species (strains)	Test	Result		Reference
		With activation	Without activation	
Aspergillus nidulans	Reverse mutation	ND	-	Prasad and Pramer, 1968 (cited in IUCLID) & Prasad, 1970
Saccharomyces cerevisiae	Gene mutation	-	-	Litton Bionetics, 1976 (cited in BUA, 1990)
Saccharomyces cerevisiae	Mitotic recombination	-	-	Waters *et al*., 1982

ND = not done; - = negative; + = positive.

Table 11 - Genotoxicity of *o*-DCB *in vitro*: Mammalian systems

Species and cell type	Test	Result		Reference
		With activation	Without activation	
CHO	Chromosomal aberration	- -	- -	Loveday *et al*., 1990 Tennant *et al*., 1987
CHO	Chromosomal aberration	- -	- -	Bioassay Systems, 1983 (cited in BUA, 1990) Waters *et al*., 1982
CHO	HGPRT assay	-	-	Bioassay Systems, 1984 (cited in BUA, 1990)
CHO	SCE	+ +	- -	Loveday *et al*., 1990 Tennant *et al*., 1987
Primary hepatocytes (rat)	DNA damage & repair	ND ND	- -	Shimada *et al*., 1983 (cited in BUA, 1990) Williams *et al*., 1989
Mouse L5178Y cells	Mouse lymphoma assay	+ +	- -	Tennant *et al*., 1987 Myhr & Caspary, 1991
Lymphocytes (human)	Inhibition of DNA synthesis	-	+	Perocco *et al*., 1983

CHO, Chinese hamster ovary cells; HGPRT, hypoxanthine guanine phosphoribosyl transferase; SCE, sister chromatid exchange; ND, not done.

11.8.2 *In vivo* testing

The results of *in vivo* genotoxicity testing with *o*-DCB are generally negative and are summarised in Table 12. Studies with *Drosophila melanogaster* (sex-linked recessive mutation and eye mosaic assay), chromosomal aberration in rat bone marrow and DNA damage in rats were all negative. A positive micronuclei assay in mouse bone marrow was not confirmed in a recent well-conducted study.

Table 12 - Genotoxicity of *o*-DCB *in vivo*

Species (sex)	Test	Result	Reference
Insects			
Drosophila melanogaster	Sex-linked recessive mutation	-	Bioassay Systems, 1983 (cited in BUA, 1990)
Drosophila melanogaster	Sex-linked recessive mutation	-	NTP, 1989
Drosophila melanogaster	Eye mosaic assay	-	Vogel and Nivard, 1993
Drosophila melanogaster	Eye mosaic assay	-	Vogel and Nivard, 1993
Mammals			
Rat bone marrow (male)	Chromosomal aberration	-	Reustle and Scriber, 1979 (cited in BUA, 1990)
Rat bone marrow (male and female)	Chromosomal aberration	-	Bioassay Systems, 1983 (cited in BUA, 1990)
Rat (female)	DNA damage	-	Kitchin *et al*., 1992
Mouse bone marrow (male)	Micronucleus	+	Mohtashamipur *et al*., 1987
Mouse bone marrow (male)	Micronucleus	-	Shelby *et al*., 1993

The role of *o*-DCB as an inducer of DNA synthesis was assessed using an *in vivo-in vitro* replicative DNA synthesis assay with hepatocytes derived from male $B6C3F_1$ mice. The animals were administered *o*-DCB (1000 or 2000 mg/kg bw) by the oral route and hepatocytes prepared 24, 39 or 48 hours later. Replicative DNA synthesis was assessed after the addition of [methyl-^{3}H]-thymidine followed by autoradiography. Results were negative for both doses at all time points (Miyagawa *et al*., 1995).

11.8.3 Human exposure

In a case of accidental human exposure to *o*-DCB, 26 laboratory workers were exposed for 4 days (8 hours/day) to *o*-DCB vapour, estimated by the authors to be no greater than 100 ppm (610 mg/m^3). A total of 1345 cultured peripheral blood cells from affected individuals were examined and compared to 942 cultured cells from 11 unexposed individuals. The mean value of chromosomal aberrations in the exposed group was 8.92% compared to 2.02% for the control group. Further testing of 15 exposed individuals 6 months later (only 300 cells examined) showed a significant reduction in the number of chromosomal aberrations (Zapata-Gayon, 1982). Due to the relatively low number of cells examined little confidence can be attributed to findings of this study. The authors claimed the effect to be reversible after several months but as the cells involved are constantly removed from the peripheral circulation and replaced, this claim needs to be treated with caution.

11.9 Carcinogenicity

In a 2-year study of both sexes of rats (strain F344/N) and mice (strain B6C3F$_1$) *o*-DCB (0, 60 or 120 mg/kg bw) was administered by gavage (5 days/week). The survival of male and female mice and female rats was similar to control animals. Technical difficulties with the gavage process resulted in a decreased survival rate for high-dose males compared to controls. Details of the non-carcinogenic effects are presented in Section 11.5.1. A dose-related increased incidence of renal tubular regeneration was observed in male rats (control, 8/48; low dose, 12/50; high dose 17/49). Although the incidence of pheochromocytoma in male rats was increased in the low-dose group (16/50) the high-dose incidence (6/49) was lower than the control animals (9/50) with no significant dose-response trend being evident. The incidence of malignant histiocytic lymphoma in male (control, 0/50; low-dose, 1/50; high-dose 4/50) and female (control, 0/49; low-dose, 0/50; high-dose, 3/49) mice was significantly increased ($p < 0.05$). However, the findings were dismissed as the numbers of animals with all types of lymphomas (combined), which is considered to be a better indicator, had not increased. Under the conditions of the study, *o*-DCB was not considered to be carcinogenic in rats or mice (NTP, 1985).

Herren-Freund and Pereira (1986) concluded that *o*-DCB did not initiate or promote tumour formation using the γ-glutamyltranspeptidase-positive foci assay as an indicator of carcinogenicity. Male and female rats (strain Sprague-Dawley) were treated with diethylnitrosamine (DENA; 0.5 mmol/kg), a tumour initiator, one day after a two thirds hepatectomy followed by i.p. injections 1 and 5 weeks later of *o*-DCB (1 mmol/kg bw; 147 mg/kg bw). The number of positive foci from treated rats were not significantly different from control animals.

12. Human Health Effects

12.1 Irritant effects

The effect of *o*-DCB on human skin (inner forearm) was examined by means of the attachment of a glass cylinder to the skin of 2 subjects and placement of the liquid within the cylinder. After 15 minutes, a burning sensation was noticed at the site of application that increased in intensity over the next hour and disappeared after the liquid was removed. The skin became red, as did the surrounding area. At 24 hours the site was dark red and blistered. A brown pigmentation subsequently developed, which was still present 3 months later (Riedel, 1941).

Irritation to the eyes and respiratory passages of humans was reported to occur on exposure to *o*-DCB at 100 ppm (Elkins, 1959).

12.1 Case reports

There are few reports concerning the effects of *o*-DCB on humans and no reports of clinical studies on volunteers. In cases of accidental exposure the extent of exposure is not known and the involvement of other chemicals uncertain. No studies were located demonstrating a clear causal relationship between *o*-DCB exposure and death.

Cases in which *o*-DCB has been associated with human toxicity include:

- A 47-year-old male glazier developed contact dermatitis after handling window frames treated with *o*-DCB. Subsequent investigation involving a patch test indicated sensitivity to *o*-DCB (Downing, 1939).
- An 18-year-old female worker developed headaches, fatigue, vertigo, bone-marrow hyperplasia, acute haemolytic anaemia and leukocytosis after chronic exposure to a dry-cleaning fluid composed of 95% *o*-DCB and 5% *p*-DCB (Gadrat *et al*., 1962).
- Seven cases of haematological disorders attributed to exposure to chlorobenzenes were described by Girard *et al*. (1969). Those attributed to *o*-DCB exposure include:
  - A 53-year-old male shoemaker who used glue-containing *o*-DCB (2%) for 16 years developed chronic lymphoid leukaemia, splenomegaly and hepatomegaly.
  - A 15-year-old female who used a cleaner composed of *o*-DCB (37%) to clean her clothes developed acute myeloblastic leukaemia.
  - A 40-year-old male who worked with and cleaned electrical equipment over a period of 10 years with a solvent containing a mixture of the three isomers of dichlorobenzene developed chronic lymphoid leukaemia.
  - A 55-year-old woman used 1 to 2 litres of dichlorobenzene per annum for household cleaning developed acute myeloblastic leukaemia.
  - A 40-year-old male with work-related exposure to *o*-DCB, in addition to other chlorobenzenes, developed a myeloproliferative syndrome.

Due to the unknown nature of other chemicals involved in the products used, their concentrations and lack of information on exposure levels and duration of exposure, the clinical effects described above can not be confidently attributed to *o*-DCB exposure alone.

In another case report:

- Twenty six laboratory workers consisting of 8 males (range 26 to 46 years, mean 36 years) and 18 females (range 20 to 60 years, mean 30.9 years) were exposed to the vapour of *o*-DCB for 4 days (8hr/day) which had been deployed as a pest control measure in a basement laboratory. Reported clinical symptoms included headache, vertigo, nausea, malaise and most individuals reported eye, nose and throat irritation. One individual developed a partial facial oedema (Zapata-Gayon, 1982).

12.2 Epidemiological studies

There have been no well-controlled epidemiological studies. Confounding factors are concomitant exposure to other agents and inadequate details of exposure conditions and previous or existing medical conditions.

Medical examination of employees (number not specified) exposed to *o*-DCB, average concentration 15 ppm (range 1 to 44 ppm; based on 40 workroom air samples, duration of exposure not specified) did not show any evidence of "organic injury or of untoward hematological effects attributed to exposure to *o*-dichlorobenzene" (Hollingsworth *et al.*, 1958).

Nine males with a mean age of 54.1 years (range 32 to 66 years) and a mean working time of 24.1 years (range 13 to 35 years) in a factory using chlorobenzenes (mono-, *para*- and *ortho*-dichlorobenzene) were identified as having chloracne based on the presence of polymorphic dermatosis, predominately comedones and cysts. All patients had conjunctivitis and reported gastrointestinal complaints including nausea with occasional vomiting and as having paresthesia of the lower extremities. Five of the workers had developed a diffuse melanotic discolouration and four developed hyperpigmentation of the face. Liver function tests were abnormal and radiology indicated enlargement of the liver. The symptoms described were present for at least two years after leaving the company. Analysis of water from the work site gave 15 ppm of chloracne inducing substances. Analyses of air samples were recorded as being inconclusive (Vazquez *et al.*, 1996). Due to the inadequacy of data on exposure levels and no data were presented with respect to exposure to other work related compounds or other substances including medication, a causal relationship between the symptoms described and *o*-DCB exposure cannot be demonstrated.

13. Hazard Classification

The purpose of this section is to evaluate the physicochemical data, kinetic and metabolism studies, human and animal experimental studies (including *in vivo* and *in vitro* data) in order to determine the potential hazard to human health that exposure to *o*-DCB might entail.

Workplace substances are classified as 'hazardous' to health if they meet the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1999a), and 'dangerous' in terms of physicochemical hazards, if they satisfy the criteria of the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) (Federal Office of Road Safety, 1998).

The classifications for *o*-DCB are incorporated in the following assessment of physicochemical and health hazards.

13.1 Physico-chemical hazards

o-DCB is a colourless or pale yellow volatile liquid (vapour pressure 1.96 hPa at 25°C) with a boiling point of 180.4°C and a flash point of 66°C. The ignition temperature is 648°C.

Classification status:

o-DCB does not meet the ADG Code (FORS, 1998) criteria for physicochemical properties.

13.2 Kinetics, metabolism and mechanisms

o-DCB is readily absorbed by ingestion and inhalation. In animals, *o*-DCB is widely distributed in the body particularly to the adipose tissue, the liver and kidneys. The biological residence time is short with complete excretion, predominately in the urine, generally occurring within 48 hours of exposure. Due to the lipophilic nature of *o*-DCB, it is thought that the major mechanism for the transport of this compound across cellular membranes is by passive diffusion.

The metabolism of *o*-DCB by rats and mice occurs by hepatic cytochrome P450 enzymes (CYP2E1 and CYP2B1/2) and in humans by CYP2E1 only, with the initial formation of epoxide intermediates. The metabolic fate of the epoxides can be conjugation with glutathione, hydrolysis by epoxide hydrolase to dihydrodiols or rearrangement to form dichlorophenols. Subsequent oxidation of the dichlorophenols results in the formation of hydroquinone derivatives, which can further oxidise to benzoquinones.

Metabolic differences exist between rats, mice and humans with respect to the kinetics and profile of metabolites produced from *o*-DCB. The rank order for the kinetics of *o*-DCB metabolism by hepatic microsomes is human > mouse > rat. The formation of reactive epoxides and hydroquinone/benzoquinone species correlates with covalent

binding and hepatotoxicity. Mice produce more reactive metabolites as indicated by covalent binding to macromolecules. Inhibitor studies utilising mouse microsomes found an increase in hydroquinone formation with reduced covalent binding, indicating an important role for benzoquinones as reactive metabolites in this species. In contrast, the addition of glutathione to rat microsomes diminished covalent binding with concomitant increased formation of the GSH-conjugates indicating that in the rat, epoxides are important reactive metabolites. Human metabolism of *o*-DCB, as determined by hepatic microsomal metabolism, results in the non-reactive 3,4-epoxide that is converted to a dihydrodiol and 2,3- and 3,4-dichlorophenol.

Hepatic injury in the rat as a response to *o*-DCB exposure appears to be bimodal. The formation of a reactive epoxide and of hydroquinone/benzoquinone species in the liver gives rise to covalent binding to cellular components with subsequent cellular injury. In addition, oxidative stress induced by activation of Kupffer cells, a resident macrophage population in the liver, has been implicated in mediating *o*-DCB-induced hepatotoxicity. On activation these phagocytic cells secrete substantial quantities of the reactive oxygen metabolite, superoxide, which on dismutation yields hydrogen peroxide. Prior administration of superoxide dismutase or desferioxamine, a scavenger of superoxide and an iron chelator respectively, significantly reduced hepatic injury suggesting that hydroxyl radical formation by the iron-catalysed Haber-Weiss reaction contributes to such injury. The role of *o*-DCB-induced oxidative stress has been demonstrated, *in vivo*, by the presence of increased lipid peroxidation products in the livers and plasma of treated animals.

13.3 Health hazards

Acute effects

Animal studies with rats and mice have shown *o*-DCB to induce acute hepatotoxic effects.

The LD_{50} for a single oral exposure to *o*-DCB for the rat ranges from 1516 to 2138 mg/kg bw. The LC_{100} for the rat is ≤ 977 ppm (5.9 mg/L) for a 10 hour exposure. During a 4 hour exposure, 1 of 20 rats died at 941 ppm (5.6 mg/L) (Hollingsworth *et al.*, 1958).

In humans, the acute effects of *o*-DCB by ingestion or inhalation are reported to be headache, nausea, vomiting, vertigo, malaise and unconscious.

Classification status:

o-DCB has been assigned the ADG Code (FORS, 1998) *Class 6.1 (Toxic substances)*, based on human experience.

o-DCB meets the Approved Criteria (NOHSC, 1999a) for *acute lethal effects* (R22) by the oral route. Insufficient information exists to classify for dermal exposure. It does not meet the criteria for inhalation exposure.

o-DCB does *not* meet the Approved Criteria (NOHSC, 1999a) for *non-lethal (irreversible) effects* (R40) after a single exposure.

Irritant effects

Skin irritation

The application of *o*-DCB to human skin for 15 minutes resulted in a burning sensation and subsequent development of erythema and blistering within 24 hours. The affected area subsequently became hyperpigmented, an effect which persisted for a number of months.

There are no animal skin irritation studies.

Classification status:

o-DCB meets the Approved Criteria (NOHSC, 1999a) for *skin irritation* (R38).

Eye irritation

Rabbits exhibited pain and "slight conjunctival irritation" after direct exposure of the eye to liquid *o*-DCB. The inflammatory response was resolved within one week. Inadequate data exist to characterise the human ocular response to *o*-DCB although it has been reported to cause eye irritation in humans at 100 ppm (Elkins, 1959). OECD test guidelines for the testing and evaluation strategy for eye irritation/corrosion (1998) take into account skin irritancy in determining the potential of a substance to cause eye irritation.

Classification status:

o-DCB meets the Approved Criteria (NOHSC, 1999a) for *eye irritation* (R36).

Respiratory irritation

Exposure to *o*-DCB vapour at 100 ppm has been reported to cause some respiratory irritation in humans (Elkins, 1959). The RD_{50}, based on reflex bradypnea, for male mice exposed to *o*-DCB vapour was found to be 182 ppm (De Ceaurriz, *et al*., 1981) and 163 ppm (Zissu, 1985).

Olfactory epithelial lesions were observed in mice exposed to the *o*-DCB vapour at 64 ppm (Zissu, 1995).

Classification status:

o-DCB meets the Approved Criteria (NOHSC, 1999a) for *irritation to the respiratory system* (R37).

Sensitisation

There are no animal or human studies related to sensitisation by the dermal or inhalation routes. However, one case report of an individual experiencing dermatitis and giving a positive patch test to *o*-DCB has been described (Downing, 1939).

Classification status:

Insufficient data exist to classify *o*-DCB for *sensitising effects (skin or inhalation)* (R43 or R42).

Severe effects (non-carcinogenic) after repeated or prolonged exposure

Symptoms reported after prolonged human exposure to *o*-DCB have included headache, nausea, fatigue and vertigo. Bone-marrow hyperplasia has been reported and haematological disorders have also been noted, particularly anaemia and leukocytosis, although the role of *o*-DCB as the causative agent in these cases is uncertain. No cases of fatalities directly associated with exposure to *o*-DCB were found in the literature.

Several studies of rats and mice from 10 days to 2 years duration with administration of *o*-DCB by gavage indicate that adverse effects include increases in liver and kidney weights and hepatotoxicity. The lowest dose at which these effects were observed was 100 mg/kg bw per day, in a 90-day oral study of rats.

Reports of the effects of inhalation of *o*-DCB in animals are limited to one inadequate study. In rats and mice, pathological changes in hepatocellular morphology were observed in all tested animals after inhalation exposure to 50 ppm for 24 hours.

There are no studies addressing the effects of dermal exposure to *o*-DCB.

Classification status:

o-DCB does *not* meet the Approved Criteria (NOHSC, 1999a) for *severe effects after repeated/prolonged exposure* (R48) as the oral and inhalation doses required to produce adverse effects exceeds 50 mg/kg bw/day and 0.25 mg/l, 6h/day respectively.

Reproductive effects

There have been no reports of adverse reproductive effects in humans attributed to *o*-DCB described in the literature.

The developmental effects of *o*-DCB in rabbits and rats has been studied and the results indicate that exposure levels that do not induce maternal toxicity do not affect embryonic or foetal development. No data are available for effects on fertility in animals.

Classification status:

There are no data to classify *o*-DCB for *fertility effects* (R60).

o-DCB does *not* meet the Approved Criteria (NOHSC, 1999a) for *developmental effects* (R61).

Genotoxicity

Studies undertaken *in vitro* using a number of test systems have generally resulted in negative findings. The results of Ames testing (with or without metabolic activation), using several strains of *S. typhimurium*, were negative for *o*-DCB. Similarly, tests with *B. subtilis* and *E. coli* have given negative results in recombination or DNA damage and repair assays with the exception of two tests (one each of *B. subtilis* and *E. coli*) which were positive but only in the absence of metabolic activation. Mutation assays with *A. nidulans and S. cerevisiae* (with or without metabolic activation) yielded negative results.

Testing with mammalian cell lines for chromosomal aberration, the HGPRT assay and DNA damage and repair assays have given negative results. Positive results were obtained for sister chromatid exchange and the mouse lymphoma assay in the presence of metabolic activation. A test for inhibition of DNA synthesis with human lymphocytes was positive only in the absence of metabolic activation.

The results of *in vivo* testing with *Drosophila melanogaster* using sex-linked recessive mutation or eye mosaic assays have been negative. In other *in vivo* studies, examination of rat bone marrow cells for chromosome aberrations and rat liver for DNA damage produced negative results. While a positive result was obtained for a mouse micronucleus assay, the result could not be repeated in a more recent, well-conducted study.

Although a small number of *in vitro* tests proved positive for *o*-DCB, *in vivo* studies have produced negative results with the exception of one micronucleus study which was negative in a later study. Based on the weight of evidence, *o*-DCB is unlikely to be genotoxic.

Classification status:

o-DCB does *not* meet the Approved Criteria (NOHSC, 1999a) for *mutagenic effects*.

Carcinogenicity

No treatment-related increases in neoplastic lesions were observed in either rats or mice (males or females) exposed to *o*-DCB up to a dose of 120 mg/kg bw during a 2-year oral carcinogenicity study. Although an increasing trend in histiocytic lymphomas was observed in male and female mice, the importance of these tumours was discounted as the combined incidence of all types of lymphoma was not significantly greater than the controls of either sex.

Classification status:

o-DCB does *not* meet the Approved Criteria (NOHSC, 1999a) for *carcinogenicity*.

14. Effects on Organisms in the Environment

No ecotoxicity tests were provided by applicants. Several published papers were available for this assessment and have been supplemented with results from the IUCLID data sheet (IUCLID, 1996) and the BUA Report (1990). Additionally, results from the US EPA Ecotox Database have been reported where available. These may be considered validated data as they have been published in reputable journals.

14.1 Fish

Available toxicity data for fish are summarised below. Where the published papers have been viewed, a brief description of the tests are provided after Table 13.

Table 13 - Toxicity to fish

Species	Test Duration	Result (mg/L)	Reference
Acute			
Brachydanio rerio (zebra fish)	48 hours	LC_{50} = 6.8	Calamari *et al*., 1983.
	96 hours	LC_{50} = 5.2	IUCLID
Oncorhynchus mykiss (Rainbow trout)	48 hours	LC_{50} = 2.3	Calamari *et al*., 1983.
	96 hours	LC_{50} = 1.61	Ahmad *et al*., 1984
	96 hours	LC_{50} = 1.58	Call *et al*., 1983
	144 hours	LC_{50} = 1.54	Call *et al*., 1983
Cyprinodon variegatus (Sheepshead minnow)	96 hours	LC_{50} = 9.7	Heitmuller *et al*., 1981.
Lepomis macrochirus (Bluegill sunfish)	96 hours	LC_{50} = 5.6	Buccafusco *et al*., 1981.
	96 hours	LC_{50} = 27	Dawson *et al*., 1977
Menidia beryllina (Inland silverside)	96 hours	LC_{50} = 7.3	Dawson *et al*., 1977
Pimephales promelas (Fathead minnow)	96 hours	LC_{50} = 57	Curtis and Ward, 1981.
	96 hours	LC_{50} = 9.5	Curtis *et al*., 1979
Oryzias latipes (Japanese rice fish)	48 hours	LC_{50} = 10	Yoshioka *et al*., 1986a
Chronic			
Pimephales promelas (larvae)	28 days (?)	NOEC* = 2	US EPA, 1985

* NOEC = no observed effect concentration.

The acute toxicity data listed in Table 13 were all derived in closed flow through systems.

Calamari *et al*. (1983) tested a number of chlorinated benzenes in closed systems to control volatilisation. While the paper states a 24 h exposure period for fish, the results are reported as 48 h LC_{50}s. The results are indicative of moderate toxicity, and are in general agreement with other reported results for the same species.

Curtis and Ward (1981) undertook testing on fathead minnow, with fish observed for a minimum of 14 days prior to testing. Ten chemicals were tested, and with the concentration vs. mortality results, the 96 h LC_{50}s were determined through either probit, moving average or the binomial test method, although it is not apparent which method was used for *o*-DCB. Water samples taken at the beginning and end of each test were analysed for toxicant concentration, although these are not provided in the report. The result was an LC_{50} of 57 ppm indicative of only slight toxicity. This contrasts to the result of 9.5 ppb reported in the US EPA Ecotox Database, and is in general contrast to the remainder of results where all LC_{50} values fall within the 1 to 10 ppm except one measurement for bluegill sunfish with an LC_{50} of 27 ppm.

Buccafusco *et al*. (1981) provided details of testing to bluegill sunfish. Test chambers were 19.6 L wide-mouthed glass jars containing 15 L test solution. In an effort to control volatilisation, the test jars were capped. Ten fish were randomly selected from a test population and added to each jar within 30 min prior to the addition of the test substance, and jars immediately capped. Data reported were based on the nominal concentration with the LC_{50} and 95% confidence interval (C.I.) determined by the moving average angle method. No observations with respect to sub-lethal effects are made, and an LC_{50} of 5.6 ppm was determined (95% C.I. 4.8 to 6.6 ppm).

Based on the scale of Mensink (1995) *o*-DCB can be considered moderately to slightly toxic to fish from acute exposure. However, certain other data tabulated in the BUA report indicated results for static tests where the test media and fish were subjected to continual aeration. Under these conditions the derived LC_{50} values were significantly higher than indicated above, and this was attributed to stripping of the volatile *o*-DCB from the water by air. No observations regarding sublethal effects are made about the acute tests in the BUA report, but it is to be noted that in their studies on bioconcentration using rainbow trout, Oliver and Niimi (1983) observed no deaths in the fish populations over 119 days at 47 µg/L and for 105 days in the flow-through technique at 940 µg/L. Note, the original study has not yet been obtained, and is required in this instance as the concentrations reported in the bioaccumulation section of BUA (1990) are 0.047 and 0.940 µg/L, which are three orders of magnitude less than those reported here.

The only reference to chronic toxicity is some US EPA work on fathead minnow larvae. No details on experimental conditions were given, but the data indicate that *o*-DCB is also slightly to moderately toxic to this species under chronic exposure conditions.

14.2 Aquatic invertebrates

A number of original papers referred to in BUA (1990) and the US EPA's Ecotox Database were obtained for this assessment. Where original papers were sighted, they are referenced in the Table 14 with a short summary of the tests following the table. Papers not obtained have been referenced to the US EPA (2000) Ecotox Database. As these are

from published articles, so may be considered peer reviewed, hence validated, for the purpose of this assessment.

Table 14 - Toxicity to aquatic invertebrates

Species	Test Duration	Result (mg/L)	Reference
Acute Toxicity			
Daphnia magna	24 hours, **closed**	EC_{50} = 0.78 (measured)	Calamari *et al*., 1983
	48 hours, **closed**	EC_{50} = 2.35	Abernathy *et al*., 1986
	48 hours, **closed**	IC_{50} = 3.77	Hermens *et al*., 1984
	48 hours, **static**	EC_{50} = 2.2	Canton *et al*., 1985
	48 hours, **static**	EC_{50} = 2.4	LeBlanc, 1980
Ceriodaphnia dubia	48 hours, **static**	EC_{50} = 0.66	Rose *et al*., 1998
Artemia (Brine Shrimp)	24 hours	EC_{50} = 15	Abernathy *et al*., 1986
Palaemontetes pugio (Salt water grass shrimp)	96 hours	LC_{50} = 10	Curtis and Ward, 1981
	96 hours	LC_{50} = 9.4	Curtis *et al*., 1979
Mercenaria mercenaria (Hard clam)	48 hours, **static**	EC_{50} >100	Davis and Hidu, 1969
Mysidopsis bahia (Opossum shrimp)	96 hours	LC_{50} = 1.97	US EPA, 1978
Tanytarsus dissimilis (Midge)	48 hours, **static**	LC_{50} = 12	Call *et al*., 1983
Tetrahymena pyriformis (Ciliate)	24 hours, **static**	LC_{50} = 51	Yoshioka *et al*., 1985
Chronic Toxicity			
Daphnia magna	14 days	EC_{50} = 0.55 mg/L	Calamari *et al*., 1983
	16 days	LC_{50} = 1.5	Hermens *et al*., 1984
	21 days, semi static	NOEC = 0.63 mg/L	Kuhn *et al*., 1989
Mercenaria mercenaria (Hard clam)	12 days, **flow-through**	EC_{50} = 0.25-10 (growth) LC_{50} >100	Davis and Hidu, 1969

Calamari *et al*. (1983) tested a number of chlorinated benzenes in closed systems to control volatilisation. Effective concentrations for immobilisation data on *Daphnia* were calculated from curves fitted by eye on log probability paper and not elaborated, being very close to the concentrations with 0 and 100% immobilised animals. Fertility data were elaborated from older methodology to obtain instantaneous growth rates. A 24 h IC_{50} of 0.78 ppm was derived which is lower than other acute values. A 14 d EC_{50} of 0.55 ppm was obtained from fertility tests on *Daphnia magna*.

Abernathy *et al*. (1986) tested the acute toxicities of 38 hydrocarbons and chlorinated hydrocarbons to two planktonic crustaceans, freshwater *Daphnia magna* and the saltwater *Artemia* (brine shrimp). Saturated aqueous solutions of single compounds were prepared and diluted to provide at least 5 exposure concentrations plus a control for each test. Test chambers were filled and sealed in 33 mL glass vials. LC_{50}s were calculated using a graphical method. The results showed a 48 h LC_{50} of 16 mmol/m^3 for *Daphnia* and 102 mmol/m^3 for *Artemia*, which translate to 2.35 mg/L and 15 mg/L respectively.

A detailed description of experimental methodology conducted by Hermens *et al*. (1984) was not provided. While it was referenced, the methodology has not been obtained. The acute IC_{50} values were calculated by logit transformation while the 16 day LC_{50} value was determined by a log/probit plot.

Curtis and Ward (1981) tested ten chemicals including *o*-DCB on the estuarine grass shrimp *P. pugio*. They were observed for a minimum of 10 days prior to testing. The tests were performed in synthetic seawater. Five organisms were placed in each of two duplicate aquaria for a total of 10 organisms per concentration. At least five concentrations were tested in a 0.6 geometric series with at least two control aquaria for each test series. The 96 h LC_{50}s were determined through either probit, moving average or the binomial test method, although it is not apparent which method was used for *o*-DCB. Water samples taken at the beginning and end of each test were analysed for toxicant concentration, although these are not provided in the report. The result was an LC_{50} of 10 ppm indicative of only slight toxicity.

Further results available in the US EPA Ecotox Database (US EPA, 2000) largely support those described above.

Using the scale described in Mensink (1995), *o*-DCB can be said to be at least moderately toxic to aquatic invertebrates under acute exposure conditions, with two results indicative of high toxicity (EC_{50} of 0.78 ppm and 0.66 ppm to *Daphnia* and *Ceriodaphnia* respectively). Under conditions of chronic exposure, NOECs and EC_{50} values tend to lie in the 0.1 to 0.01 ppm, which are indicative of moderate toxicity.

o-DCB has the potential to interfere with the embryonic development of sea urchins (Oshida, 1977; Pagano *et al.*, 1988). Evidence of abnormal developments in the hard clam were found after exposure to relatively high concentrations (10 mg/L) of the chemical (US EPA, 2000).

14.3 Algae/Aquatic plants

A number of results for the inhibition of algal growth caused by *o*-DCB to various algal species are summarised in the BUA Report and in the IUCLID data sheet. The full experimental conditions and protocols used in the studies were not documented in the available summaries. Only Calamari *et al*. (1983) was available. A selection of the more significant results are reproduced and discussed below.

The study by Calamari *et al*. (1983) on *Selenastrum capricornutum* monitored the photosynthetic uptake of ^{14}C from labelled bicarbonate in the presence of *o*-DCB, and found the 3 hour EC_{50} as 10 mg/L. In a separate study these workers determined the 96 hour EC_{50} for this species in a closed system as 2.2 mg/L. Algal growth was evaluated by measuring *in vivo* the fluoimetric units. Test vessels were monitored in order to maintain constant concentration and to allow the sampling of the culture medium without opening the vessel. Data on algal growth were not mathematically elaborated as the usual statistical methods were not considered applicable owing to the high number of organisms and the fact that they change number during the test. However, the 96 h EC_{50} values were extrapolated from empirical curves fitted by eye on log-probability paper with percentage of growth inhibition and log of concentration on the axes. This result is indicative of moderate toxicity (Mensink, 1995).

Other test results provided in BUA (1990) and the US EPA Ecotox Database indicate much less sensitivity to algae than that determined by Calamari *et al*. (1983), with EC_{50}s in the range of 10 to 100 ppm which are indicative of slight toxicity.

Testing conditions for determining these other results are not known. It may be that tests were conducted in open systems which, for a volatile chemical, would be expected to result in lower sensitivity being demonstrated. Also of interest is research outlined in Millington *et al* (1988) where it was demonstrated that the value of standard algal growth inhibition tests using different growth media is questionable. In this study, the lowest concentrations at which significant inhibition of algal growth occurred after 120 hours incubation were determined for the algal species *Chlorella vulgaris, S. capricornutum* and *S. subspicatus* using three different growth media. These media were Bolds basal medium (BBM), OECD and US EPA. These media showed no difference for *S. capricornutum* with significant inhibition found at 80 ppm for all three. However, *S. subspicatus* showed half the sensitivity (significant inhibition at 100 ppm) with the OECD and EPA media as for the BBM media (50 ppm), and *C. vulgaris* was even more diverse with significant inhibition determined at 5 ppm (BBM), 10 ppm (OECD) and 100 ppm (EPA). Therefore, the results outlined above in Table 15 may be influenced by the protocol used to undertake testing.

Table 15 - Toxicity to algae and aquatic plants

Species	Test Duration	Result (mg/L)	Reference
Selenastrum capricornutum	96 hours	EC_{50} = 2.2 NOEC = 0.88	Calamari *et al*., 1983
	96 hours	EC_{50} = 71.1	US EPA, 1978
	96 hours	EC_{50} = 76.1 NOEC <10	US EPA, 1978
	96 hours	ErC_{50} = 98 EC_{50} = 91.6 (chlorophyll impairment)	US EPA, 1985
Scenedesmus subspicatus (green algae)	48 hours, **static**	EC_{50} = 14	Kuhn and Pattard, 1990
Skeletonema costatum (marine algae)	96 hours	EC_{50} = 44.2 (Chlorophyll impairment	US EPA, 1978

14.4 Micro-organisms

Both BUA (1990) and IUCLID summarise a large number of tests on the toxicity of *o*-DCB to a variety of bacteria. Only a selection of these, selected to give an indicative range of results, will be described here (Table 16).

Table 16 - Toxicity data for micro-organisms

Species	Test Duration	Result (mg/L)	Reference

Nitrosomonas	24 hours	EC_{50} = 47	IUCLID
Bacillus (TL 81) – from activated sludge	30 minutes exposure	EC_{50} = 169 ± 13	Liu and Thomson, 1984
Activated sludge bacteria	3 hours (OECD TG 210)	EC_{50} = 100	Yoshioka *et al*., 1986b
Photobacterium phosphoreum	5 Min. exposure (Microtox test)	EC_{50} = 10.3 ± 3.6	McFeters *et al*., 1983
Photobacterium phosphoreum	30 Min. exposure (Microtox test)	EC_{50} = 4.0	Kaiser and Ribo, 1985
	5 Min. exposure (Microtox test)	EC_{50} = 2.7	

Most of the results tabulated above indicate that *o*-DCB can be described as slightly to practically non-toxic to micro-organisms. Specifically, sewage sludge bacteria and a species of *Nitrosomonas* showed only slight to practically no toxic effects when exposed to the chemical. However, no observations from the tests are available. Two studies on a phosphorescent bacteria used in the Microtox test indicated moderate to slight toxicity to this species when assessed on the basis of reduction in bioluminescence.

14.5 Predicted no effect concentration (PNEC) for the aquatic environment

There are a significant number of experimental test results for this chemical to the aquatic compartment, covering all trophic levels. A number of chronic results are available for aquatic invertebrates.

The lowest chronic value obtained was a 14 day EC_{50} of 0.55 ppm for *Daphnia magna* as derived in Calamari *et al*., (1983). Results highlighted in this paper were consistently lower (often significantly) than other results, the reason for which is uncertain. Certainly, the method for calculating results is old (values were extrapolated from empirical curves fitted by eye on log-probability paper), although most results reported above have not had the test reports or published papers obtained, so other more accepted methods (eg probit analysis) can not be assumed.

Nonetheless, the use of this EC_{50} is considered acceptable for determining a PNEC in this case as it is supported to some extent by a 21 day NOEC of 0.63 ppm on the same organism as reported in the US EPA Ecotox Database (US EPA, 2000).

While there are a large number of acute data covering all trophic levels, chronic data are scarce with only one unvalidated test for fish. Therefore, an assessment factor of 100 has been chosen. The PNEC has therefore been determined to be 5.5 µg/L for *o*-DCB in water.

14.6 Terrestrial micro-organisms

Walton *et al*. (1989) studied the effects of *o*-DCB on the respiration of soil bacteria. Silt loam containing 1.5% of organic carbon, and sandy loam containing 0.66% of organic carbon were both treated with 1 g/kg of *o*-DCB, and after wetting were incubated in the dark at 20°C for 6 days. Although the rate of CO_2 evolution was depressed for the first few days of the experiment, the rate was not significantly different from the untreated controls at the end of the 6 day period.

Mehagh *et al*. (1998) found that *o*-DCB had no deleterious effects on soil micro-organisms up to levels of 50 µg/kg, and also found that the metabolic activity of the biomass shifted to enhance degradation of *o*-DCB. The latter effect was marked in the presence of decaying plant roots. A second paper from the same laboratory (Thompson *et al*, 1999) found that although *o*-DCB levels of 65 µg/kg and above caused significant decrease in hyphal fungal length, soil bacteria were significantly more tolerant, with observable population decreases only at *o*-DCB levels of 3.25 mg/g (dw). Further, there was evidence that *o*-DCB at levels up to 325 µg/kg stimulated counts of *Pseudomonas*.

Two studies are summarised in BUA (1990) aimed at quantifying fungicidal activity of *o*-DCB. St'ota and Toman (1957) investigated the fungicidal activity of the compound against smut fungi (*Tilletia foetida*), which grows on wheat. These workers found that a reduction in infected wheat ears resulted when the seeds had been treated with up to 6.3 mg/kg of *o*-DCB. A 4 week incubation found *o*-DCB prevented mould fungus from growing in wet hay in a concentration of 10 g/kg dry weight whereas, at a level of 5 g/kg dry weight, growth was delayed but not completely inhibited (Schenk and Kennedy, 1955).

14.7 Terrestrial plants

Yukimoto (1983) investigated the phytotoxicity of a series of chlorinated benzenes to photosynthesis in spinach leaves. This worker found that these compounds have some inhibitory effect on photosynthesis, and for *o*-DCB obtained the following results; IC_7 = 10.3 mg/L, IC_{46} = 59 mg/L and IC_{85} = 103 mg/L. Other earlier studies are described in BUA (1990), but adverse effects on plant growth and development do not appear to be significant unless exposure to the chemicals is at high levels. For example, St'ota and Toman (1957) found 40% inhibition of growth of wheat seedlings in a greenhouse when *o*-DCB was applied to the soil at levels of 5.6 g/kg or higher.

14.8 PNEC for soil

While available information indicates that deleterious effects on plant growth and development are not manifest unless the exposure levels are very high, the data are insufficient for realistic estimations of the Predicted No Effect Concentration (PNEC) of *o*-DCB on terrestrial life. Accordingly, a very conservative PNEC is estimated by dividing the 5.6 g/kg level found by St'ota and Toman (1957) by a factor of 1000, giving a PNEC of 6 mg/kg.

15. Occupational Risk Characterisation

In this section, the results of the hazard and occupational exposure assessments have been integrated to characterise the risk of adverse effects to workers potentially exposed to *o*-DCB.

Results from the risk characterisation process provide the basis for health risk management strategies (i.e., methods to reduce exposure and/or increase worker awareness of potential hazards and safe handling of *o*-DCB).

15.1 Methodology

The risk to human health from exposure to *o*-DCB has been characterised using margin of exposure methodology commonly adopted in international assessments (EC, 1994; OECD, 1994).

For health effects caused by repeated or prolonged exposure, risk(s) have been characterised as follows:

1. Identification of the critical effect(s).

2. Identification of the most appropriate/reliable NOAEL (if available) for the critical effect(s).

3. Where appropriate, comparison of the NOAEL with the estimated human dose (EHD) or exposure, to provide a margin of exposure (MOE), that is:

$$MOE = \frac{NOAEL}{EHD}$$

   Where actual exposure monitoring data are unavailable or insufficient, the EHD may be determined using exposure assessment models, such as the UK EASE model.

4. Characterisation of risk, by evaluating whether the MOE indicates a concern for the human population under consideration.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. In deciding whether the MOE is of sufficient magnitude, expert judgement is required. Such judgements are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process, such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability.

15.2 Critical health effects

15.2.1 Acute effects

The critical effects from acute exposure to *o*-DCB vapour to humans are eye, respiratory and skin irritation.

No human deaths directly attributable to acute *o*-DCB toxicity have been reported.

15.2.2 Chronic effects

Effects from long-term, repeated (chronic) exposures are not well characterised in human populations. Therefore, the risk characterisation is based upon the critical health effect in animals. A number of repeat dose studies have been carried out on a limited number of animal species (by different routes of exposure). The critical chronic effect is hepatotoxicity based on consistently observed effects in animals.

Oral exposure

Chronic oral studies have been conducted with rats and mice. In the rat the critical endpoints are hepatic effects and haematological changes and with the mouse, mineralisation of muscle tissue in males. For the rat, the $NOAEL_{(oral)}$ was 60 mg/kg bw per day and a $LOAEL_{(oral)}$ of 100 mg/kg bw per day based on hepatotoxicity (increased liver weight). For the mouse, the $LOAEL_{(oral)}$ was 120 mg/kg bw per day based on increased renal tubular regeneration in males. The NOAEL was 60 mg/kg bw per day for males and a NOAEL could not be established for females. For the purposes of risk characterisation, the most appropriate $NOAEL_{(oral)}$ is 60 mg/kg bw per day.

Inhalation exposure

Inhalation data are limited to one 26-week study of rats and guinea pigs. For the rat, the $NOAEL_{(inhalation)}$ was 49 ppm (294 mg/m^3) and the $LOAEL_{(inhalation)}$ was 96 ppm (577 mg/m^3) based on decreased body weights in males. In the guinea pig, the NOAEL was 49 ppm (294 mg/m^3) while the $LOAEL_{(inhalation)}$ was 96 ppm (577 mg/m^3) based on increased spleen weights in males. However, the inhalation study is considered inadequate for risk characterisation because of limited reporting of the results.

Dermal exposure

There are no data on repeated dermal exposure.

15.3 Occupational health and safety risks

Occupational health risks may result from acute and/or chronic exposure to *o*-DCB via inhalation and dermal exposure.

15.3.1 Risk from physico-chemical hazards

Risks of fire and/or explosion during handling and use of *o*-DCB are low.

15.3.2 Acute health risks

Irritation to the respiratory system, eyes and skin may occur where ventilation is inadequate or direct contact with *o*-DCB occurs.

15.3.3 Chronic health risks

Despite the fact that exposures are not well characterised for occupational scenarios with potential exposure to *o*-DCB, either in Australia or overseas, information on known use profiles and data obtained from the UK EASE model have enabled preliminary estimates of risk to be made. Exposures have been assessed for formulation and end use scenarios. The critical effect is hepatotoxicity in rats and mice via the oral route. Therefore, margins of exposure (MOE) were calculated using the most reliable NOAEL, that is, the $NOAEL_{(oral)}$ of 60 mg/kg bw.

Formulation *o*-DCB products

The formulation of products containing *o*-DCB is typically a semi-closed process involving the pumping of *o*-DCB into a blending tank where it is combined with other chemicals at ambient temperature. The filling of product containers is also semi-enclosed and automated further reducing the extent of exposure. Consequently, it is assumed that dermal exposure is unlikely to contribute significantly to body burden during formulation processes. Respondents to the NICNAS industry survey indicated that local exhaust ventilation is used during formulation.

There are no monitoring data for Australian workplaces, however, the UK EASE model predicts air levels of *o*-DCB to be within the range of 0.5 to 3 ppm (0.3 to 2.0 mg/kg bw) under reported conditions of use. Thus MOE of 120 to 30 are expected. Taking into account the intermittent nature of the exposure (approximately 5 days per year) the risk of chronic effects is likely to be low.

End-users of *o*-DCB products

Workers engaged in cleaning items with *o*-DCB-containing products are likely to experience dermal exposure via the hands, depending on work practices, in addition to inhalation exposure. It is assumed that the products are used in a non-dispersive pattern of use with dilution ventilation. Consequently, the total body burden ranges from 7.2 to 34.1 mg/kg bw per day (Section 8.4) and MOE of 8.4 to 1.8 are expected. However, in practice the MOE is expected to be significantly larger due to the intermittent nature of the exposure, the small quantities involved and the dilute nature of the products (2.5 to 70% *o*-DCB w/v). Therefore, the risk of chronic effects for end-users is likely to be low.

It should be noted, however, that the presence of other organic solvents in several products may modify the dermal absorption and toxicity of *o*-DCB.

15.3.4 Uncertainties in the calculation of margins of exposure

A consideration of uncertainties in the risk characterisation process is necessary when discussing the acceptability and implications of estimated MOE. Examples of uncertainties inherent in the assessment of risk for *o*-DCB are as follows:

Inadequate data

- lack of exposure monitoring data;
- lack of representative worker exposure profiles (i.e., degree of worker exposure may vary from workplace to workplace);
- inadequate data on human health effects following chronic exposure; and
- lack of a NOAEL/LOAEL for hepatotoxic effects for prolonged inhalation of *o*-DCB in rats (or any other species).

Assumptions in the assessment process

- that absorption and bioavailability of *o*-DCB via inhalation is similar in humans and rats;
- that dose-response relationships are likely to be similar (on a ppm in air basis) in rats and humans;
- that 75% absorption via inhalation occurs in humans;
- that the theoretical dermal absorption rate is 0.7 mg/cm^2/hr; and
- that 100% absorption from ingestion occurs in rats.

16. Environmental Risk Characterisation

o-DCB is a volatile and water soluble chemical with its major industrial use in Australia being as a component of special industrial solvents for degreasing/decarbonising. Release is expected to be predominantly to the atmosphere although exposure to aquatic systems may also result. Monitoring data from around the world confirms the widespread transport of this chemical with substantial detection obtained in air, surface water and sediments. Limited monitoring in Australia has detected *o*-DCB in sewage treatment plant effluents in a small number of samples taken. Overall, the level of monitoring in Australia has not been substantial, and not all environmental compartments have been tested. However, given the lack of local manufacture, modest use rates and relatively well defined use patterns it is unlikely that ambient levels would be similar to overseas experience, and considerably lower levels in all environmental compartments could be expected.

16.1 Atmospheric risk

No experimental data on environmental organisms exposed through the gas phase are available, so it is not possible to conduct a hazard assessment for those residing in the atmosphere.

However, abiotic effects can be assessed. While direct photolysis is not considered likely, the atmospheric half-life is relatively short (expected to be <50 days) due to reaction with photochemically produced hydroxyl radicals. The chemical contains chlorine substituents which suggests it may have a potential effect on stratospheric ozone. However, with half-lives for migration to the stratosphere of 3 to 10 years (Bunce, 1994), this chemical would not be expected to persist long enough in the troposphere to be of concern.

Nonetheless, Webster *et al* (1998) state that transport times to the Arctic can be measured in weeks. Therefore, with a half-life of 24 to 38 days for *o*-DCB, it can be expected that the chemical could undergo significant transport in the atmosphere and may migrate to the poles. No measurements appear to be available from these regions.

For chemicals to be considered persistent organic pollutants (POPs), they need to meet certain criteria with respect to persistence, bioaccumulation and the potential for long range transport. *o*-DCB meets the criteria for persistence in air (half-life > 2 days), and therefore possibly the criterion for long range transport. Half-lives in soil and sediments need to be greater than six months, but there are no measurements in this area so no conclusions can be drawn. However, *o*-DCB fails the persistence in water criterion of two or six months, and also fails the bioaccumulation criterion (whole organism) of BCF>5000. Therefore, *o*-DCB can not be considered a POP.

o-DCB is not expected to pose an environmental risk through atmospheric exposure.

16.2 Aquatic risk

For releases to water the worst-case PEC in receiving waters from activities associated with product formulation has been estimated as 0.22 mg/L, which may occur 5 days each year. However, the PNEC for water has been estimated as 55 μg/L which is around 4 times lower than the (worst-case) PEC. Although use patterns of the chemical in Australia are unlikely to result in water concentrations of the magnitude of the PEC, this calculation indicates that the risks associated with use and disposal of products containing *o*-DCB are not trivial under all circumstances. All efforts should be made by formulators and end users of products containing *o*-DCB to minimise release to the water compartment. A small number of effluent samples monitored by Sydney Water detected *o*-DCB at levels as high as 64 ppb. Assuming 10:1 dilution in receiving waters, a surface water PEC of 6.4 ppb would result giving a PEC/PNEC <1.

It is to be noted that where surface waters were monitored in Australia, *o*-DCB was not detected at a detection limit of 0.5 μg/L.

Within sediments, evidence suggests *o*-DCB will be present at higher concentrations than receiving waters where exposed. However, no benthic tests are available in which to conduct a meaningful risk assessment for sediments. It is reasonable to assume that *o*-DCB associated with the sediments is in fact adsorbed and so not bioavailable. If this were not the case, the chemical would be expected to volatilise. Based on this, the risk to benthic organisms is anticipated to be low. However, anaerobic degradation studies indicate that *o*-DCB is resistant to biodegradation under the conditions expected in sediments. Additionally, the much higher levels found in sediments (see Section 7.2.2) than surface waters indicate possible accumulation in this compartment. Nevertheless, relatively little *o*-DCB (approximately 4 tonnes per annum throughout Australia) is expected to be released to water (hence to sediment), and this is not expected to be an area of concern.

Overall, the available evidence supports a conclusion of usually a low risk to the aquatic environment. However, large spills of the chemical into localised water courses as a result of accident or inappropriate disposal could cause adverse environmental effects – particularly to aquatic invertebrates such as *Daphnia*. Care should be exercised in disposing of the contaminated water.

16.3 Terrestrial risk

It is estimated that as a result of industrial activity, around 500 kg of *o*-DCB may be released to the soil compartment annually. This is expected to be in localised areas, but due to the volatility of the compound, and its expected mobility in the soil, it is not anticipated to reach high levels. However, some of the compound may be irreversibly bound to the soil, and hence may persist for extended periods. While it is not expected that concentrations are likely to be such to cause adverse environmental effects, any that do occur are likely to be isolated.

Some of the compound will be released into the sewer, and according to the Simple Treat Model of the European Commission, a maximum of 8 kg may become associated with sewage sludge throughout Australia each day. However, in the worst possible case the overall concentration in the sludge is not expected to exceed 0.3%, and once applied to soil this would be expected to be considerably reduced as a result of volatilisation. Consequently, there is no anticipated risk from *o*-DCB resulting from application of sewage sludge to soil.

It is expected that the use of *o*-DCB will present a low terrestrial environmental risk.

17. Public Health Risk Characterisation

There are no public health risks concerning domestic use of *o*-DCB, as no retail sales for the use of *o*-DCB (or of products containing *o*-DCB) were identified with the exception of one pharmaceutical product (not considered in this assessment).

Public health risks arising from industrial use will be limited to accidental spills and waste containing *o*-DCB. No reports on adverse effects following accidental spills or contact with industrial waste containing *o*-DCB have been received. The risk to public health from the continued use of *o*-DCB is likely to be low.

18. Risk Management

In this section, measures currently employed in the management of human health risks from occupational and consumer exposure to *o*-DCB are discussed. The information reviewed includes national and international standards, together with relevant guidance material, MSDS and labels.

Relevant information was provided by importers of *o*-DCB and formulators of products in which *o*-DCB is an ingredient.

The key elements in the management of risks discussed in this section include:

- workplace control measures;
- hazard communication (including training and education);
- monitoring and regulatory controls; and
- emergency procedures.

18.1 Workplace control measures

According to the NOHSC *National Model Regulations for the Control of Workplace Hazardou Substances* (NOHSC, 1994c), exposure to hazardous substances should be prevented or, where this is not practicable, adequately controlled, so as to minimise risks to health and safety. *o*-DCB is classified as a hazardous substance in accordance with the NOHSC Approved Criteria. The *National Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) lists the hierarchy of controls measures, in priority order, that should be implemented to eliminate or minimise exposure to hazardous substances. These are:

- elimination;
- substitution;
- isolation;
- engineering controls;
- safe work practices; and
- personal protective equipment.

Control measures are not mutually exclusive and effective control usually requires a combination of these measures. Particular attention needs to be given to control measures that minimise inhalation of *o*-DCB.

18.1.1 Elimination and substitution

Elimination is the removal of a chemical from a process and should be the first option considered when minimising risks to health.

In situations where it is not feasible or practicable to eliminate the use of a chemical, substitution should be considered. Substitution includes replacing the chemical with a less hazardous substance or the same substance in a less hazardous form.

18.1.2 Isolation

Isolation as a control measure aims to separate employees, as far as practicable, from the chemical hazard. This can be achieved by distance or enclosure.

The formulation of products containing *o*-DCB is a simple blending process that takes place under closed or semi-closed conditions. For example, at one company *o*-DCB is pumped from 250 kg steel drums into a stainless steel blending tank. The blended product is then gravity fed into product containers and capped.

18.1.3 Engineering controls

Of 4 formulators responding to a survey, all used exhaust ventilation during production. In addition, 2 formulators used fume extraction equipment coupled to the blending tanks.

18.1.4 Safe work practices

No safe work practices were identified that can be characterised as unique to *o*-DCB. Common safe work practices employed include storage in closed containers in well-ventilated areas and away from incompatible materials, and immediate clean-up of spills.

18.1.5 Personal protective equipment

Where other control measures are not practicable or adequate to control exposure, personal protective equipment should be used. In practice, personal protective equipment used for handling *o*-DCB includes the following:

- overalls;
- chemical-resistant apron;
- safety glasses; and
- gloves.

18.2 Emergency procedures

The availability of an emergency response plan to deal with unexpected releases of *o*-DCB, such as large spills, is good practice. All employees need to be trained in accident and emergency procedures.

All plans/procedures should be fully documented and available to all workers. Local emergency services should be consulted on the appropriateness of emergency procedures developed. No emergency response plans for *o*-DCB were submitted for assessment.

18.3 Hazard communication

18.3.1 Assessment of Material Safety Data Sheets

MSDS are the primary source of information for workers involved in the handling of chemical substances. Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (Model Regulations) (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers are obliged to provide an MSDS to their customers for all hazardous substances.

A sample MSDS for *o*-DCB, prepared in accordance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994d), is provided at Appendix 4. The sample MSDS, prepared from information obtained for the assessment of *o*-DCB, is for guidance purposes only. Under the National Model Regulations, manufactures and importers have the responsibility to compile their own MSDS and ensure that the information is up-to-date and accurate.

A total of 3 MSDS for technical grade and 1 MSDS for analytical grade *o*-DCB were received for assessment. The 4 MSDS were assessed against the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994d). The results of the MSDS assessment are presented in Table 17.

In general, the supplied MSDS were of adequate quality with appropriate information supplied. The major deficiencies were limited information on acute central nervous system and irritancy effects, contradictory first aid instructions and inadequate contact telephone numbers. Refer to Section 18.5.4 regarding discussion of appropriate safety phrases.

Table 17 - Findings of the MSDS assessment

Type of Information	Number of MSDS
Statement of hazardous nature	3/4
Product Identification	
Correct CAS number	3/4
Physical description/properties	4/4
Health Hazard Information	
Acute effects	
Harmful if swallowed	4/4
Ingestion effects (irritation to the mucus membranes of the mouth, pharynx, oesophagus and gastrointestinal tract)	2/4
Irritating to the eye	4/4
Irritating to the skin (degreasing effect, burning sensation, redness)	4/4
Irritating to the upper respiratory tract (mucosal irritation, coughing, dyspnea (difficulty in breathing))	3/4
Effects on central nervous system (headache, dizziness, confusion, incoordination, narcosis)	2/4
Chronic effects	
Liver effects – hepatomegaly, necrotic lesions	3/4
First Aid Advice	
Do not induce vomiting (risk of aspiration)	2/4
Do not give milk or oils	1/4
Advice to physician	4/4
If poisoning occurs, contact a doctor or Poisons Information Centre	3/4
Precautions For Use	
Correct value for TWA and STEL exposure standard	4/4
Control of vapours by adequate ventilation	4/4
Eye protection	4/4
Gloves protection	4/4
Safe Handling Information	
Statement of combustible nature	4/4
Statement that hydrogen chloride or phosgene form on combustion	4/4
Adequate information on extinguishing media (CO_2, foam, dry chemical, water spray)	4/4
Contact Point	
Contact person nominated	4/4
Direct phone number for contact person	1/4
Emergency telephone number provided	0/4

TWA = time-weighted average; STEL = short-term exposure limit.

18.3.2 Assessment of labels

Under the NOHSC Model Regulations (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers of industrial chemicals are obliged to provide labels in accordance with the NOHSC *Code of Practice for the Labelling of Workplace Substances* (Labelling Code) (NOHSC, 1994e).

The information needed on labels for containers with a capacity of more than 500 g of *o*-DCB include:

- signal word 'Hazardous';
- identification information
- product name
- chemical name
- risk phrases;
- directions for use (where appropriate);
- safety phrases;
- first aid instructions;
- emergency procedures;
- supplier details; and
- reference to MSDS.

12 labels were provided for assessment, comprising 3 labels for technical grade *o*-DCB and 9 for products containing *o*-DCB for industrial use. As all the products are intended for industrial use they should be labelled in accordance with the Labelling Code (NOHSC, 1994e). The findings of the label assessment are summarised in Table 18.

Table 18 - Findings of the label assessment

Information provided	Number of Labels
Signal word	
HAZARDOUS, POISON or TOXIC	11/12
Identification information	
Chemical name	11/12
Safety phrases	
Do not breathe vapour (S23)	11/12
First aid instructions (or similar statement)	
If poisoning occurs contact a doctor or Poisons Information Centre	11/12
In case of contact with eyes, rinse immediately with plenty of water for 15 minutes. Contact a doctor or Poisons Information Centre if irritation persists	11/12
In case of contact with skin, remove contaminated clothing, wash affected area immediately with soap and water. Contact a doctor or Poisons Information Centre if irritation persists	11/12
Do not induce vomiting	10/12
Do not give milk, oils or alcohol	2/12
Information on emergency procedures	2/12
Reference to MSDS	6/12

The major deficiencies of the labels supplied for assessment were inadequate first aid instructions and inadequate information on emergency procedures. Only half of the labels referred the reader to an MSDS for further information.

The risk phrases required prior to this Assessment (from the List of Designated Hazardous Substances [NOHSC: 10005(1994)]) were 'Harmful if swallowed' (R22) and 'Irritating to eyes, respiratory system and skin' (R36/37/38). Eight of the 12 labels contained these risk phrases.

18.3.3 Education and training

Guidelines for the induction and training of workers potentially exposed to hazardous substances are provided in the NOHSC Model Regulations (NOHSC, 1994c). Specifically, matters that need to be addressed for *o*-DCB include:

- the potential adverse health effects of *o*-DCB;
- specific protective equipment to be worn; and
- explanation of data contained in MSDS and labels.

No staff training material was provided for assessment.

18.4 Other regulatory controls

The following sections comprise regulations/standards promulgated with the aim of protecting workers from adverse exposures to *o*-DCB in Australia.

18.4.1 Atmospheric monitoring

Under the NOHSC Model Regulations (NOHSC, 1994c), employers are required to carry out an assessment of the workplace for all hazardous substances, the methodology of which is provided in the NOHSC *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* (NOHSC, 1994f). When the assessment indicates that the risk of exposure via inhalation is significant, atmospheric monitoring should be conducted to measure *o*-DCB levels in the workplace as a precursor to the implementation of suitable control measures to reduce exposure. Subsequent monitoring will be required to ensure that such measures are effective.

This assessment has been unable to identify any occupational monitoring efforts associated with the use of *o*-DCB.

18.4.2 Occupational exposure standard

The current national occupational exposure standard for *o*-DCB is 50 ppm (301 mg/m^3) peak limitation (NOHSC, 1995g). For peak limitations this is a maximum level of exposure. Monitoring should be conducted in the shortest analytical period and a single measurement should not exceed 15 minutes. This standard was adopted from the ACGIH, prior to 1992. The standard was set to prevent "serious irritation". The ACGIH adopted a new standard in 1992 of 25 ppm TWA and 50 ppm STEL. The basis of the standard was that the TWA of 25 ppm and STEL of 50 ppm should provide workers with a greater degree of protection against potential liver damage seen in laboratory animals at exposures of 50 ppm (Cameron *et al*., 1937; Hollingsworth *et al*., 1958) and against eye and upper respiratory irritation reported for workers exposed at 100 ppm (Hollingsworth *et al*., 1958; Elkins, 1959).

Overseas and Australian occupational exposure limits for *o*-DCB are listed in Table 19. Most countries have an 8 hour TWA of 50 ppm, with some more recent standards being 8 hour TWA of 25 ppm and STEL of 50 ppm.

The occupational risk characterisation (Section 15) identified the critical effect to be hepatotoxicity and the $NOAEL_{(oral)}$ was 60 mg/kg bw per day. Although inhalation is the more appropriate route of exposure, the inhalation study was considered inadequate. However, it should be noted that the $NOAEL_{(inhalation)}$ in the rat of 49 ppm is equivalent to approximately 57 mg/kg bw per day (for 6 hour exposure per day assuming 100% absorption, an average rat weight of 215 g and a respiratory rate of 0.16 m^3/day (NIOSH, 1990)). Hence the most relevant NOAEL for consideration in establishing an exposure standard for repeated exposure is 60 mg/kg bw per day (which is approximately equivalent to 50 ppm). As the current NOHSC standard is 50 ppm STEL, the National Commission should give consideration to reviewing the standard.

Table 19 - Occupational exposure limits for *o*-DCB

Country	TWA		STEL		Year adopted
	ppm	mg/m³	ppm	mg/m³	
Australia	-	-	50	301[a]	1990
Austria	50	301	-	-	
Belgium	50	301	-	-	
Denmark	50	301	-	-	
Finland[b]	50	301	75	451	
France			50	301	
Germany	50	301	-	-	1998
Ireland	-	-	50	301	
Japan	25	150	-	-	
Netherlands	25	150	50	301	
United Kingdom	-	-	50	301	
United States (ACGIH)	25	150	50	301	1992
(OSHA)			50	300	1993
Sweden	-	-	50	300	1984
Switzerland	50	300	100	600	

Based on ACGIH (1998). TWA = time-weighted average; STEL = short-term exposure level. [a] = Peak limitation; [b] = with skin notation.

18.4.3 Health surveillance

In accordance with NOHSC Model Regulations (NOHSC, 1994c), employers have a responsibility to provide health surveillance in those workplaces where the workplace assessment indicates that exposure to a hazardous substance may lead to an identifiable substance-related disease or adverse health effect. *o*-DCB is not listed in Schedule 3 (list of substances requiring health surveillance) and as such there are no formal requirements for health surveillance programs for exposed workers.

18.4.4 Standard for the Uniform Scheduling of Drugs and Poisons

o-DCB is listed (as *ortho*-dichlorobenzene) in Schedule 6 of the Drugs and Poisons Schedule (SUSDP, Australian Health Ministers' Advisory Council, 1997). Its availability is not restricted, but it must be labelled with the following safety directions (SD) and first aid instructions:

Safety directions:

- Avoid contact with eyes (SD1);

- Avoid contact with skin (SD4); and
- Avoid breathing dust (or) vapour (or) spray mist (SD8).

First aid instructions:

- If poisoning occurs, contact a doctor or Poisons Information Centre;
- If swallowed, do NOT induce vomiting. Give a glass of water;
- Avoid giving alcohol;
- If skin contact occurs, remove contaminated clothing and wash skin thoroughly; and
- If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

Based upon the toxicological profile of *o*-DCB, the continued scheduling of *o*-DCB in Schedule 6 of the "Standard for the Uniform Scheduling of Drugs and Poisons" is warranted. As there are no retail sales for the domestic use of *o*-DCB (or of products containing *o*-DCB) identified, there are no additional public health regulatory controls proposed.

18.4.5 Australian Code for the Transport of Dangerous Goods by Road and Rail

o-DCB is listed (as *o*-Dichlorobenzene) in the Australian Code for the Transport of Dangerous Goods (ADG) Code (FORS, 1998). It is classified as a 'Toxic' (Class 6.1) and assigned to Packing Group III. The substance is assigned to this classification/packaging group based on human experience rather than strict application of the UN criteria.

18.5 Environmental regulatory controls

o-DCB is toxic to certain aquatic species, and a worst-case calculation has indicated that in some situations release of the chemical may cause damage to the aquatic environment. There appears to be the potential for accumulation of *o*-DCB in sediments. No Australian data exists for this compartment, and levels should be monitored where possible to determine whether accumulation is a factor. This is particularly the case for soils which have been amended with sewer sludge.

No specific regulatory controls are envisaged, but it is suggested that State and Territory authorities be made aware of formulators and users of products containing *o*-DCB within their areas of jurisdiction. This will allow for appropriate monitoring activities if required.

18.5.1 Waste Disposal

o-DCB should be sent to licensed liquid waste disposal contractors where possible.

Because *o*-DCB is significantly toxic to certain aquatic species, care should be exercised in disposing of contaminated water.

19. Discussion and Conclusions

The manufacture of *o*-DCB does not occur in Australia. Approximately 10 tonnes/year are imported and formulated into industrial degreasers/decarbonisers and paint stripping products. A much larger volume (> 70 tonnes) of *o*-DCB is used in agricultural applications and not considered in this assessment. No products containing *o*-DCB were identified during this assessment which were available for use by the public.

19.1 Health effects

Animal studies have shown *o*-DCB to be of low acute toxicity by either the oral or inhalation route. Acute toxic effects reported in animals are hepatotoxicity in rats and mice. Limited data indicate that *o*-DCB is not corrosive but does cause irritation to the skin, eyes and upper respiratory tract in animals and humans.

The systemic health effects of *o*-DCB in humans are poorly characterised and based predominately on cases of accidental exposure. The effects reported from case studies include headache, fatigue, nausea, vertigo and skin, eye and respiratory irritation. Bone-marrow hyperplasia, acute haemolytic anaemia and several cases of leukaemia have been reported to be associated with *o*-DCB exposure. However, a causal relationship can not be established due to concomitant exposure to other chemicals and as other possible contributing factors were not discussed in the case reports.

There have been no adverse reports described in the literature for reproductive effects in humans or animals and investigations of the genotoxic effect of *o*-DCB using several test systems indicate that the chemical is unlikely to be genotoxic.

The potential of *o*-DCB to induce tumours has been investigated in the rat and mouse in one well-conducted study by the oral route. There was no evidence of *o*-DCB-induced tumour formation in either species during the two-year study. The NOAEL for non-neoplastic effects was 60 mg/kg bw while the LOAEL was 120 mg/kg bw due to increased renal tubular regeneration in male mice.

Based on the health effects observed in animals and humans, *o*-DCB has been previously classified as R22 (harmful if swallowed) and R36/37/38 (irritating to eyes/respiratory system/skin). This assessment concludes that the risk phrases should be R22 (harmful if swallowed) and R36/37/38 (irritating to eyes/respiratory system/skin).

The presence of small amounts of *p*-dichlorobenzene as a contaminant of industrial or technical grade *o*-DCB does not affect these conclusions.

19.2 Occupational health and safety

In 1998, at least 13 companies were involved in the handling or formulation of *o*-DCB in Australia. The formulation of *o*-DCB is generally semi-automated and usually involves a maximum of 3 workers per company. Production of formulated products is infrequent and the duration of exposure during such processes varied from 6 to 7 hours/day for

approximately 5 days/year. The products are used for degreasing/decarbonising and paint removal applications and generally used in small amounts on an intermittent basis.

The major route for occupational exposure to *o*-DCB is by inhalation with lesser exposure by dermal contact. Occupational exposure in Australia can occur during the formulation of products or from end-use of finished products containing *o*-DCB.

Based on current knowledge concerning the uses of *o*-DCB in Australia, it is concluded that, due to intermittent exposure and its relatively low toxicity, *o*-DCB is unlikely to pose a significant health risk to workers engaged in the formulation of products containing *o*-DCB or in the use of *o*-DCB products. As no monitoring data were available, occupational exposures were estimated. To further refine the exposures and risk characterisation, monitoring data would be of assistance.

An assessment of submitted MSDS and labels revealed a general compliance with the NOHSC requirements. The most common deficiencies for MSDS were generally limited information on human health effects, both acute and chronic, and conflicting first aid information. Three of 4 MSDS did not include an emergency contact telephone number.

19.3 Public health

From industrial uses, the only public exposure will be from accidents and spills thus the risk to the public will be low.

19.4 Environment

A significant percentage of *o*-DCB imported into Australia is expected to be released from use of products in the industrial domain, predominantly degreasing/ decarbonising solvents and paint strippers.

The chemical is biodegradable under aerobic conditions and relatively soluble in water. Its removal from aqueous systems occurs predominately by volatilisation, and at equilibrium, around 98% of the chemical would be expected to partition to the atmosphere where it will break down through reaction with hydroxyl radicals. Large discharges to relatively small water volumes could constitute a risk to the aquatic environment. However, concentrations likely to occur in aquatic systems are expected to be generally of low concern, and this expectation is supported by limited monitoring data from Australia and around the world. A relatively low aquatic risk is predicted.

Additionally, the relatively short atmospheric lifetime of *o*-DCB indicates concentrations will not occur at levels harmful to the atmosphere. While widespread transport within the troposphere is likely, the chemical is not expected to reach the stratosphere and therefore not expected to have an influence on global warming or ozone depletion.

19.5 Data gaps

Although the toxicity of *o*-DCB has generally been well investigated for a number of endpoints, the effects of *o*-DCB on fertility are currently unknown. Monitoring data for Australian workplaces where *o*-DCB is used would be of assistance in refining the risk characterisation.

para-Dichlorobenzene

Technical grade *o*-DCB can contain variable amounts of *p*-dichlorobenzene (typically about 15%) as an impurity. It is concluded that due to the relatively small quantities of *o*-DCB used in Australia and that the material is used intermittently in diluted form the *p*-dichlorobenzene is likely to present a low level of risk. An assessment of the health and environmental effects of *p*-DCB has been published by NICNAS [*para*-Dichlorobenzene, *Priority Existing Chemical No. 13 – Full Public Report*].

20. Recommendations

20.1 Hazard classification

The recommended classification for *o*-DCB based on the health hazard assessment of currently available data and in accordance with the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)], is:

R22 Harmful if swallowed
R36 Irritating to eyes
R37 Irritating to respiratory system
R38 Irritating to skin

Consistent with this classification, products containing *o*-DCB should be classified as follows:

Table 20 - Classification of *o*-DCB products

***o*-DCB concentration**	**Classification**	
20 - <25%	R36/37/38	Irritating to eye, respiratory system and skin.
≥ 25%	R22; R36/37/38	Harmful if swallowed; Irritating to eyes, respiratory system and skin.

The safety and first aid phrases agreed by NICNAS are:

S23 Do not breathe vapour
S60 This material and its container must be disposed of as hazardous waste.
S61 Avoid release to the environment. Refer to special instructions/safety data sheets.

20.2 Hazard communication

20.2.1 Material Safety Data Sheets

The NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994d) provides guidance for the preparation of MSDS.

It is recommended that Australian suppliers of *o*-DCB amend their MSDS taking into account the deficiencies identified by this assessment with particular attention being given to the following:

- inclusion of acute central nervous system effects;

- inclusion of appropriate first aid advice; and
- inclusion of an Australian emergency contact number.

A sample MSDS for *o*-DCB is provided at Appendix 3.

20.2.2 Occupational exposure standard

It is recommended to NOHSC that the occupational exposure standard for *o*-DCB be reviewed and that the following data be taken into consideration:

- respiratory irritation in humans at 100 ppm; and
- the $NOAEL_{(oral)}$ of 60 mg/kg bw and a $LOAEL_{(oral)}$ of 100 mg/kg bw for increases in absolute and relative liver weight.

20.3 Environment

It is recommended that *o*-DCB should be disposed of by licenced liquid waste contractors where possible.

In the event of a major spill involving *o*-DCB, the chemical should be prevented from entering drains and watercourses. Runoff from water spray, or water used to wash an area following spillage should be prevented from entering drains.

It is recommended that State and Territory authorities be made aware of formulators and users of products containing *o*-DCB within their areas of jurisdiction. This will allow for appropriate monitoring activities if required.

20.4 Public health

First Aid Instructions

During the course of this assessment, *o*-DCB was referred to the National Drugs and Poisons Schedule Committee (NDPSC) due to a concern that, as a volatile liquid, the First Aid Instruction (FAI) to induce vomiting may increase rather than decrease its toxic effects. Consequently, it was recommended that the NDPSC consider the proposal that FAI b. be replaced with FAI c.

That is, to delete:

b. If swallowed, and if more than 15 minutes from a hospital, induce vomiting, preferably using Ipecac Syrup APF.

and replace with:

c. If swallowed, do NOT induce vomiting. Give a glass of water.

The recommendation was subsequently adopted by the NDPSC in May 2000. Consequently, company MSDSs should reflect the amended first aid instructions.

As the agricultural and pharmaceutical uses of *o*-DCB were outside the scope of this assessment, it is recommended that the Priority Existing Chemical report on *o*-DCB be forwarded to the National Registration Authority for Agricultural and Veterinary Chemicals and the Therapeutic Goods Administration for their consideration.

21. Secondary Notification

Under Section 65 of the Act, the secondary notification of *o*-DCB may be required where an introducer (importer or manufacture) of *o*-DCB becomes aware of any circumstances which may warrant a reassessment of its hazards and risks. Specific circumstances include:

a) the function of *o*-DCB has changed, or is likely to change, significantly;

b) the amount of *o*-DCB introduced into Australia has increased, or is likely to increase significantly;

c) manufacture of *o*-DCB has begun in Australia; or

d) Additional information has become available to the introducers as to the adverse health and/or environmental effects of *o*-DCB.

The Director must be notified within 28 days of the introducer becoming aware of any of the above or other circumstances prescribed under Section 65 of the Act.

Appendix 1

List of *o*-DCB products

This appendix provides a list of industrial products containing *o*-DCB that were marketed in Australia in 1998/99 (Table 21). The list includes the trade name of each product, the use and the amount (in % w/w) of *o*-DCB in the product.

This list is not intended to be exhaustive but is considered to be representative of current *o*-DCB usage in Australia as indicated by information provided by formulators and distributors of *o*-DCB products. Formulations may have changed since the preparation of the list and some products may no longer be commercially available.

Table 21 - List of industrial products containing *o*-DCB

Product	Use[1]	*o*-DCB (% w/v)
ACC – HD	Diesel turbocharger cleaner	61
Air Cooler Cleaner	Diesel engine air-system cleaner	21
Applied 8-800	Paint remover	<10
Ardrox 2468	Paint remover[2]	<10
Ardrox 690	Decarboniser & paint remover[2,3]	70
Carbosolve 1	Decarboniser	60
Diesocarb	Decarboniser/degreaser	41
Hot Tank Cleaner	Decarboniser & paint remover	68
Odorid	Deodorant	43
Refusal	Paint remover	30 - 60
Technol	Degreaser	70

[1] For industrial use only; [2] for use by immersion; [3] recommended operating temperature 55 to 65°C.

Appendix 2

Formulae for Estimating Occupational Exposure

1. Formulae for exposure calculations

After exposure to a substance, the total body dose (D) is the sum of the doses resulting form absorption of vapour (D_v) and dermal absorption of liquid (D_l).

Thus, $D = D_v + D_l$ (equation 1)

As vapour absorption (D_v) comprises absorption across the lungs (D_{iv}) and dermal absorption of vapours (D_{dv}),

then $D_v = D_{iv} + D_{dv}$ (equation 2)

hence $D = (D_{iv} + D_{dv}) + D_{dl}$ (equation 3)

(i) Exposure to vapour

The daily dose due to absorption of vapour by inhalation is given by:

$$D = \frac{C \times R \times E \times B}{BW} \text{ mg/kg bw per day} \quad \text{(equation 4)}$$

where C = concentration of substance in air (mg/m^3),
R = inhalation rate (m^3/h),
E = exposure duration (h/day),
B = bioavailability of vapour across the lungs (1= 100%),
BW = average body weight of worker (kg).

(ii) Exposure to liquid

The daily dose due to exposure to liquid (D_{dl}) is given by:

$$D_{dl} = \frac{W \times S \times A \times E \times F}{BW} \text{ mg/kg bw per day} \quad \text{(equation 5)}$$

where W = weight fraction of substance in product, e.g. 0.1 for a 10% solution,
S = skin absorption rate (mg/cm^2/h)
A = skin surface area exposed (cm^2),
E = exposure duration (h/day),
F = skin contact time (as a fraction of exposure duration, e.g. 0.2 for 20% of time)
BW = average body weight of worker (kg).

2. Calculation of dermal absorption rate for humans (theoretical)

Based on the methodology of Potts and Guy (1992) the theoretical dermal absorption rate (AR) for humans can be calculated as follows:

(i) Permeability coefficient (Kp) for *o*-DCB

$$log\ Kp = -6.3 + (0.71 \times log\ K_{ow}) - 0.0061 \times MW \text{ (cm/sec)}$$

where $log\ Kp$ = permeability coefficient,
$log\ K_{ow}$ = octanol/water partition coefficient,
MW = molecular weight

so $log\ Kp = -6.3 + (0.71 \times \log 3.4) - 0.0061 \times 147.0$
$= -6.3+0.377-0.897$
$= -6.820$

and $Kp = 1.515 \times 10^{-7}$ cm/sec

or $= 9.09 \times 10^{-6}$ cm/min
or $= 5.5 \times 10^{-4}$ cm/hr

(ii) Dermal Absorption rate (AR) for *o*-DCB

$$AR = Kp \times dose\ concentration$$

at a concentration of 100% *o*-DCB (1.3056 g/cm^3 at 20^{o}C)

$$AR = 5.5 \times 10^{-4} \times 1.3056$$
$= 7.2 \times 10^{-4}$ g/cm^2/hr

or $= 0.7$ mg/cm^2/hr

Table 22 - Skin surface area values

Skin Location	Area (cm^2)
Hands	840
Forearms	1140
Upper arms	1430
Arms	2280
Head	1180

Table 22 lists the skin surface area values, as standard estimates, for adult males (U.S. EPA, 1985).

3. Exposure Calculations for Occupational Scenarios

Calculations for occupational end-use exposure scenarios are calculated below, based on the above formulae.

Inhalation exposure

Standard risk assessment values were used for all exposure calculations. A body weight of 70 kg and an inhalation rate of 1.3 m^3/h were used for the physiological parameters. The inhalation rate is that determined for occupational exposure during light work activities (OECD, 1993; European Commission, 1994). As no data were available for the bioavailability of *o*-DCB across the lungs, calculations were performed making the standard assumption that 75% of the compound is bioavailable. A standard 8 hour working day was assumed.

Table 23 - Inhalation exposure values

***o*-DCB (ppm)**	0.1	0.3	0.5	3	10	50
Inhaled dose (mg/kg bw per day)	0.1	0.2	0.3	2.0	6.7	33.6

Dermal exposure

Dermal exposure is only estimated for end-use scenarios because it is unlikely to occur during formulation. For the dermal exposure calculation it has been assumed that a product comprising 70% (w/v) *o*-DCB is used for 8 hours per day. Incidental skin contact is likely during end-use, where F = 0.01. It is assumed that the total surface area of both hands is exposed to *o*-DCB.

$$D_{dl} = \frac{0.7 \times 0.7 \text{ mg/cm}^2\text{/h} \times 840 \text{ cm}^2 \times 8 \text{ h} \times 0.01}{70 \text{ kg}} \text{ mg/kg/day}$$

$$= 0.47 \text{ mg/kg/day}$$

Appendix 3

Sample Material Safety Data Sheet for *ortho*-Dichlorobenzene

Date of issue	07 October 2015	Page 1	of Total 6

***ortho*-Dichlorobenzene is classified as Hazardous according to the National Occupational health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)].**

Company details

Company name

Address

State Postcode

Telephone number Emergency telephone number

Facsimile number Telex number

Identification

Product name
1,2-Dichlorobenzene

Other names
ortho-dichlorobenzene; *o*-dichlorobenzene; *o*-DCB;

Manufacturer's product code

UN number
1591

Dangerous goods class and subsidiary risk
6.1 Toxic Substances

Hazchem code
2Z

Poisons Schedule number
Schedule 6

Use
Degreaser; decarboniser; paint stripper; industrial odour control.

Physical description and properties

Appearance
Clear or pale yellow liquid with penetrating aromatic odour.

Melting point
-16.7°C (1.94°F)

Boiling point
180°C (356°F)

Vapour pressure
1.96 hPa at 25°C

Specific gravity
1.3 (water = 1)

Flashpoint
66°C (150°F) (closed cup)

Flammability limits
Upper 9.2% Lower 2.2%

Solubility in water
155.8 mg/l (at 25°C)

Other properties

Odour: Pleasant aromatic odour
Vapour Density: 5.05 g/cm^3 (at 20°C)
Autoignition temperature: 648°C

Ingredients

Chemical Name: 1,2-dichlorobenzene **CAS Number: 95-50-1** **Proportion:**

Health hazard information

HEALTH EFFECTS

Acute

Inhalation: Vapour may be irritating to the upper respiratory tract. May cause headache, nausea, vertigo, mucosal irritation, coughing and breathing difficulties. High doses may cause depression of the central nervous system.

Skin: May cause burning sensation with redness, blistering and discolouration of skin.

Eye: Vapour may be irritating to the eyes.

Swallowed: Symptoms may include, headache, nausea, vomiting and central nervous system depression.

Chronic

Skin: No evidence of sensitisation in animals or humans.

Systemic: Has been shown to cause liver damage in animals.

FIRST AID

Inhalation: Remove from exposure to fresh air immediately. Victim may appear intoxicated. Keep warm and at rest until fully recovered. If breathing is laboured and patient cyanotic (bluish colouration of skin and mucus membranes) give oxygen. If the victim is not breathing, clear airway and apply artificial respiration. Call a doctor.

Skin: Remove contaminated clothing. Wash affected area immediately with copious quantities of water and non-abrasive soap (at least 15 minutes). Seek medical attention if irritation develops.

Eye: Irrigate immediately with copious quantities of water or normal saline for at least 15 minutes. Seek medical attention.

Swallowed: Do not give anything by mouth if victim is losing consciousness, unconscious or convulsing. Do not induce vomiting, give a glass of water. Do not give milk or oils. Seek medical attention.

Alcohol consumption may accelerate the onset and severity of symptoms caused by ingestion of *o*-DCB.

Contact a *Poisons Information Centre* for further information.

ADVICE TO DOCTOR

Treatment is symptomatic and supportive. No specific antidote.

Precautions for use

EXPOSURE STANDARD

Australian Exposure Standard: 50 ppm (301 mg/m^3) STEL

ENGINEERING CONTROLS

Control airborne concentrations below the exposure standard.

Use only with adequate ventilation.

Local exhaust ventilation may be necessary for some operations, e.g. open process equipment.

PERSONAL PROTECTION

Wear overalls, rubber footwear, safety glasses and gloves in accordance with manufacturer's recommendations. A respirator with full-face protection may be required where engineering controls are inadequate, such as during clean-up of large spills.

An emergency eye wash station should be available in the immediate work area.

Self contained breathing apparatus (SCBA) and complete protective clothing should be worn during fire fighting.

FLAMMABILITY

Combustible liquid.

Safe handling information

STORAGE and TRANSPORT

Regulated dangerous goods. Store in a cool, dry place away from naked flame and sources of ignition. Keep container closed. Ensure adequate ventilation.

Store away from incompatible materials (see FIRE/EXPLOSION HAZARD).

SPILLS and DISPOSAL

Evacuate unprotected personnel from spillage area.

Shut off all possible sources of ignition following spillage.

Increase ventilation in contaminated area. Use water spray to reduce vapours.

Clean-up personnel should wear self-contained breathing apparatus and full protective clothing.

Large spills should be contained by the use of sand or other non-combustible absorbent material. The contaminated material should subsequently be transferred to suitable containers for disposal in accordance with all Local, State and Federal regulations at an approved waste disposal facility.

In the event of a major spill, prevent chemical from entering drains and watercourses.

Runoff from water spray, or water used to wash area following spillage should be prevented from entering drains.

FIRE/EXPLOSION HAZARD

Incompatible materials: incompatible with aluminium and aluminium alloys.

Vapour is heavier than air.

Toxic and irritant vapours and gases, including oxides of carbon, hydrogen chloride and phosgene, may be formed on combustion.

Fire fighting:

- wear SCBA and complete protective clothing.
- Water fog, foam, alcohol foam, carbon dioxide or dry chemical extinguishing media may be used.

Other information

Animal toxicity data:

Acute (inhalation) LD_{50} (4hr) > 5.7 mg/litre (rat).

Acute (oral) LD_{50}: 1516 to 2138 mg/kg bw (rat).

Acute (dermal) LD_{50}: Not available.

Developmental data: Negative results.

Mutagenic data: Negative results for mutagenicity by several test systems.

Environmental data:

Acute:

Daphnia magna	48h EC_{50}	2.2-2.4 mg/L
Ceriodapnia dubia	48h EC_{50}	0.66 mg/L
Brachydanio rerio (Zebra fish)	96h EC_{50}	5.2 mg/L
Oncorhynchus mykiss (Rainbow trout)	96h EC_{50}	1.6 mg/L
Lepomis macrochirus (Bluegill sunfish)	96h EC_{50}	5.6-27 mg/L
Pimephales promelas (Fathead minnow)	96h EC_{50}	9.5-57 mg/L

Further information:

National Industrial Chemicals Notification and Assessment Scheme, Full Public Report - Priority Existing Chemical No. 14 - *ortho*-Dichlorobenzene, NOHSC, 2001.

Contact point

Contact name | Telephone number

Position title

Address

State | Postcode | Country

References

Abernathy, S., Bobra, AM., Shiu, WY., Wells, PG. and Mackay, D. (1986) Acute lethal toxicity of hydrocarbon and chlorinated hydrocarbons to two planktonic crustaceans: the key role of organism-water partitioning. Aquat Toxicol, **8**:163-174.

Ahmad, N., Benoit, D., Brooke, L., Call, D., Carlson, A., DeFoe, D., Huot, J., Morairity, A. and Richter J. (1984) Aquatic toxicity tests to characterise the hazard of volatile organic chemicals in water: a toxicity data summary – parts I and II. EAP 600/3-84-009. Duluth, MN, US EPA Environmental Research Lab.:103p (cited in US EPA, 2000).

Allis, JW., Simmons, JE., House, DE., Robinson, BL. and Berman, E. (1992) The differential hepatotoxicity and cytochrome P450 responses of Fisher-344 rats to the three isomers of dichlorobenzene. J Biochem Toxicol, **7**:257-264.

Amoore, JE. and Hautala, E. (1983) Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol **3**:272-290.

Anderson, KJ., Leighty, EG. and Takahashi, MT. (1972) Evaluation of herbicides for possible mutagenic properties. J Agr Food Chem, **20**:649-656.

APHA (1995) Standard methods for the examination of water and waste water. 17th ed. Washington, DC, American Public Health Association.

Azouz, WM., Parke, DV. and Williams, RT. (1955) Studies in detoxication. 62. The metabolism of halogenobenzenes. Ortho- and para-dichlorobenzenes. Biochem J, **59**:410-415.

Ballschmiter K and Scholz C. (1980) Mikrobieller Abbau von Chlorierten Aromaten: VI. Bildung von Dichlorphenolen und Dichlorbrenzkatechinen aus Dichlorbenzolen im mikromolarer Lösung durch *Pseudomonas sp*. Chemosphere **9**:457-467 (cited in BUA, 1990).

Ban, M., Hettich, D., Goutet, M. and Binet, S. (1998) Serum-borne factor(s) of 1,1-dichloroethylene and 1,2-dichlorobenzene-treated mice inhibited in vitro antibody forming cell response and natural killer cell activity. Toxicol Lett, **94**:93-101.

Banerjee, S., Yalkowsky, SH., and Valvani, SC. (1980) Water solubility and octanol/water partition coefficients of organics. Limitations of the solubility-partition coefficient correlation. Environ Sci Technol, **14**:1227-1229.

Beck, U (1986) Nucleus-chlorinated aromatic hydrocarbons, in Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., Weinheim ,VCH Verlagsgesellschaft mbH.

Belfroid A., Seinen W., van Gestel K. and Hermens J. (1993) The acute toxicity of chlorobenzenes for earthworms (*Eisenia andrei*) in different exposure systems. Chemosphere, **26**:2265-2277.

Bioassay Systems (1983) Nine reports regarding the effects of various chlorinated benzenes – with cover letter dated 051183. EPA/OTS Doc. No. 40-8320545, 1-19, 126-148, 161-181 (cited in BUA, 1990).

Bioassay Systems (1984) In vitro gene mutation assay (HGPRT locus) in cultured Chinese hamster ovary cells on ortho-dichlorobenzene. EPA/OTS Doc. No. 40-8420664, 1-23 (cited in BUA, 1990).

Bobra, A., Shiu, WY. and Mackay, D. (1985) Quantitative structure activity relationships for the acute toxicity of chlorobenzenes to *Daphnia magna*. Environ Toxicol Chem, **4**:297-305.

Bogaards, JJP., Van Ommen, B., Wolf, CR. and Van Bladeren, PJ. (1995) Human cytochrome P450 enzyme selectivities in the oxidation of chlorinated benzenes. Toxicol Appl Pharmacol, **132**:44-52.

Bomhard, E. *et al*. (1996) Unpublished report No. 25124, Bayer AG, 29.05.1996.

Bouwer, EJ. (1985) Secondary utilisation of trace halogenated organic compounds in biofilms. Environ Prog, **4**:43-46 (cited in BUA, 1990).

Bouwer, EJ. and McCarty, PL (1984) Organic contaminant behaviour during rapid infiltration of secondary wastewater at the Phoenix 23rd Avenue Project. Water Res, **18**:463-472.

Bouwer, EJ., McCarty, PL. and Lance, JC. (1981) Trace organic behaviour in soil columns during rapid infiltration of secondary wastewater. Water Res, **15**:151-159.

Bouwer, EJ., McCarty, PL. and Rice, RC. (1982) Removal of trace chlorinated organic compounds by activated carbon and fixed film bacteria. Environ Sci Technol, **16**:836-843.

Brondeau, MT., Bonnet, P., Guenier, JP., Simon, P. and De Ceaurriz, J. (1990) Adrenal-dependent leucopenia after short term exposure to various airborne irritants in rats. J Appl Toxicol, **10**:83-86.

Browning, E. (1937) Toxicity of industrial organic solvents: summaries of published work, Medical Research Council, Industrial Health Research Board No. 80, London, His Majesty's Stationary Office, 212-215 (cited in Hollingsworth *et al.*, 1958).

BUA (1990) *o*-Dichlorobenzene (1,2-Dichlorobenzene), BUA Report 53 (September 1990), Wissenschaftliche Verlagsgesellschaft Stuttgart, S. Hirzel, 1993.

Buccafusco, RJ., Ells, SJ. and LeBlanc, GA. (1981) Acute toxicity of priority pollutants to Bluegill Sunfish (*Lepomis macrochirus*). Bull Environ Contam Toxicol, **26**:446-452.

Bunce, N (1994) Environmental chemistry. Second edition. Winnipeg, Canada, Wuerz Publishing Ltd.

Bunce, N., Landers, J., Langshaw, J. and Nakai, J. (1987). Laboratory experiments to assess the importance of photochemical transformation during the atmospheric transport of chlorinated aromatic pollutants. 80th Annual Meeting of APCA, June 21-26, 1987, New York (cited in Government of Canada, 1993).

Calamari, D. (1993). Chemical exposure predictions. USA, Lewis Publishers.

Calamari, D., Galassi, S., Setti, F. and Vighi, M. (1983) Toxicity of selected chlorobenzenes to aquatic organisms. Chemosphere, **12**:253-262.

Call, D., Brooke, L., Ahmad, N. and Richter, J. (1983). Toxicity and metabolism studies with EPA priority pollutants and related chemicals in freshwater organisms. EPA 600/3-83-095. Duluth, MN, US EPA:120 p (cited in US EPA, 2000).

Cameron, GR., Thomas, JC., Ashmore, SA., Buchan, JL., Warren, EH. and McKenny-Hughes, AW. (1937) The toxicity of certain chlorine derivatives of benzene, with special reference to *o*-dichlorobenzene. J Path Bacteriol, **44**:281-295.

Canton, JH. *et al.* (1985) Toxicity, biodegradability and accumulation of a number of Cl/N containing compounds for classification and establishing water quality criteria. Regul Toxicol Pharmacol, **5**:123-131.

Carswell, TS. (1928) Physical properties of *o*-dichlorobenzene. Ind Eng Chem, **20**: 728.

Casserly, DM., Davis, EM., Downs, TD. and Guthrie, RK. (1983) Sorption of organics by *Selenastrum capricornutum*. Water Res. **17**:1591-1594.

Chapman, P., Downie, J., Maynard, A. and Taylor, L. Coal and deodorizer residues in marine sediments – contaminants or pollutants?. In *Environmental Toxicology and Chemistry*. Vol 15, No. 5. pp 638-642. SETAC, 1996.

Chiou, CT., Porter, PE. and Schmedding, DW. (9183) Partition equilibria of nonionic compounds between soil organic matter and water. Environ Sci Technol, **17**:227-231.

Cobb, HD., Atherton, R. and Olive, W. (1974) An ecological approach to the problem of biodegradation of phenol wastes. Springfield, Va, National Technical Information Service (NTIS) (Report No. AFOSR-TR-75-0070), pp 1-18 (cited in BUA, 1990).

Conkle, JP., Camp, BJ., Welch, BE. (1975) Trace composition of human respiratory gas. Arch Environ Health, **30**:290-295.

Connell D. 1990. Bioaccumulation of Xenobiotic Compounds. Boca Raton, CRC Press.

Connor, TH., Thesis, JC., Hanna, HA, Monteith, DK. and Matney, TS. (1985) Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol Lett, **25**:33-40.

Curry, HL. and Gilkerson, WR. (1957) The temperature dependence of ion pair dissociation constants. I. *o*-Dichlorobenzene. J Am Chem Soc, **70**:4021-4023.

Curtis, GP., Roberts, PV. and Reinhard, M. (1986) A natural gradient experiment on solute transport in a sand aquifer. 4. Sorption of organic solutes and its influence on mobility. Water Resour. Res. **22**:907-916.

Curtis M., Copeland, T. and Wart, C. (1979) Acute toxicity of 12 industrial chemicals to freshwater and saltwater organisms. Water Res. 13:137-141 (cited in US EPA, 2000).

Curtis, MW. and Ward, CH. (1981) Aquatic toxicity of forty industrial chemicals: testing in support of hazardous substance spill regulation. J Hydrol **51**:359-367.

Davis, H. and Hidu, H. (1969) Effects of pesticides on embryonic development of clams and oysters and on survival and growth of the larvae. Fish Bull, **67**:393-404 (cited in US EPA, 2000).

Davis, EM., Moore, JD., Frieze, TR. and Scherm, M. (1983) Efficiency of waste stabilisation ponds in removing toxic organics. Water Resour Symp, **10** (Toxic Mater.: Methods Control):95-107 (cited in BUA, 1990).

Dawson, G., Jennings, A., Drozdowski, D. and Rider, E. (1977) The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J Hazard Mater, **1**:303-318 (cited in US EPA, 2000).

De Ceaurriz, JC., Micillino, JC., Bonnet, P. and Guenier, JP. (1981) Sensory irritation caused by various industrial airborne chemicals. Toxicol Lett, **9**:137-143.

Deitsch, JJ. and Smith, JA. (1999) Sorption and desorption rate comparisons for 1,2-dichlorobenzene to a peat soil. Environ Toxicol Chem,**18**:1701-1707.

DeMarini, DM. and Brooks, HG. (1992) Induction by phage lambda by chlorinated organics: detection of some single-species/single-site carcinogens. Environ Mol Mutagen, **19**:98-111.

Demirjian, YA., Joshi, AM. and Westman, TR. (1987) Fate of organic compounds in land application of contaminated municipal sludge. J Water Pollut Control Fed, **59**:32-38 (cited in BUA, 1990).

Den Besten, C., Vet, JJR., Besselink, HT., Kiel, GS., Van Berkel, BJM., Beems, R. and Van Bladeren, PJ. (1991) The liver, kidney, and thyroid of chlorinated benzenes. Toxicol Appl Pharmacol, **111**:69-81.

Den Besten, C., Ellenbroek, M., Van Der Ree, MAE., Rietjens, IMCM. and Van Bladeren, PJ. (1992) The involvement of primary and secondary metabolism in the covalent binding of 1,2- and 1,4-dichlorobenzenes. Chem Biol Interactions, **84**:259-275.

Downing, JG. (1939) Dermatitis from orthodichlorobenzene. J Am Med Assoc, **112**:1457 (cited in Hollingsworth *et al*., 1958).

Dreisbach, RR. and Shrader, SA. (1949) Vapour pressure-temperature data on some organic compounds. Ind. Eng. Chem. **41**, pp 2879-2880.

Dura, G., Krasovski, GN., Zholdakova, ZI. and Mayer, G. (1985) Prediction of toxicity using quantitative structure-activity relationship. Arch Toxicol Suppl **8**:481-487.

Environment Australia (1998) Sources of dioxins and furans in Australia: air emissions. Canberra, AGPS.

EHC (1991) IPCS Environmental Health Criteria 128: Chlorobenzenes other than hexachlorobenzene. Geneva, WHO.

Elkins, H. B. (1959) The chemistry of industrial toxicology. 2nd ed. New York, John Wiley and Sons Inc.

EPA (1985) Health assessment document for chlorinated benzenes. Final Report. EPA/600/8-84/0015F. Order No. PB85-150332, National Technical Information Service, Springfield, Va., 1-1- pp 14-77 (cited in BUA, 1990).

EPA (1988) Method T014-1. Compendium of methods for the determination of toxic organic compounds in ambient air. U. S. Department of Commerce. EPA 600/4-89/017.

European Commission (1994) Technical Guidance Documents in support of the Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances in accordance with Council Regulation (EEC) No 793/93. Luxembourg, European Commission.

European Commission (1996), Technical guidance document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances, part II.

Fisher, R., Barr, J., Zukoski, CF., Putnam, CW., Sipes, IG., Gandolfi, AJ. and Brendel, K. (1991) *In-vitro* hepatotoxicity of three dichlorobenzene isomers in human liver slices. Human Exper Toxicol **10**:357-363.

Fisher, RL., Hasal, SJ., Sipes, IG., Gandolfi, AJ. and Brendel, K. (1995) Comparative metabolism and toxicity of dichlorobenzenes in Sprague-Dawley, Fischer-344 and human liver slices. Human Expt Toxicol, **14**:414-421.

Gadrat, J., Monnier, J., Ribert, A. and Bourse, R. (1962) Anémie hémolytique aiguë chez une ouvrière d'une teinturerie exposée aux inhalations de chlorobenzènes. Arch Mal Prof, **23**:710-714.

Garrison, AW. (1969) Analytical studies of textile wastes. Am Chem Soc (Div Water, Air Waste Chem) **9**:51-59.

Girard, R., Tolot, F., Martin, P. And Bourret, J. (1969) Hémopathies graves et exposition à des dérivés chlorés du benzène (à propos de 7 cas). J Med Lyon, **50**:771-773

Gaines, TB. and Linder, RE. (1986) Acute toxicity of pesticides in adult and weanling rats. Fundam Appl Toxicol, **7**:299-308.

Goltz, RD., Badalamenti, S. and Ogg, RN. (1983) Treatability of hazardous waste leachate at publicly owned treatment works. Natl. Conf. Manage. Uncontrolled Hazard Waste Sites, Hazard Mater. Control Res. Inst. : Silver Spring, Md. pp 202-208 (cited in BUA, 1990).

Government of Canada, Environment Canada, Health Canada (1993) Canada Environment Protection Act. Priority Substances List Assessment Report. 1,2-Dichlorobenzene. Canada Communication Group.

Gunawardhana, L, Mobley, SA. and Sipes, IG. (1993) Modulation of 1,2-dichlorobenzene hepatotoxicity in the Fisher-344 rat by a scavenger of superoxide anions and inhibition of Kupffer cells. Toxicol Appl Pharmacol, **119**:205-213.

Hardy, CJ. and Jackson, GC. (1987) Huntingdon Research Centre Ltd., Report No. RNP 274/87580.

Haigler, BE., Nishino, SF. and Spain, JC. (1988) Degradation of 1,2-dichlorobenzene by a *Pseudomonas sp*. Appl Environ Microbiol, **54**:294-301 (cited in BUA, 1990).

Hasmall, SC. and Roberts, RA. (1997b) Hepatic ploidy, nuclearity, and distribution of DNA synthesis: a comparison of nongenotoxic hepatocarcinogens with noncarcinogenic liver mitogens. Toxicol Appl Pharmacol, **144**:287-293.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. and Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. Environ Mutagen, **5** (Suppl 1):3-142.

Hayes, WC., Hanley, TR., Jr., Gushow, TS., Johnson, KA., and John, JA. (1985) Teratogenic potential of inhaled dichlorobenzenes in rats and rabbits. Fundamental & Appl Toxicol, **5**:190-202.

Heitmuller, P., Hollister, T. and Parrish, P. (1981) Acute toxicity of 54 industrial chemicals to Sheepshead Minnows (*Cyprinodon variegatus*). Bull Environ Contam Toxicol, **27**:596-604 (cited in US EPA, 2000).

Herbold, B. (1988) Unpublished Report No. 16902, Bayer AG, 14.7.1988.

Hermens, J., Canton, H., Jenssen, P. and De Jong, R. (1984) Quantitave structure activity relationships and toxicity studies of mixtures of chemicals with anaesthetic potency: acute lethal and sublethal toxicity to *Daphnia magna*. Aquat Toxicol **5**:143-154.

Herr, DW. and Boyes, WK. (1997) A comparision of the acute neuroactive effects of dichloromethane, 1,3-dichloropropane, and 1,2-dichlorobenzene on rat flash evoked potentials (FEPs). Fundamen Appl Toxicol, **35**:31-48

Herren-Freund, SL. and Pereira, MA. (1986) Carcinogenicity of by-products of disinfection in mouse and rat liver. Environ Health Perspect, **69**:59-65.

Hissink, AM., Van Ommen, B. and Van Bladeren, PJ. (1996a) Dose-dependent kinetics and metabolism of 1,2-dichlorobenzene in rat: effect of pretreatment with phenobarbital. Xenobiotica, **26**:89-105.

Hissink, AM., Oudshoorn, MJ., Van Ommen, B., Haenen, GRMM. and Van Bladeren, PJ. (1996b) Differences in cytochrome P450-mediated biotransformation of 1,2-dichlorobenzene by rat and man: implications for human risk assessment. Chem Res Toxicol **9**:1249-1256.

Hissink, AM., Van Ommen, B. and Van Bladeren, PJ. (1996c) Species and strain differences in the hepatic cytochrome P450-mediated biotransformation of 1,2- and 1,4-dichlorobenzene; implications for human risk assessment. Hum Exp Toxicol, **15**:935 (abstract).

Hissink, AM., Van Ommen, B., Krüse, J. and Van Bladeren, PJ. (1997) A physiologically based pharmacokinetic (PB-PK) model for 1,2-dichlorobenzene linked to two possible parameters of toxicity. Toxicol Appl Pharmacol, **145**:301-310.

Hoechst (1985) “Ergenbis der Abwasserbiologischen von o-Dichlorobenzol”; Bericht Nr. OEK W85-169 vom 05.06.1985., Hoechst AG, Frankfurt/Main, 1985 (cited in BUA, 1990).

Hofler, F., Schneider, J. and Mockel, HJ. (1986) Analytical investigations on the composition of gaseous effluents from a garbage dump. Fresenius Z Anal Chem, **325**:365-368 (cited in BUA, 1990).

Hoglen, NC., Younis, HS., Hartly, DP., Gunawardhana, L., Lantz, RC. and Sipes, IG. (1998) 1,2-dichlorobenzene-induced lipid peroxidation in male Fisher 344 rats is Kupffer cell dependent. Toxiocol Sci, **46**:376-385.

Hollingsworth, RL., Rowe, VK., Oyen, F., Torkelson, TR. and Adams, EM. (1958) Toxicity of *o*-dichlorobenzene: studies on animals and industrial experience. Arch. Ind. Health, **17**:180-187.

Howard P (1989) Volume 1. Large production and priority pollutants. Handbook of environmental fate and exposure data for organic chemicals. Lewis Publishers.

Howard P, Boethling R, Jarvis W, Meylan W, Michalenko E. (1991) Handbook of environmental degradation rates. Lewis Publishers Inc.

IUCLID (1996) International Uniform Chemical Information Database (IUCLID) Data Sheet. 1,2-dichlorobenzene. In: European Chemicals Bureau, IUCLID International Uniform Chemical Information Database, Existing Chemicals, Edition 1-1996 CD-ROM. Ispra, Italy, European Commission.

Junk, GA. and Richard, JJ. (1984) Vapour phase sampling of organic compounds. In: Keith, L.H. ed. Identification and analysis of organic pollutants in air. Boston, Butterworth, pp 61-78.

Kaiser, KLE. and Ribo, JM. (1985) QSAR of toxicity of chlorinated aromatic compounds. Pharmacochem. Libr., **8** (QSAR Toxicol. Xenobiochem.) pp 27-38 (cited in BUA, 1990).

Kato, Y. and Kimura, R. (1997) Role of 3,4-dichlorophenyl methyl sulfone, a metabolite of *o*-dichlorobenzene, in the changes in hepatic microsomal drug-metabolizing enzymes caused by *o*-dichlorobenzene administration in rats. Toxicol Appl Pharmacol, **145**:277-284.

Kincannon, DF., Stover, EL., Nichols, V. and Medley, D. (1983b) Removal mechanisms for toxic priority pollutants. J Water Pollut Cont Fed, **55**:157-163 (cited in BUA, 1990).

Kincannon, DF., Weinert, A. Paddor, R. and Stover, EL. (1983a) Predicting treatability of multiple organic priority pollutant wastewaters from single pollutant treatability studies. Proc Ind Waste Conf, **37:**641-650 (cited in BUA, 1990).

Kirk, PWW., Rogers, HR. and Lester, JN. (1989) The fate of chlorobenzenes and permethrins during anaerobic sewage sludge digestion. Chemosphere, **18**:1771-1784.

Kitchin, KT., Brown, JL. and Kulkarni, AP. (1992) Predictive assay for rodent carcinogenicity using in vivo biochemical parameters: operational characteristics and complementarity. Mut Res, **266**:253-272.

Knezovich, JP. and Harrison, FL. (1988) The bioavailability of sediment sorbed chlorobenzenes to larvae of the midge *Chironomus decorus*. Ecotoxicol Environ Saf, **15**:226-241.

Koch, R., *et al*., (1985) Z gesamte Hyg, 31:524-526 (cited in IUCLID, 1996).

Korhonen, IOO. (1983) Glass-capillary gas chromatography of chlorobenzenes on SE-30 and Carbowax 20M columns. Simultaneous determinations of chlorobenzenes and chlorophenols. Chromatographia, **17**:195-199.

Kuhn, E., Colberg, P., Schnoor, J., Wanner, O., Aehnder, A. and Schwarzenbach, R. (1985) Microbial transformation of substituted benzenes during infiltration of river water to groundwater: laboratory column studies. Environ Sci Technol, **19**:961-968 (cited in BUA, 1990).

Kuhn, R. and Pattard, M. (1990) Results of the harmful effects of water pollutants to green algae (*Scenedesmus subspicatus*) in the cell multiplication inhibition test. Water Res. **24**:31-38 (cited in US EPA, 2000).

Kuhn, R., Pattart, K., Pernak, K. and Winter, A. (1989) Results of the harmful effects of water pollutants to *Daphnia magna* in the 21 day reproduction test. Water Res. **23**:501-510 (cited in US EPA, 2000).

Kulkarni, SG., Doung, H., Gomila, R. and Mehendale, HM. (1996) Strain differences in tissue repair to 1,2-dichlorobenzene. Arch Toxicol, **70**:714-723.

Kumagi, S. and Matsunaga, I. (1995) Identification of urinary metabolites of human subjects exposed to o-dichlorobenzene. Int Arch Occup Environ Health, **67**:207-209.

Lawlor, T., Haworth, S. R. and Voytek P. (1979) Evaluation of the genetic activity of nine chlorinated phenols, seven chlorinated benzenes, and three chlorinated hexanes. Environ Mutagen, 1:143 (Abstract).

LeBlanc, G. (1980). Acute toxicity of priority pollutants to Water Flea (*Daphnia magna*). Bull Environ Contam Toxicol, **24**:684-691 (cited in US EPA, 2000).

Leung, MF., Geoghegan-Barek, K., Zamansky, GB. And Chou, IN. (1990) Microtubule disassembly induced by sensitizing halogenated nitrobenzene derivatives. Toxic. In Vitro, **4**:252-263.

Lewis, RJ. (1997) Hawley's Condensed Chemical Dictionary. 13th ed. New York, John Wiley and Sons.

Lide, DR., Frederikse HPR. 1994 CRC Handbook of Chemistry and Physics. 74th ed. P83. Boca Raton, CRC Press.

Ligocki, MP., Leuenberger, C. and Pankow, JF. (1985) Trace organic compounds in rain II. Gas scavenging of neutral organic compounds. Atmos Environ, **19**:1609-1617 (in Government of Canada, 1993).

Litton Bionetics (1976) Mutagenicity evaluation of o-dichlorobenzene. Report submitted to Rohm and Haas Company, Spring House, Pennsylvania by Litton Bionetics, Inc., Kensington, Maryland, LBI Project No. 2547, EPA/OTS Doc. No. 878212180, 1-10 (cited in BUA, 1990).

Liu, D. and Thomson, K. (1984) Quantitative toxicity assessment of water insoluble chemicals. In: Drug and Chemical Toxicity, Vol.1, Toxicity Screening Procedures using Bacterial Systems; Liu and Dutka (eds), Marcel Dekker, pp 139-145 (cited in BUA, 1990).

Loveday, KS., Anderson, BE., Resnick, MA. and Zeiger, E. (1990) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. Environ Mol Mutagen, **16**:272-303.

Mackay, D. and Shiu, WY. (1981) A critical review of Henry's law constants for chemicals of environmental interest. J Phys Chem Ref Data, **10**:1175-1199 (cited in BUA,1990).

Mackay, DM., Ball, WP. and Durant, MG. (1986) Variability of aquifer sorption properties in a field experiment on groundwater transport of organic solutes: methods and preliminary results. J Contam Hydrol, **1**:119-132 (cited in BUA, 1990).

Mansour, M., Hustert, K., Moza, PN. and Kettrup, A. (1989) Photochemischer Abbau von Chlorierten Aromatischen Verbindungen durch Sauerstoffspezies in Aqutischen Systemen. VDI Berichte Nr. 745, pp 927-936 (cited in BUA, 1990).

Matsui, S., *et al*., (1989) Wat Sci Tech, 21:875-887 (cited in IUCLID, 1996).

McCall, P., Swann, R., Laskowski, D., Unger, S., Vrona, S. and Dishburger, H. (1980) Estimation of chemical mobility in soil from liquid chromatographic retention times. Bull Environ Contam Toxicol, **24**:190-195.

McDonald, RA., Schrader, SA. and Stull, DR. (1959): Vapour pressure and freezing points of 30 organics. J. Chem. Eng. Data, **4**, 311-313.

McFeters, GA., Bond, PJ., Olsen, SB. and Tchan, YT. (1983) A comparison of microbial bioassays for the detection of aquatic toxicants. Water Res, **17**:1757-1762 (cited in BUA, 1990).

McGregor, DB., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C. and Caspary, WJ. (1988) Response of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagenesis, **12**:85-154.

Mehag, AA., Wyatt, CL., Thompson, IP., Bailey, MJ. , Ellis , RJ. and Maguire, N. (1998) Response of soil microbial biomass to 1,2-dichlorobenzene addition in the presence of plant residues. Environ Toxicol Chem, **17**:1462-1468.

Mensink, BJWG., Montforts, M., Wijkhuizen-Maslankiewicz, L., Tibosch, H. and Linders, JBHJ. (1995) Manual for summarising and evaluating the environmental aspects of pesticides, July 1995. Report no. 679101022. Netherlands, National Institute of Public Health and the Environment.

Merck. 1989. The Merck Index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Rahway, NJ, Merck and Company, Inc.,.

Mes, J., Davies, DJ., Turton, D. and Sun, D. (1986) Levels and trends of chlorinated hydrocarbon contaminants in the breast milk of Canadian women. Food Addit Contam, **3**:313-322.

Miller, MM., Wasik, SP., Huang, GL., Shiu, WY., Mackay, D. (1985) Relationship between octanol/water partition coefficient and aqueous solubility. Environ Sci Technol, **19**:522-529.

Millington, LA., Goulding, KH. and Adams, N. (1988) The influence of growth medium composition on the toxicity of chemicals to algae. Water Res, **22**:1593-1597.

Miyagawa, M., Takasawa, H., Sugiyama, A., Inoue, Y., Murata, T., Uno, Y. and Yoshikawa, K. (1995) The in vivo-in vitro replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mut Res, **343**:157-183.

Mohtashamipur, E., Triebel, R., Straeter, H. and Norpoth, K. (1987) The bone marrow clastogenicity of eight halogenated benzenes in male NMRI mice. Mutagenesis, **2**:111-113.

Morita, M., Mimura, S., Ohi, G., Yagyu, H. and Nishizawa, T. (1975) A systematic determination of chlorinated benzenes in human adipose tissue. Environ Pollut, **9**:175-179.

Morita, T., Asano, N., Awogi, T., Sasaki, YF., Sato, S., Shimada, H., Sutou, S., Suzuki, T., Wakata, A., Sofuni, T. and Hayashi, M. (1997) Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (Groups 1, 2A and 2B). The summary report of the 6th collaborative study by CSGMT/JEMS.MMS. Mut Res, **389**:3-122.

Mortimer, M. and Connell, D. (1995) Effect of exposure to chlorobenzenes on growth rates of the crab *Portunus pelagicus* (L) Environmental Science and Technology **29**(8). American Chemical Society.

Murakami, M. and Fukami, J. (1986) Relationship between specific molecular connectivity indices and teratogenicity, carcinogenicity, and mutagenicity of chlorinated benzenes and a biphenyl. Bull Environ Contam Toxicol **37**:633-637.

Myhr, BC. and Caspray, WT. (1991) Chemical mutagenesis at the thymidine kinase locus in L5178Y lymphoma cells. Environ Mol Mutagen, **18**:51-83.

Nakamura, S., Oda, Y., Shimada, T., Oki, I. and Sugimoto, K. (1987) SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK 1002: examination with 151 chemicals. Mut Res, **192**:239-246.

Nedelcheva, V., Gut, I., Souček, P. And Frantík, E. (1998) Cytochrome P450 catalyzed oxidation of monochlorobenzene, 1,2- and 1,4-dichlorobenzene in rat, mouse, and human liver microsomes. Chem Biol Interact, **115**:53-70.

NIOSH (1990). National Institute for Occupational Safety and Health, Criteria for a recommended standard – occupational exposure to ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate. DHHS (NIOSH) Publication No. 90-118, Cincinnati, Ohio, U.S. Department of Health and Human Services.

NIOSH (1994) National Institute for Occupational Safety and Health Method 1003. NIOSH Manual of Analytical Methods. 4th ed. Cincinnati, Ohio, U. S. Department of Health and Human Services. National Institute for Occupational Safety and Health.

Nohmi, T., Miyata, R., Yoshikawa, K. and Ishidate, M., Jr. (1985) Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Bacterial mutagenicity tests. Bull Natl Inst Hyg Sci, **103**:60-64.

NOHSC (1999a) Approved criteria for classifying hazardous substances [NOHSC:1008(1999)]. Sydney, National Occupational Health and Safety Commission.

NOHSC (1999b) List of designated hazardous substances [NOHSC:10005(1999)]. Sydney, National Occupational Health and Safety Commission.

NOHSC (1994c) Control of workplace hazardous substances (National Model Regulations [NOHSC:1005(1994)] and National Code of Practice [NOHSC:2007(1994)]). Canberra, ACT, Australian Government Publishing Service.

NOHSC (1994d) National code of practice for the preparation of material safety data sheets [NOHSC:2011(1994)]. Canberra, ACT, Australian Government Publishing Service.

NOHSC (1994e) National code of practice for the labelling of workplace hazardous substances [NOHSC:2012(1994)]. Canberra, ACT, Australian Government Publishing Service.

NOHSC (1994f) Guidance note for the assessment of health risks arising from the use of hazardous substances in the workplace [NOHSC:3017(1994)]. Canberra, ACT, Australian Government Publishing Service.

NOHSC (1995g) Exposure standards for atmospheric contaminants in the occupational environment (Guidance Note [NOHSC:3008(1995) and National Exposure Standards [NOHSC:1003(1995)]). Canberra, ACT, Australian Government Publishing Service.

NTP (1985) Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (CAS No. 95-50-1) in F344/N rats and B6C3F$_1$ mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR-255. NIH Publication No. 86-2511.

NTP (1989) Annual plan for fiscal year 1989. National Toxicology Program, NTP-89-167, June 1989 (cited in IUCLID).

OECD (1993) Occupational and consumer exposure assessments, OECD Environment Monographs No. 70. Paris, France, OECD.

Oliver, BG. (1984) Uptake of chlorinated organics from anthropogenically contaminated sediments by oligochaete worms. Can J Fish Aquat Sci, **41**:878-883 (cited in BUA, 1990).

Oliver, BG. (1987) Biouptake of chlorinated hydrocarbons from laboratory spiked and field sediments by oligochaete worms. Environ. Sci and Technol, **21**:785-790.

Oliver, BG. and Bothen, KD. (1982) Extraction and clean-up procedures for measuring chlorobenzenes in sediments and fish by capillary gas chromatography. Intern J Environ Anal Chem, **12**:131-139 (cited in BUA, 1990).

Oliver, BG. and Nicol, KD. (1982) Chlorobenzenes in sediment water and selected fish from Lakes Superior, Huron, Eyrie and Ontario. Environ Sci Technol, **16**:532-536 (cited in BUA, 1990).

Oliver, BG and Niimi, AJ. (1983) Bioconcentration of chlorobenzenes from water by Rainbow Trout: correlations with partition coefficients and environmental residues. Environ Sci Technol, **17**:287-291 (cited in BUA, 1990).

Ono, Y., *et al*., (1992) Wat Sci Tech, 26:61-69 (cited in IUCLID, 1996).

Oshida, PS.(1977) Toxicity of chlorinated benzene to sea urchin embryos. Coastal Water Res Proj Annu Rept (South Calif.) pp 187-192 (cited in BUA, 1990).

Pagano, G. *et al*.(1988) Comparative toxicities of benzene, chlorobenzene and dichlorobenzene to sea urchin embryos and sperm. Bull Environ Contam Toxicol, **40**:481-488.

Periera, WE., Rostad, CE., Chiou, CT. , Brinton, TI., Barber, LB., Demcheck, DK. and Demas, CR. (1988) Contamination of estuarine water, biota and sediment by halogenated organic compounds: a field study. Environ Sci Technol, **22**:772-778 (cited in BUA, 1990).

Perocco, P., Bolognesi, S. and Alberghini, W. (1983) Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured in vitro. Toxicology Letters, **16**:69-75.

Piwoni, MD., Wilson, JT., Walters, DM., Wilson, BH. and Enfield, CG. (1986) Behaviour of organic pollutants during rapid infiltration of wastewater into soil: processes, definition and characterisation using a microcosm. Hazard Waste Hazard Mater, **3**:43-55 (cited in BUA, 1990).

Potts, RO. and Guy, RH. (1992). Predicting skin permeability. Pharm Res, **9**:663.

Prasad, I. (1970) Mutagenic effects of the herbicide 3,4-dichloroproprionanilide and its degradation products. Can J Microbiol, **16**:369-372.

Prasad, I. and Pramer, D. (1968). Mutagenic activity of some chloroanilines and chlorobenzenes. Genetics, **20**:212-213.

Reustle, JA. and Scribner, HE. (1979) o-Dichlorobenzene: Myelotoxicity and cytogenetic study in rats. Report of the Rohm and Haas Company, Pennsylvania; EPA/OTS Doc. No.878212182, 1-71 (cited in BUA, 1989).

Riedel, H. (1941) Einige Beobachtungen über Ortho-Dichlorobenzol. Arch Gewerbepath Gewerbhyg, **10**:546-549.

Roberts, PV., Goltz, MN. and Mackay, DM.(1986) A natural gradient experiment on solute transport in a sand aquifer. 3 Retardation estimates and mass balances for organic solutes. Water Resour Res, **22**:2047-2058 (cited in BUA, 1990).

Robinson, M., Bercz, JP., Ringhand, HP., Condie, LW. and Parnell, MJ. (1991) Ten- and ninety-day toxicity studies of 1,2-dichlorobenzene administered by oral gavage to Sprague-Dawley rats. Drug & Chemical Toxicol, **14**:83-112.

Rohm and Haas. (1979) o-Dichlorobenzene. Microbial mutagen test. Report of the Rohm and Haas Company, Pennsylvania; EPA/OTS Doc. No. 878212181 (cited in IUCLID).

Rose, R., Warne, M. and Lim, R. (1998) Quantitative structure-activity relationships and volume fraction analysis for nonpolar narcotic chemicals to the Australian Cladoceran *Ceriodaphnia dubai*. Arch Environ Contam Toxicol, **34**:248-252 (cited in US EPA, 2000).

RTECS (1989) Registry of toxic effects of chemical substances. Compiled by the National Institute of Occupational Safety and Health of the US Dept. of Health and Human Services. MICROMEDEX Inc, (accessed 15/11/00).

Russi, H., Kotzias, D. and Korte, F. (1982) Photoindzierte Hydroxylierungsrektionen Organischer Chemikalien in Naturlichen Gerwassern – Nitrate als Potentielle OH Radikalquellen. Chemosphere, **11**:1041-1048 (cited in BUA, 1990).

Sax, NI and Lewis RJ Sr. 1996. Sax's Dangerous Properties of Industrial Materials. 9th ed. New York, NY, Van Nostrand Reinhold Company.

Schenk, R. and Kennedy, W. (1955) Laboratory evaluation of fungicides for the preservation of moist hay. Agron, J, **47**:64-69 (cited in BUA, 1990).

Shelby, MD., Erexson, GL., Hook, GJ. and Tice, RR. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ Mole Muta, **21**:160-179.

Shelby, MD. and Whitt, KL. (1995) Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. Environ Mole Muta, **25**:302-313.

Shimada, T., McQueen, CA. and Williams, GM. (1983) Study of the effects on cultured liver cells of three chlorinated benzenes. Report of the Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York. EPA/OTS Doc. No. 40-8420666, 1-41 (cited in BUA, 1990).

Shimizu, N., Yasui, Y. and Matsumoto, N. (1983) Structural specificity of aromatic compounds with special reference to mutagenic activity in *Salmonella typhimurium* – a series of chloro- or fluro-nitrobenzene derivatives. Mut Res, **116**:217-238.

Slimak, K., Johnston, P. and Hodge, V. Materials balance for chlorobenzenes. US EPA Report EPA-560/13-80-0001 (PB80-173651), 1980 (cited in Government of Canada, 1993).

Smith, JH., Bomberger, DC. and Haynes, DL. (1980) Prediction of the volatilisation rates of high volatility chemicals from natural water bodies. Environ Sci Technol, **14**:13332-1337 (cited in BUA, 1990).

Springer, W. and Rast, HG. (1988) Biologischer Abbau Mehfach Halogenierter Mono- Poly-zyklischer Aromaten"; GWF. Gas-Wasserfach: Wasser Abwasser, **129**:70-75 (cited in BUA, 1990).

St'ota, Z. and Toman, M. (1957) Phytotoxizitat und Fungiziditat Chlorsubstituierter Derivate des Benzoles in Bezug zu deren Konstitution. Biologia, **12**:683-692.

Stauffer, TB. and MacIntyre, WG. (1986) Sorption of low polarity organic compounds on oxide minerals and aquifer materials. Environ Toxicol Chem **5**:949-955.

Stover, EL. and Kincannon, DF. Biological treatability of specific organic compounds found in chemical industry wastewaters. Proc Ind Waste Conf, 36 th, pp 1-16, 1982 (cited in BUA, 1990).

Stover, EL. and Kincannon, DF. (1983) Contaminated groundwater treatability – A case study. J Am Water Works Assoc, **75**:292-298 (cited in BUA, 1990).

Stine, ER., Gunawardhana, L. and Sipes, IG. (1991) The acute hepatotoxicity of the isomers of dichlorobenzene in Fischer-344 and Sprague-Dawley rats: Isomer-specific and strain-specific differential toxicity. Toxicol Appl Pharmacol, **109**:472-481.

Sydney Water (January 1996). Risk assessment. Ecological and human health risk assessment of chemicals in sewage treatment plant discharges to ocean waters. Sydney Water Corporation Limited.

Tennant, RW., Margolin, BH., Shelby, MD., Zeiger, E., Haseman, JK., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B. and Minor, R. (1987) Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science, **236**:933-941.

Tennant, RW., Stasiewicz, S. and Spalding, JW. (1986) Comparison of multiple parameters of rodent carcinogenicity and in vitro genetic toxicity. Environ Mut, **8**:205-227.

Thomas, KW., Pellizzari, ED. and Cooper, SD. (1991) A canister based method for collection and GC/MS analysis of volatile organic compounds in human breath. J Anal Toxicol, **15**:54-59.

Thomas, RG. (1982) Volatilisation from water. In: Lyman, W.J., Rheel, WF. and Rosenblatt, DH. eds, Handbook of chemical property estimation methods, McGraw- Hill Book Company.

Thompson, IP., Bailey, Boyd, EM., Maguire, N., Mehag, AA. and Ellis , RJ. (1999) Concentration effects of 1,2-dichlorobenzene on soil microbiology. Environ Toxicol and Chem, **19**:1891-1898.

Umemura, T., Saito, M., Takagi, A. and Kurokawa, Y. (1996) Isomer-specific acute toxicity and cell proliferation in livers of B6C3F1 mice exposed to dichlorobenzene. Toxicol Appl Pharmacol, **137**:268-274.

Umemura, T., Tokumo, K. and Williams, G.M. (1992) Cell proliferation induced in the kidneys and livers of rats and mice by short term exposure to the carcinogen p-dichlorobenzene. Arch Toxicol, **66**:503-507.

United Kingdom Department of the Environment; Standing Committee Anal. (1986) Chlorobenzenes in water, organochlorine pesticides and PCBs in turbid waters, halogenated solvents and related compounds in sludge and waters, 1985. Methods Exam. Waters Assoc. Mater., 1-10.

US EPA (1985) Development of statistical distributions or ranges of standard factors used in exposure assessments. Washington, DC, Office of Research and Development, Office of Health and Environmental Assessment. EPA 600/8-85-010. Available from: NTIS, Springfield, VA. PB85-242667.

US EPA (1978) In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646, US EPA, Duluth, MN:9 p (cited in US EPA, 2000).

US EPA (1987) Occurrence of synthetic organic chemicals in drinking water, food, and air. Revised Draft Report. US EPA, Office of Drinking Water (PB98-192520). 175 pp (cited in Government of Canada, 1993).

US EPA (1999) ASTER Ecotoxicity profile: 1,2-dichlorobenzene - [CAS No 95-50-1]. United States Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Mid-Continent Ecology Division. Telnet address: ecotox.epa.gov.

US EPA (2000) ECOTOX: Ecotoxicology Database. U.S. Environmental Protection Agency. Office of Research and Development National Health and Environmental Effects Research Laboratory Mid-Continent Ecology Division. Scientific Outreach Program. Report Generated April 2000.

Valentovic, MA., Ball, JG., Anestis, D. and Madan, E. (1993) Modification of P450 activity and its effect on 1,2-dichlorobenzene toxicity in Fischer 344 rats. Toxicol, **79**:169-180.

Vazquez, ER., Macias, PC., Tirado, JGO., Solana, CG., Casanova, A. and Moncada, JF. P. (1996) Chloracne in the 1990's. Int J Dermatol, **35**:643-645.

Veith, GD., Macek, KJ., Petrocelli, SR. and Carroll, J. (1980) An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish; aquatic toxicology, Proc. 3rd Annu. Symp. Aquat. Toxicol., ASTM Special Technical Publication 707. Eaton, J. G., Parrish, P. R. and Hendrics, A.C. (eds.), Am. Soc. Test. Mater., 116-129, 1980 (cited in BUA, 1990).

Verschueren, K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY, Van Nostrand Reinhold Company, 477-478.

Verschueren, K. 1996. Handbook of environmental data on organic chemicals. 3rd ed. New York, NY, John Wiley and Son, 667-670.

Vogel, EW. and Nivard, MJM. (1993) Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromsomal mitotic recombination. Mutagenesis, **8**:57-81.

Wahner, A. and Zetzsch, C. (1983) Tate constants for the addition of OH to aromatics (benzene, p-chloroaniline and o-, m- and p-dichlorobenzene) and the unimolecular decay of the adduct. Kinetics into a quasi-equilibrium. (Part) 1. J Phys Chem, **87**:4945-4951 (cited in BUA, 1990).

Wallace, LA. (1987) The total exposure assessment methodology (TEAM) study: summary and analysis: volume I. Office of Research and Development U. S. Environmental Protection Agency 600/6-87/002a.

Wallace, LA, Pellizzari, ED, Hartwell, TD, Davis, V., Michael, LC. and Whitmore, RW. (1989) The influence of personal activities on exposure to volatile organic compounds. Environmental Res, **50**:37-55.

Walton, BT., Anderson, TA., Hendricks, MS. and Tamalge, SS. (1989) Physiochemical properties as predictors of organic chemical effects on soil microbial respiration. Environ Toxicol Chem, **8**:53-63.

Wang, M. and Jones, K. (1994) Behaviour and fate of chlorobenzenes in spiked and sewage sludge-amended soil. Environ Sci Technol, **28**:(11)

Wang, M., McGrath, S. and Jones, K. (1995) Chlorobenzenes in field soil with a history of multiple sewage sludge applications. Environ Sci Technol, **29**:356-362.

Washall, JW. and Wampler, TP. (1988) Purge and trap analysis of aqueous samples with cryofocusing. Am Lab, (July): 70-74.

Waters, MD., Sandhu, SS., Simmom, VF., Mortelmans, KE., Mitchell, AD., Jorgenson, TA., Jones, DCL., Valencia, R. and Garrett, NE. (1982) Study of pesticide genotoxicity. Basic Life Sciences, **21**:275-320.

Weber, WJ., Jones, BE. and Katz, LE. (1987) Fate of toxic organic substances in activated sludge systems and integrated PAC systems. Water Sci Tecnol, **19**:471-482 (cited in BUA, 1990).

Webster, E., Mackay, D. and Wania, F. (1998) Evaluating environmental persistence. Environ Toxicol Chem, **17**:2148-2158.

Wegman, RCC., Bank, CA. and Greve, PA (1981) Environmental pollution by a chemical waste dump. Stud Environ Sci, **17**:349-357 (cited in BUA, 1990).

Williams, GM., Mori, H. and McQueen, CA. (1989) Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mut Res, **221**:263-286.

Wilson, J., Smith, G., Cochran, J., Barker, J. and Roberts, P. (1987) Field evaluation of a simple microcosm simulating the behaviour of volatile organic compounds in sub-surface materials. Water Resour Res, **23**:1547-1553 (cited in BUA, 1990).

Worne, HE. (1972) The activity of mutant microorganisms in the biological treatment of industrial wastes. Zeitschrift des BECEWA (Belgisches Zentrum fur Waseruntersuchung, **22**:61-71 (cited in BUA, 1990).

Yoshioka, Y., Mizuno, T., Ose, Y. and Sato, T. (1986a) The estimation for toxicity of chemicals on fish by physico-chemical properties. Chemosphere, **15**:195-203 (cited in BUA, 1990).

Yoshioka, Y., Ose, Y. and Sato, T. (1985) Testing for the toxicity of chemicals with *Tetrahymena pyriformis*. Sci Total Environ, **43**:149-157 (cited in US EPA, 2000).

Yoshioka, Y., Nagase, H, Ose, Y. and Sato, T. (1986b) Evaluation of the Test Method "Activated Sludge, Respiration Inhibition Test" Proposed by the OECD"; Ecotoxicol. Environ. Saf., **12**:206-212.

Yukimoto, M. (1983) Effect of organophosphorus insecticides on Hill Reaction. J Pesticide Sci, **8**:63-68.

Zapata-Gayon, C., Zapata-Gayon, N. and Gonzalez-Angulo, A. (1982) Clastogenic chromosomal aberrations in 26 individuals accidentally exposed to *Ortho*-dichlorobenzene vapors in the National Medical Center in Mexico City. Arch Environ Health, **37**:231-235.

Zenser, L. P., Lang, A. and Knecht, U. (1997) *N*-Acetyl-*S*-(dichlorophenyl)cysteines as suitable biomarkers for the monitoring of occupational exposure to 1,2-dichlorobenzene. Int Arch Occup Environ Health **69**:252-254.

Zissu, D. (1995) Histopathological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J Appl Toxicol, **15**:207-213.

Zoeteman, B., Harmsen, K., Linders, J., Morra, C. and Slooff, W. (1980) Persistent organic pollutants in river water and ground water of the Netherlands. Chemosphere, **9**:231-249 (cited in BUA, 1990).

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