FULL PUBLIC REPORT

2-butoxyethanol

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Preface

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

The principal aim of NICNAS is to help protect people and the environment from the harmful effects of industrial chemicals by finding out the risks to occupational health and safety, to public health and the environment.

NICNAS has two major parts: one focussing on the risks associated with new chemicals before importation or manufacture; and another focussing on existing industrial chemicals already in use in Australia. As there are many thousands of existing industrial chemicals in Australia, NICNAS has a mechanism of prioritising assessments by declaring certain existing chemicals to be Priority Existing Chemicals (PECs). This report provides the full public report of a PEC assessment. A summary report is also publicly available and has been published in the Commonwealth *Chemical Gazette*.

NICNAS is administered by Worksafe Australia. Assessments under NICNAS are done in conjunction with the Environment Protection Agency and Department of Health and Family Services.

This assessment report has been prepared by the Director Chemicals Notification and Assessment in accordance with the Act. This report has not been subject to tripartite consultation or endorsement by the National Occupational Health and Safety Commission.

Copies of the full public report can be purchased from Commonwealth Government Bookshops.

In accordance with Section 40 of the Act, a person may apply to the Director for variation of this full public report using the approved form by 29 October 1996. A fee must be paid with the application.

On publication of the Summary Report in the Chemical Gazette of 1 October 1996, the chemical will no longer be a Priority Existing Chemical in accordance with Section 62 of the Act.

For the purposes of subsection 78(1) of the Act, copies of full public reports may be inspected by the public at the Library, Worksafe Australia, 92-94 Parramatta Road, Camperdown, NSW 2050, between 10 a.m. and 12 noon and 2 p.m. and 4 p.m. each weekday except on public holidays.

A pamphlet giving further details of the PEC program and approved forms to apply for variation of this report are available from Worksafe Australia. Please contact the Chemical Assessment Division at the address shown below.

GPO Box 58

SYDNEY NSW 2001

AUSTRALIA

or

334-336 Illawarra Road

MARRICKVILLE NSW 2204

AUSTRALIA

Telephone: +61 (02) 8577 8800

Fax: +61 (02) 8577 8888.

Abstract

2-Butoxyethanol is a glycol ether which is used in over 430 cleaning products in Australia. Cleaning products containing 2-butoxyethanol are used in a large number of industries in Australia and by a large number of people. In the contract cleaning industry alone, it is estimated that there are approximately 65,000 cleaners. Many of the products are available for sale to the public. Cleaning products which may contain 2-butoxyethanol include general surface cleaners, floor strippers, window cleaners, spot cleaners, rust removers and ink and resin removers.

The use of cleaning products containing 2-butoxyethanol has caused concern due to the high potential for occupational and public exposure, reports of adverse health effects in some workers (for example, irritation of the eyes, nose and throat) and the established toxicity of related glycol ethers, (for example, the reproductive toxicity of 2-methoxyethanol and 2-ethoxyethanol).

2-Butoxyethanol is well absorbed via the inhalational, dermal and oral routes. It is widely distributed throughout the body and efficiently metabolised to 2-butoxyacetic acid (BAA), which is rapidly excreted in urine. Studies in humans and animals have shown that the metabolic pathways are similar.

The critical health effect from animal studies is haemolysis of the blood cells (rat NOAEL 24.6 ppm), with other effects such as liver and kidney damage being secondary to haemolysis. The severity of the effect, caused mainly by BAA, differs markedly between species, with rats and mice the most sensitive, rabbits less sensitive, and then guinea pigs. Humans appear to be the least sensitive from the results of *in vitro* studies and *in vivo* inhalational studies. Haemolytic effects in humans have been observed after the deliberate ingestion of large doses. No haemolytic effects have been confirmed with occupational exposure.

The reproductive effects observed with related glycol ethers, 2-methoxyethanol and 2-ethoxyethanol, have not been demonstrated with 2-butoxyethanol. In animal reproductive toxicity studies, adverse effects were observed only at doses which were severely toxic to the adults. Similarly, no evidence of teratogenicity was observed with 2-butoxyethanol. Immunotoxicity studies in animals were negative and studies indicate 2-butoxyethanol is probably not genotoxic.

The critical health effects from acute exposure to 2-butoxyethanol are eye and respiratory irritation. In controlled studies in humans, eye and respiratory irritation occurred at 113 ppm, with headache and nausea at 100 ppm. Human evidence indicates that 2-butoxyethanol may be slightly irritating to the skin on repeated exposure. It is not a skin sensitiser.

Based on the assessment of health effects, 2-butoxyethanol should be classified in accordance with the Approved Criteria for Workplace Hazardous Substances as 'Harmful by inhalation, in contact with skin, and if swallowed' (risk phrases R20/21/22), 'Irritating to respiratory system' (R37), and 'Irritating to the eyes' (R36).

The occupational risk assessment found that, for most work situations, the atmospheric concentration of 2-butoxyethanol is unlikely to be high enough to cause irritation, but where vapours and/or aerosols are generated, for example, during spray use or when heat is applied, irritant effects and possibly headache and nausea may be experienced. The assessment found that skin absorption can occur in the absence of irritation and may contribute significantly to the total dose absorbed. The assessment found that the risk of haemolysis in workers employed in the manufacture, formulation or use of cleaning products containing 2-butoxyethanol in Australia is minimal. However, there is a concern where workers are exposed on a prolonged basis (particularly dermal exposure) to high concentrations of 2-butoxyethanol (30% and more).

The risk to human health can be determined by an assessment of the workplace. Areas of concern identified in the risk assessment include spray use, use of heat, and prolonged dermal exposure to cleaning solutions or products containing high concentrations of 2-butoxyethanol (30% or more). In these situations, it is recommended that consideration be given to substituting 2-butoxyethanol with safer alternatives which have been thoroughly tested and demonstrated to have a lower toxicity, irritancy and potential for skin absorption in humans. At the very least, the 2-butoxyethanol content in cleaning products should be reduced to concentrations where the risk to human health is minimal. It is also recommended that suppliers and end-users review their methods of application, for example, by replacing spray use with use as a liquid stream.

Due to the low concentration of 2-butoxyethanol in most domestic cleaning products and their intermittent use by the public, the public health risk is expected to be minimal.

In an assessment of MSDS and labels submitted by formulators, deficiencies were noted in several areas. It is therefore recommended that suppliers review their MSDS and labels in accordance with regulatory requirements and recommendations in this report. For MSDS, more specific information about 2-butoxyethanol is required. For labels, the appropriate risk phrases for products used industrially are required, together with a better indication of the hazards of spray use and precautions for handling. Accordingly, it is recommended that the safety phrase 'Do not breathe vapour or spray' be on the label for products which may be used in spray form in the workplace.

The risk to the environment is expected to be low as 2-butoxyethanol is readily biodegradable and is of low toxicity to aquatic organisms. However, it should not be disposed of to landfill as it may leach to groundwater due to its expected high mobility in soil and low adsorption potential.

Contents

Abbreviations

ABSA	Australian Building Services Association
ACGIH	American Conference of Governmental Industrial Hygienists
ADG	Australian Code for the Transport of Dangerous Goods by Road and Rail
ADH	alcohol dehydrogenase
AICS	Australian Inventory of Chemical Substances
ALDH	aldehyde dehydrogenase
AQUIRE	Aquatic Toxicity Information Retrieval database (US EPA)
ASTER	Assessment Tools for the Evaluation of Risk database (US EPA)
ATP	adenosine triphosphate
BAA	2-butoxyacetic acid
BAA-GLN	N-butoxyacetylglutamine
BAL	2- butoxyacetaldehyde
BAT	"Biologischer Arbeitsstoff-Toleranz-Wert" (biological tolerance value for occupational exposures)
2-BE	2-butoxyethanol
BEG	2-butoxyethanol glucuronide
BEI	biological exposure index
BES	2-butoxyethanol sulfate
BOD	biochemical oxygen demand
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CMA	Chemical Manufacturers Association (USA)
CNS	central nervous system
CO_2	carbon dioxide
Con A	concanavalin A
cP	centipoise

EC_{50}	median effective concentration
ECETOC Chemicals	European Centre for Ecotoxicology and Toxicology of
EEC	European Economic Community
EG	ethylene glycol
EINECS Substances	European Inventory of Existing Commercial Chemical
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
gd	gestational day
Hgb	haemoglobin
hPa	hectopascal
HPLC	high performance liquid chromatography
HPV	high production volume
HSE	Health and Safety Executive (UK)
ISO	International Standards Organisation
IUPAC	International Union for Pure and Applied Chemistry
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest observable adverse effect level
MAK workplace	"Maximale Arbeitsplatz-Konzentration " (maximum
	concentration)
MATC	maximum acceptable toxicant concentration
MCH	mean corpuscular (or cell) haemoglobin
MCHC	mean corpuscular (or cell) haemoglobin concentration
MCV	mean corpuscular (or cell) volume
MDA	malonylaldehyde
$mg/cm^2/h$	milligrams per square centimetre per hour
mg/kg bw	milligrams per kilogram body weight
mN/m	millinewtons per metre
MSDS	Material Safety Data Sheet

NIOSH (USA)	National Institute for Occupational Safety and Health
nm	nanometer
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
PBPK	physiologically-based pharmacokinetic
PFB	pentafluorobenzyl
PFBB	pentafluorobenzylbromide
PHA	phytohaemagglutinin
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
QSAR	Quantitative Structure Activity Relationship
RBC	red blood cell
RD_{50} rate	concentration which causes a 50% decrease in respiratory
SCE	sister chromatid exchange
SIAR	SIDS Initial Assessment Report
SIDS	Screening Information Data Set
STEL	short-term exposure limit
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TNP-LPS	trinitrophenyl-lipopolysaccharide
TWA	time-weighted average
UDS	unscheduled DNA synthesis
µmol	micromole
US EPA	Environmental Protection Agency of the USA

1. Introduction

The chemical 2-butoxyethanol (CAS no. 111-76-2) was declared by the Minister for Industrial Relations as a priority existing chemical (PEC) under the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) by notice in the *Chemical Gazette* of 5 April 1994. The declaration was specific for the use of 2-butoxyethanol in cleaning products.

The declaration was made on the basis that there were reasonable grounds for believing that the formulation, handling and use of cleaning products containing 2-butoxyethanol may give rise to a risk of adverse health effects. In summary, these grounds were:

- the high potential for occupational and public exposure due to the wide use in Australia of cleaning products containing 2-butoxyethanol;
- concern about the known and potential health hazards of 2-butoxyethanol given the high potential exposure; and
- reported adverse health effects in workers using cleaning products containing 2-butoxyethanol.

In accordance with the Act, manufacturers and importers of 2-butoxyethanol for its use in cleaning products, and importers of cleaning products containing 2-butoxyethanol, applied for the assessment of 2-butoxyethanol as a PEC. Information for the assessment was received from manufacturers (in Australia and overseas), importers, formulators, end-users, State and Territory departments, other interested persons, and from a comprehensive literature search. A questionnaire was sent to formulators to obtain Material Safety Data Sheets and labels for many of the cleaning products and to obtain information about the formulation process and worker exposure.

2. Background

2.1 The glycol ethers

2-Butoxyethanol belongs to a group of chemicals known as glycol ethers, which are compounds formed by reacting an alcohol with an alkyl oxide such as ethylene or propylene oxide. 2-Butoxyethanol is one of the monoalkyl ethers, which have the general formula R-O-R'-OH, where R is an alkyl group, for example, methyl (CH_3), and R' is $-CH_2CH_2-$ for the ethylene glycol monoalkyl ethers and $-CH_2CH_2CH_2-$ for the propylene glycol monoalkyl ethers. A list of typical glycol ethers is provided in Table 1 showing structural similarities and differences.

The glycol ethers are liquids which are miscible with water and most organic solvents, so they are widely used as solvents and in cleaners, paints and inks. A number of glycol ethers are manufactured and used in Australia.

2.2 The international perspective

There has been widespread concern over the health effects of the glycol ethers for some time. Health effects caused by some members of the glycol ether group include haematotoxicity, testicular degeneration, developmental effects and immunological effects. However, it has become increasingly evident from published studies and reports that the type and severity of health effects of members of this group of chemicals vary considerably, and so increasingly the health issues of the individual members of the group are being studied.

Concerns about the health effects of the glycol ethers have led to a number of reports being published overseas and several comparative investigations into members of the group. In the US, the EPA conducted a review (US EPA 1993) of the human health effects of the glycol ethers. In Europe, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (1982; 1985; 1995) and the UK Health and Safety Executive (HSE) (1985) published reports on the health effects of the glycol ethers.

More recently, the health effects of the individual members have been studied. ECETOC (1994) and the US National Institute for Occupational Health and Safety (NIOSH) (1990) have published criteria documents which have focussed on the setting of an occupational exposure standard for 2-butoxyethanol and the HSE has recently drafted a similar report. The US Cosmetic, Toiletry and Fragrance Association (1994) published a safety assessment for the use of 2-butoxyethanol in cosmetics.

In the USA, the introduction of regulatory controls on the glycol ethers by the EPA led to the formation of an Ethylene Glycol Ethers Panel by the Chemical Manufacturers Association (CMA). The association has sponsored testing to further investigate the health effects of the glycol ethers.

2-Butoxyethanol is listed under Phase 4 of the Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV) program. The primary aim of the HPV program is to investigate the hazards of chemicals produced internationally in large volumes. As a member of the OECD, Australia has agreed to assess 2-butoxyethanol in the HPV program. Data in this PEC report will form the basis of the Screening Information Data Set (SIDS) required under the program. Following the incorporation of exposure data from other OECD member countries, a SIDS Initial Assessment Report (SIAR) will be completed and reviewed internationally. It is expected that this report will cover all uses of 2-butoxyethanol, not just the use in cleaning products.

In Europe, it has been reported that cleaning agents available to the public now usually contain 2-(2-butoxyethoxy)ethanol (2-BEE), which has a lower vapour pressure and skin absorption rate than 2-butoxyethanol. Consequently, in 1994, more than 16000 tonnes of 2-BEE were used in public sector cleaning agents compared with approximately 1000 tonnes of 2-butoxyethanol. In Germany, it has been reported that the trend is towards the use of glycol ethers without a primary hydroxy group, for example, the 1-alkoxy-2-propanols.

2.3 The Australian perspective

In Australia, widespread concern by employee and public interest organisations over the use of cleaning products containing 2-butoxyethanol has persisted in recent years. In particular, concern has been expressed about the use of these products in schools.

In Australia, 2-butoxyethanol is imported by several companies and manufactured by ICI Australia. Most cleaning products containing 2-butoxyethanol are formulated in this country, and a relatively small number are imported.

This report focuses on the use of 2-butoxyethanol in cleaning products in Australia because of the specific concerns raised in this context. The report includes an assessment of the exposure and risks to workers, the public and the environment of 2-butoxyethanol from this use. However, information in the report, for example, the assessment of health effects data and other hazards, is also relevant for the other uses of 2-butoxyethanol, and the methodology used in the risk assessment is expected to have application in other uses.

Table 1 - Typical Glycol Ethers

Class	Name	Alkyl Group(s)	Structural Formula	CAS No.
Ethylene Glycol Ethers:				
Monoalkyl	2-Methoxyethanol	methyl	CH_3-O-CH_2-CH_2-OH	109-86-4
	2-Ethoxyethanol	ethyl	C_2H_5-O-CH_2-CH_2-OH	110-80-5
	2-Butoxyethanol	butyl	C_4H_9-O-CH_2-CH_2-OH	111-76-2
	2-Phenoxyethanol	phenyl	C_6H_5-O-CH_2-CH_2-OH	122-99-6
	1,2-Dimethoxyethane	methyl	CH_3-O-CH_2-CH_2-O-CH_3	110-71-4
Dialkyl	2,(2-Methoxyethoxy)ethanol	methyl, ethyl	CH_3-(O-CH_2-CH_2)$_2$-OH	111-77-3
	2-(2-n-Butoxyethoxy)ethanol	ethyl, butyl	C_4H_9-(O-CH_2-CH_2)$_2$-OH	112-34-5
	Bis(2-methoxyethyl)ether	methyl, ethyl	CH_3-(O-CH_2-CH_2)$_2$-O-CH_3	111-96-6
Trialkyl	2-[2-(2-Ethoxyethoxy)ethoxy]ethanol 2,5,8,11-Tetraoxadodecane	ethyl, ethyl, ethyl methyl, ethyl, ethyl	C_2H_5-(O-CH_2-CH_2)$_3$-OH CH_3-(O-CH_2-CH_2)$_3$-O-CH_3	112-50-5 112-49-2
Propylene Glycol Ethers:				
Monoalkyl	1-Ethoxy-2-propanol	ethyl	CH_3-CH(OH)-CH_2-O-C_2H_5	1569-02-4
	1-Butoxy-2-propanol	butyl	CH_3-CH(OH)-CH_2-O-$(CH_2)_3$-CH_3	5131-66-8
	2-Methoxypropanol-1	methyl	CH_3-CH(O-CH_3)-CH_2-OH	1589-47-5
Dialkyl	(2-Methoxymethylethoxy)-propano (2-Ethoxy-methylethoxy)-propanol l	methyl, propyl ethyl, propyl	CH_3-(O-C_3H_6)$_2$-OH C_2H_5-(O-C_3H_6)$_2$-OH	34590-94-8 300025-38-8
Trialkyl	[2-(2-Methoxymethylethoxy)methylethoxy]-propanol	methyl, propyl, propyl	CH_3-(O-C_3H_6)$_3$-OH	25498-49-1

3. Applicants

Amway of Australia Pty Ltd

46 Carrington Rd, Castle Hill, NSW 2154

Ecolab Pty Ltd

6 Hudson Ave, Castle Hill, NSW 2154

ICI Australia Operations Pty Ltd

1 Nicholson St, Melbourne, Vic 3000

S C Johnson Pty Ltd

160 Epping Rd, Lane Cove, NSW 2066

3M Australia Pty Ltd

950 Pacific Highway, Pymble, NSW, 2073

Redox Chemicals Pty Ltd

30-32 Redfern St, Wetherill Park, NSW 2164

Swift and Company Ltd

85 Egerton St, Silverwater, NSW 2128

Union Carbide Chemicals (Australia) Pty Ltd

Suite 1, 1st floor, 1-7 Jordan St, Gladesville, NSW 2111

Whiteley Chemicals Australia Pty Ltd

82-84 Ivy St, Chippendale, NSW 2008.

4. Chemical identity and composition

4.1 Chemical name

2-Butoxyethanol is listed on the Australian Inventory of Chemical Substances (AICS) as Ethanol, 2-butoxy-.

The Chemical Abstracts Service (CAS) registry number is 111-76-2.

Its IUPAC name is Ethylene glycol butyl ether.

The EINECS number is 203-905-0. The EEC classification number is 603-014-00-0.

4.2 Other names

- Butoxyethanol
- n-Butoxyethanol
- 2-Butoxy-1-ethanol
- Butyl ethoxol
- O-Butyl ethylene glycol
- Butyl glycol
- Butyl monoether glycol
- EGBE
- Ethylene glycol butyl ether
- Ethylene glycol n-butyl ether
- Ethylene glycol monobutyl ether
- Ethylene glycol mono-n-butyl ether
- Glycol butyl ether
- Glycol monobutyl ether
- Monobutyl glycol ether
- 3-Oxa-1-heptanol

4.3 Molecular and structural formula

The molecular formula is $C_6H_{14}O_2$.

The molecular weight is 118.2.

The structural formula is $CH_3CH_2CH_2CH_2OCH_2CH_2OH$.

4.4 Trade names

2-Butoxyethanol is known commercially under the following trade names:

- Butyl Cellosolve®
- Butyl Icinol®
- Butyl Oxitol®
- Dowanol EB®
- Ektasolve EB®
- Gafcol EB®
- Glycol ether EB®
- Jeffersol EB®
- Poly-Solv EB®.

The known trade names of cleaning products in Australia which contain 2-butoxyethanol are listed in Appendix 1. The list was compiled from responses to a questionnaire sent to formulators in late 1994. It is not intended to be a comprehensive listing.

4.5 Chemical composition

When 2-butoxyethanol is manufactured from ethylene oxide and n-butanol, other glycol ethers such as the di- and triethylene glycol ethers are produced. Consequently, commercial 2-butoxyethanol may contain small concentrations of other glycol ethers, n-butanol and ethylene glycol.

A stabiliser, 2,6-bis(1,1-dimethylethyl)-4-methylphenol, can be added at approximately 0.01% to prevent the formation of peroxides.

For the composition of cleaning products containing 2-butoxyethanol, see section 7.5.

5. Physical and chemical properties

5.1 Physical state

2-Butoxyethanol is a colourless liquid with an unpleasant odour. The odour threshold is 0.10 ppm (NIOSH 1990).

Conversion factor (for vapour): 1ppm = 4.9 mg/m^3 (20°C, 1014 hPa).

5.2 Physical and chemical properties

Table 2 - Physical and Chemical Properties

Property	Value	Reference
Freezing point	- 77ºC	(NIOSH 1990)
Boiling point	170.8ºC	(NIOSH 1990)
Density (20ºC)	0.90 g/mL	(EUCLID 1994)
Vapour density (20ºC)	4.91 g/L	(ECETOC 1994)
Relative vapour density (air = 1)	4.1	(NIOSH 1990)
Vapour pressure (25ºC)	1.17 hPa	(ECETOC 1994)
Flash point (closed cup)	62ºC	(NIOSH 1990)
Autoignition temperature	230-245ºC	(EUCLID 1994)
Flammability limits	1.10 - 12.7%	(NIOSH 1990)
Explosive properties	not explosive	(EUCLID 1994)
Water solubility	miscible	(NIOSH 1990)
Partition coefficient (log P_{ow})	0.81	(EUCLID 1994)
Adsorption coefficient (K_{oc})	67 (calculated)	(Howard 1993)
Viscosity (25ºC)	6.4 cP	(EUCLID 1994)
Surface tension (25ºC)	27.4 mN/m	(EUCLID 1994)
Refractive index (25ºC)	1.422	(Dow 1990)

Hydrolysis:

2-Butoxyethanol is unlikely to hydrolyse as alcohols and ethers are generally resistant to hydrolysis (Howard et al 1993).

Adsorption/desorption:

A K_{oc} of 67 indicates that 2-butoxyethanol will not partition into organic matter contained in sediments and suspended solids, and should be highly mobile in soil (Howard et al 1993).

Surface tension:

2-Butoxyethanol is surface active, thereby increasing its adsorption potential.

2-Butoxyethanol is soluble in water and most organic solvents. It undergoes reactions typical of glycol ethers (Dow Chemical 1990), viz.:

- oxidation to 2-butoxyacetic acid (BAA);
- acetal formation when reacted with aldehydes under acidic conditions;
- ester formation when reacted with a carboxylic acid, for example, acetic acid, in the presence of a strong acid;
- phosphate and sulfate esters when reacted with phosphoric and sulfuric acids respectively; and
- dehydrogenation in the presence of copper at high temperatures.

6. Methods of detection and analysis

6.1 Identification

2-Butoxyethanol can be characterised using nuclear magnetic resonance spectroscopy (NMR), infra-red spectroscopy (IR) and mass spectroscopy (MS).

6.2 Determination of 2-butoxyethanol in air

6.2.1 Sampling

In standard methods for the determination of 2-butoxyethanol in air, such as personal monitoring, activated charcoal (coconut shell type) is usually used as the adsorbent. Most methods use a sampling pump to draw air onto the charcoal held in a tube, with a flow rate in the range 10-100 mL/min. The use of a 3M diffusion sampling badge to collect the sample has been reported (Sakai et al 1993).

6.2.2 NIOSH method 1403

This method (NIOSH 1990) is widely used for determining 2-butoxyethanol in air. Samples are collected in solid sorbent tubes containing coconut shell charcoal at a flow rate of 10-50 mL/min and desorbed with 5% methanol in methylene chloride. The resultant solution is analysed by gas chromatography using flame ionisation detection. The estimated limit of detection is 0.01 to 0.02 mg.

Multidimensional gas chromatography-mass spectrometry (GC-MS) has been used to improve the detection limit of the method to 5-7 µg per sample (Kennedy et al 1990).

6.2.3 OSHA method 83

This standard method (NIOSH 1990) is very similar to the NIOSH method. The recommended air volume and sampling rate for 8-hr TWA samples is 48 L at 0.1 L/min and for short term samples is 15 L collected at 1.0 L/min (15-min samples). The detection limit for a 48 L sample is 31 ppb.

6.3 Determination of 2-butoxyacetic acid in urine

Most of the methods for the determination of 2-butoxyacetic acid (BAA) in urine incorporate pH adjustment, solvent extraction, derivatisation, and then gas chromatography (GC) or high performance liquid chromatography (HPLC).

In the method recommended by NIOSH (1990) the sample is adjusted to pH 7, a small amount of water is added, and the samples are freeze-dried at -60°C overnight. BAA is then derivatised with 2,3,4,5,6-pentafluorobenzylbromide (PFBB) and a methylene chloride solution of the PFB ester is analysed gas chromatographically. The limit of detection is 0.03 mg/L (Groeseneken et al 1989).

In another GC method reported (Sakai et al 1993), BAA is extracted with a mixture of dichloromethane and isopropyl alcohol and then derivatised with trimethylsilyl-diazomethane. The esterified acids are analysed by GC using a flame ionisation

detector and a capillary column. Analytical recovery of BAA added to urine from 15 control subjects was 99% ±0.8%. The detection limit for BAA is 0.01 mg/L. This method has been recently upgraded to measure both BAA and the conjugated metabolites in urine (Sakai et al 1994). The conjugates are hydrolysed by acidifying the sample with concentrated hydrochloric acid and boiling the mixture for one hour.

BAA has also been analysed by an HPLC method which enables the simultaneous quantification of the amino acid conjugate N-butoxyacetylglutamine (BAA-GLN) (Rettenmeier et al 1993). Gas chromotography is not considered suitable for the determination of BAA-GLN as it is unstable at the temperatures required for eluting the corresponding methyl or trimethylsilyl derivatives from the GC column. Urine samples are acidified and then extracted with ethyl acetate, followed by the addition of 4-nitrobenzylbromide (in ether and acetonitrile) for derivatisation. Gradient elution HPLC is then conducted with water/acetonitrile as mobile phase on a 5µm Hypersil/ODS column with UV detection at 260 nm.

In a recently reported variation of this method, BAA was analysed by gradient elution HPLC on a µBondapak column using 0.1M ammonium acetate and acetonitrile as the mobile phase, with UV detection at 255 nm (Corley et al 1994).

6.4 Determination of 2-butoxyethanol and 2-butoxyacetic acid in blood

In general, the methods for BAA in blood are variations of the methods used for the analysis of BAA in urine.

The simultaneous ion-pair extraction and derivatisation of BAA with PFBB has been reported (Johanson and Johnssen 1991). Analysis is carried out by GC using electron capture detection.

It has been recently reported that 2-butoxyethanol and BAA in rat and human blood can be analysed using capillary gas chromatography linked to a mass spectrometer (GC-MS) (Bormett et al 1995). 2-Butoxyethanol and BAA are measured as the pentafluorobenzoyl and PFB derivatives respectively, with the quantitation limit 16-18 ng/g for both 2-butoxyethanol and BAA.

7. Use

7.1 Import and production

Approximately 700 tonnes of 2-butoxyethanol were imported into Australia during the 1993-1994 financial year from a number of countries including the Netherlands, Russia, Belgium, Singapore, Sweden, Germany and the USA. In addition, a number of cleaning products containing 2-butoxyethanol were imported into Australia.

2-Butoxyethanol is one of a number of glycol ethers manufactured in Australia by ICI Australia Operations Pty Ltd at their plant at Matraville NSW. Approximately 2000 tonnes of 2-butoxyethanol per year are manufactured.

At Matraville, 2-butoxyethanol is synthesised from the reaction of ethylene oxide and n-butanol. A number of glycol ethers are produced in the reaction, for example, the ethers of di- and triethylene glycol, so the various entities must be separated by distillation. The process, which is carried out in a sealed system, is continuous, with a production campaign usually lasting about 1-2 weeks. Other glycol ethers are synthesised at the plant from other alcohols and from propylene oxide.

2-Butoxyethanol is packed off into 205L drums, intermediate bulk containers (IBCs), or loaded directly into road tankers.

7.2 Uses of 2-butoxyethanol

2-Butoxyethanol is used in many different applications. The main use is in paints and surface coatings, followed by its use in cleaning products and then inks. Other products in Australia which contain 2-butoxyethanol include acrylic resin formulations, asphalt release agents, firefighting foam, leather protectors, oil spill dispersants and photographic strip solutions.

In international databases, 2-butoxyethanol is also listed as a solvent for greases, oils, dyestuffs and nitrocellulose resins and enamels. It has been used as an ingredient in agricultural chemicals, cosmetics and brake oils, and as a raw material in the production of acetate esters and phthalate and stearate plasticisers.

To identify the use and exposure pattern of cleaning products containing 2-butoxyethanol in Australia, and obtain MSDS and labels of the products, a questionnaire was sent in late 1994 to prospective formulators (see Appendix 2). From responses to the questionnaire, 82 formulators and 434 products were identified (see Appendix 1). It is estimated that approximately 1000 tonnes of 2-butoxyethanol per year are used in the formulation of cleaning products. No later survey was conducted to ascertain whether the cleaning products identified in the response to the questionnaire in 1994 had been reformulated.

7.3 Types of cleaning products

Analysis of the uses of the 434 cleaning products identified during the assessment revealed a wide variety of applications (as stated on the Material Safety Data Sheet and/or the label for each product). The main uses are tabled below.

Table 3 - Main Types of Cleaning Products

Use	Number	% of total	2-BE concentration (%)	
			min.	max.
surface cleaner	214	49	0.57	71
floor stripper	49	11	<1	30.5
glass/window cleaner	47	11	<1	40
carpet cleaner	40	9	<1	10-30
laundry detergent	15	4	<1.5	10-30
rust remover	11	3	<10	30-60
oven cleaner	11	2	<1	10-30
ink/resin remover	9	2	1	10 - 93
others	38	9	<10	94

For many of the products, the exact percentage of 2-butoxyethanol is not known as MSDS and/or labels were not submitted or, in some cases, only a concentration range was indicated on the MSDS. From the information submitted, most products had a concentration of 2-butoxyethanol of less than 10% (Table 4).

Table 4 - Concentration of 2-Butoxyethanol in Cleaning Products

2-BE Concentration	Number of Products	% of Total
< 10%	297	68%
10-30%	59	14%
30-60%	6	1%
10-60%	7	2%
> 60%	5	1%
unknown	60	14%

Many of the products classed as surface cleaners were actually multi-purpose cleaners which could be used in a variety of applications such as floor and wall cleaning, floor stripping, oven cleaning, grease trap cleaning, engine degreasing, vehicle washing and laundry pre-spraying. A number of products could be used in hot or cold water pressure cleaning machines.

Among the surface cleaners were a number of single purpose surface cleaning products. These included aircraft exterior cleaners, boat cleaners, upholstery cleaners,

travel wax cleaners for new vehicles, a grease trap cleaner, a decarboniser and an abbatoir hook cleaner.

Other types of cleaning products notified ('Others' in Table 3 above) included aluminium cleaner/brighteners, electrical cleaning solvents, bathroom cleaners and disinfectants, toilet cleaner/deodorants, combined cleaner/phosphate powders, a detergent for the removal of fats and greasy soils from apples, a detergent for the removal of sooty mould from citrus fruit, a hand cleaner, a fuel system cleaner, a cleaner of cylinders used in a silicone coating process, a harvester spindle cleaner, a glass and bottlewashing detergent, and an exhaust scrubber tank cleaner on underground mining locomotives.

7.4 Methods of applying cleaning products

Cleaning products work by wetting the surface, penetrating the soil or stain, lifting and removing the soil or stain, and holding the foreign material in suspension so that the surface can be rinsed or wiped.

Cleaning products are generally applied by one of the following methods:

- washing with liquid cleaner, for example, with a cloth or sponge, and wiping the surface;
- spraying the surface and then wiping;
- applying liquid cleaner by mop or brush;
- applying the cleaner as a liquid stream, for example, using a wash or squeeze bottle;
- applying the cleaning solution by machine, for example, in hot and cold water pressure cleaners, including steam and foam cleaning; or
- soaking in liquid cleaner.

In most cases, the cleaning product as marketed needs to be diluted with water prior to application. The dilution factor, which is often on the label, depends on the type of surface to be cleaned, the soil loading, and the type and method of application. For example, in degreasing and oven cleaning a dilution factor up to 1:5 is often used; as a spray for floor and wall cleaning dilution ranges from 1:10 to 1:30, and as a wash for delicate surfaces dilution ranges from 1:20 to 1:100.

A large proportion of the cleaning products are used in spray form. From the information supplied by formulators, at least 163 products are used in spray form, with spraying listed as the major method of application for 73 products. Twelve of these products are sold as pressurised aerosol containers or trigger packs.

For a number of products, end-users are directed (on the label) to use hot water (up to 80°C) for dilution. In some applications, for example, oven cleaning, end-users are

often advised (on the label) to apply the cleaning solution to a warm surface, for example, heated up to 65°C.

7.5 Formulation of cleaning products

The glycol ethers are common ingredients in cleaning products as they have a hydrophobic group to dissolve the grease or organic component of the soil or stain and a hydrophilic group to dissolve the water-soluble component. Most cleaning products also contain up to 5% surfactant, with other chemicals such as acids, alcohols and/or thickeners added to give the formulation its desired characteristics. For example, oven cleaners contain alkali, rust removers contain phosphoric acid and window cleaners contain ammonia. In most cases, cleaning products containing 2-butoxyethanol are aqueous solutions but some cleaners, for example, electrical cleaners and some carpet spotters, are hydrocarbon-based, and some window cleaners are ethanol-based.

Cleaning products are formulated by stirring the ingredients for 1-4 hours in a mixing tank, usually stainless steel and ranging in size from approximately 150-250,000L. Mixing usually takes place at room temperature and 2-butoxyethanol is generally the last, or one of the last, ingredients to be added to the mixer. It can be added directly to the mixing vessel from a 205L drum or it can be added to the mixer via a manifold and metering system from a drum or storage vessel. Smaller quantities are often pre-weighed into smaller drums or buckets before addition to the mixer.

Product is packed off into containers ranging in size from <1L (generally plastic containers) to 205L (drums). The containers are filled either by gravity feed from the mixing vessel or by pneumatic filling. The larger packs are distributed to repackagers and to the larger cleaning companies.

8. Occupational exposure

8.1 Routes of exposure

The major routes of exposure to 2-butoxyethanol are inhalation and skin absorption. 2-Butoxyethanol is a liquid which is miscible with water. It is readily absorbed through the skin, including absorption from aqueous solution, and in vapour and aerosol form.

Inhalation of 2-butoxyethanol may occur by exposure to vapours emitted from liquid 2-butoxyethanol or solutions containing the chemical, or by exposure to aerosols, for example, during the spray use of cleaning products. As 2-butoxyethanol has a relatively low volatility, emission of vapours is likely to be low. Conditions which may lead to increased generation of vapours and/or aerosols include heating and mechanical mixing.

Therefore the total exposure of workers to 2-butoxyethanol must take into account the inhalational uptake of vapours and aerosols and the dermal absorption of 2-butoxyethanol in liquid, vapour and aerosol form.

8.2 Methodology

In an assessment of occupational exposure, it is preferable to use good quality measured data, representative of the various work scenarios. When such data is unavailable or inadequate, then modelling can be used, with standard formulae often used to estimate exposure. Such estimates are often used in preliminary risk assessments to identify areas of concern which may be followed up using a more in depth assessment approach after obtaining more representative exposure data. This was the approach needed in this assessment of 2-butoxyethanol as measured data was limited, particularly for dermal exposure.

The estimates generated in this exposure assessment are considered to be 'feasible' worst-case estimates, as they describe high end or maximum exposures in 'feasible but not unrealistic' situations. The estimates are not intended to account for extreme or unusual use scenarios which are unlikely to occur in the workplace. The vast majority of occupational exposures are expected to be well below these estimates.

The formulae used to calculate exposures are detailed in Appendix 3. The constants used in the formulae, for example, inhalation rate and body weight, were consistent with those used in international assessments. The rationale behind the values used for some parameters in the formulae, for example, skin absorption and skin surface area, is detailed in Appendix 3.

In general, the critical health effect, haemolysis, is observed as a transient effect in animal studies. In repeated dose studies, haematological effects were more evident in animals during the first days of exposure, and generally full recovery from these effects was observed later in the studies. Also, 2-butoxyethanol is not bioaccumulative (see subsection 12.3.5). Therefore, occupational exposure estimates

were calculated for daily exposure (up to 8 hours) rather than for long-term average exposure.

Inhalational exposure was estimated using atmospheric monitoring data, mainly from overseas, and included extrapolation of the data in some instances. Estimates for exposure to vapour included the dermal uptake of vapour, which was estimated using data from PBPK modelling and the results of recent studies in volunteers, which showed that the dermal absorption of vapours comprises approximately 20% of the total absorption of vapours (see sections 9.2 and 9.6). As inhalational exposure estimates were based on actual monitoring data, which included data for spray use, the estimates incorporated inhalational exposure to aerosols.

The dermal absorption of liquid 2-butoxyethanol was estimated using the skin absorption rate obtained from toxicokinetic studies (see section 9.2). Liquid exposure estimates incorporated dermal exposure to aerosols.

8.2.1 Monitoring data

The monitoring data available for 2-butoxyethanol are described below and summarised in Table 5. Included are the results of local and overseas atmospheric monitoring and the results of biological monitoring (for the major metabolite, 2-butoxyacetic acid, BAA). In several of the studies, 2-butoxyethanol was being used in spray form.

Very few reports on the monitoring of workers and workplaces in Australia for 2-butoxyethanol are available. Only the following results were available:

- Regular personal and area TWA air monitoring is conducted at the manufacturing plant at Matraville, NSW. All 2-butoxyethanol results have been reported to be less than 2 ppm (9.8 mg/m^3).
- In a survey of four cleaners at three schools in the Coffs Harbour area in NSW (Rhyder 1992), 2-butoxyethanol concentrations were below the limit of detection for both personal monitoring (0.7 ppm; 3.4 mg/m^3) and TWA area monitoring (0.2 ppm; 1.0 mg/m^3). The cleaners were using a 1:4 dilution of a surface cleaner containing 1% 2-butoxyethanol and were applying the solution in both liquid and spray form during their work period at each school. One cleaner was monitored during dilution of the 1% concentrate. The area monitoring was conducted in the classroom at 1-1.5 hours after application of the cleaning solution.
- In a survey of apprentice spray painters in Sydney (Winder and Turner 1992) where 8 apprentices were exposed to a mixture of solvents which included 2-butoxyethanol, the mean TWA 2-butoxyethanol concentration was 0.4 ppm (2.0 mg/m^3).

Some overseas monitoring data are available in the open literature and in NIOSH health hazard evaluation (HETA) reports. Little data are available for formulation, with no data available for exposure during the formulation of cleaning products containing 2-butoxyethanol. In a study of 12 workers in a varnish production plant

(Angerer et al 1990), the concentration of 2-butoxyethanol in the varnish is not stated, nor is it stated whether the cleaning solutions used by the workers during their shift contained 2-butoxyethanol.

In the most comprehensive monitoring study available for workers exposed to 2-butoxyethanol during cleaning operations, the exposure of 23 workers (in France) using window cleaners was evaluated (Vincent 1993). The study comprised four groups of workers cleaning cars and two groups of office cleaners, with the results detailed in Table 5. The cleaning solutions were being applied in spray form. A poor correlation existed between 2-butoxyethanol atmospheric concentrations and BAA in urine (post-shift), possibly due to high skin absorption as most of the workers did not wear gloves. The highest BAA concentrations were obtained for a group of car cleaners who generally wore gloves but, due to the warm conditions, wore short-sleeved shirts. For the office cleaners in the study, BAA was detected in only three of the 32 post-shift urine samples. Pre-shift BAA concentrations were generally < 10 mg/g creatinine, however, an isolated reading of 99 mg/g and a few readings of approximately 30 mg/g were obtained for car cleaners.

8.2.2 Exposure duration and atmospheric concentration

A number of different work scenarios were considered in estimating exposure during the formulation and use of cleaning products containing 2-butoxyethanol. The modelled estimates of worker exposure are considered to be feasible worst-case estimates as they describe high end or maximum exposures in 'feasible but not unrealistic' situations.

The principal variables in the exposure estimates are the duration of exposure, the concentration of 2-butoxyethanol in air (for inhalational exposure) and concentration of 2-butoxyethanol in solution (for dermal exposure). The rationale behind the values used for these parameters in the various scenarios is discussed in the following relevant sections on exposure during formulation and cleaning (sections 8.4 and 8.5).

The calculations for the exposure estimates discussed in the following sections are detailed and tabled in Appendix 3.

Table 5 - Monitoring Results

Worker type	No. of workers	2-BE conc. (in product)	ppm 2-BE in air * range	mean	BAA in urine ** range	mean	Comments	Reference
Cleaning:								
Window cleaners	23						A number of measurements for each worker.	(Vincent 1993)
Cleaning cars								
- group A	2	14.4%	<0.1-1.2	0.5	9-178[+]		0.8-5h exposure, no gloves worn.	
- group B	6	21.2%	<0.1-2.8	0.84	<2-132[+]		0.3-4h exposure, no gloves worn.	
- group C	3	5.7%	<0.1		<2-37[+]		0.7-2h exposure, no gloves worn.	
- group D	2	21.2%	2.9-7.3	4.9	40-371[+]		5.3h exposure, short sleeves, gloves worn.	
Office cleaners								
- group A	8	9.8%	<0.3-0.7	0.32	<2-3.3[+]		15 min. exposure, no gloves worn.	
- group B	2	0.9%	<0.3		<2[+]		15 min. exposure, no gloves worn.	
Printing press operators	2		<0.15-0.53				Cleaning printing press rollers	(Kaiser 1990)
Print machine operators at food plant	5	10-50%	1.7-9.7	5.2			Cleaning of print machines using hydrocarbon-based wash solvent containing 2-BE.	(Salisbury and Bennett 1987)
Silk screener at fishing rod factory	1		3-5	4			Exposure to cleaning solvents (containing 2-BE) in spray form. Poor ventilation.	(Apol 1986)
Cleaner at food plant	1	0.3%	1.6				Mechanical floor scrubbing. Sampling only during operation (95 min.). Gloves, overalls, boots worn.	(Apol and Johnson 1979)
Hospital cleaners	4		<0.2				2-BE in window cleaner applied as spray. Sampling over whole shift. Gloves worn.	(Apol and Cone 1983)
School cleaners (Coffs Harbour NSW)	4	0.25%	<0.7 <0.2 (A)				Concentrations below the detection limit. Cleaning solution applied in liquid and spray form.	(Rhyder, 1992)
Formulation:								

Worker type	No. of workers	2-BE conc. (in product)	ppm 2-BE in air * range	mean	BAA in urine ** range	mean	Comments	Reference
Varnish production workers	12		<0.1-8.1	1.1	0.6-30[#]	10.5[#]	For individual results no correlation between 2-BE in air and BAA in urine.	(Angerer et al, 1990)
	12		<0.1-1.4	0.6	<0.2-61[#]	8.2[#]	Later monitoring of same group of workers.	(Sohnlein et al 1993)
Manufacture:								
Matraville plant (Sydney NSW)		100%	<0.1 <0.1-1.8 (A)				Enclosed process. Maximum (area) reading obtained during maintenance.	
USA plant		100%	<0.1 nd-1.7 (A)				Enclosed process. Maximum (area) reading obtained during drum filling. Local exhaust ventilation in place.	(Clapp et al 1984)
Other uses:								
Apprentice spray painters (Sydney NSW)	8			0.4			Exposed to mixture of solvents including 2-BE.	(Winder and Turner, 1992)
Workers in printing & electrical industries	70				0-9.9[+]		Exposure to solvents containing 2-BE. BAA control averaged 0.08 mg/g.	(Sakai et al, 1993)
- sub-group	9		0.4-0.8	0.64	1.3-9.9[+]	3.9[+]		
Parquet floor makers	9		up to 71	5.0			Exposed to wide variety of organic solvents, including 2-BE.	(Denkhaus et al 1986)
Silkscreeners	26	100%	13-36 23-169	25 63 (A)			Open spray troughs and wash table areas without ventilation or protective equipment, therefore high results.	(Kullman 1987)
Silkscreeners	16	up to 45%		6.8			Survey of a number of screen printing shops.	(Baker et al 1985)
Spray painters	5	up to 55%		2.6			Individual results not available.	

*Note: * 2-Butoxyethanol (2-BE) results are time-weighted average (TWA) values. ** BAA in urine results are expressed as reported in the literature - mg/g creatinine or mg/L urine.*
All 2-BE results are for personal monitoring unless otherwise indicated (A = area monitoring). nd = not detectable [+] BAA as mg/g creatinine [#] BAA as mg/L urine

8.3 Exposure during manufacture of 2-butoxyethanol

2-Butoxyethanol is manufactured by ICI Australia at Matraville in NSW. The process is enclosed and 2-butoxyethanol is stored in sealed tanks which are bunded to contain any spills.

Precautions are taken to minimise exposure during the transfer of 2-butoxyethanol to tankers and drums. Tankers are loaded via a mass flow meter to control the filling process so that problems such as overfilling and spillage are avoided. In drum filling, local exhaust ventilation is provided and butyl rubber gloves are worn by the operators to prevent skin contact in case of spillage.

Atmospheric monitoring is regularly conducted in the plant area for 2-butoxyethanol. Personal monitoring results for 2-butoxyethanol are generally <0.1 ppm (< 0.5 mg/m^3) for both STEL and TWA measurements. The highest monitoring results have been obtained during maintenance activities, where a TWA result of 1.8 ppm (8.8 mg/m^3) has been recorded in area monitoring. Therefore, inhalational exposure during manufacture is low.

These results for inhalational exposure during manufacture are supported by monitoring data available for a US plant (Clapp et al, 1984). For a similar process, where the manufacturing operation is also enclosed, the highest results were obtained during drum filling, with a TWA result of 1.7 ppm (8.3 mg/m^3) obtained in area monitoring. The highest personal monitoring reading was 0.1 ppm (0.5 mg/m^3). During drum filling, local exhaust ventilation was in place to minimise inhalational exposure in case of spills.

Due to the enclosure of the process and control measures taken to minimise skin contact, for example, during transfer to tankers, dermal exposure at the Matraville plant is incidental and therefore likely to be low. The main source of potential exposure is during maintenance activities. Purging of plant and equipment is standard practice on site. However, maintenance personnel are provided with butyl rubber gloves and long-sleeved overalls, so exposure is not expected to be significant. Incidental dermal exposure to liquid 2-butoxyethanol was calculated to be 0.2 mg/kg/day (see Appendix 3).

Taking 1.8 ppm (8.8 mg/m^3) as a maximum air concentration, the combined dermal and inhalational exposure would not be expected to exceed 1.4 mg/kg/day. From this assessment, the exposure of workers to 2-butoxyethanol during manufacture in Australia is low.

8.4 Exposure during formulation of cleaning products

8.4.1 Potential for exposure

In Australia, approximately 1000 tonnes of 2-butoxyethanol are formulated into cleaning products each year. During the assessment, 82 companies were identified, some producing cleaning products at more than one site, with at least 200 workers involved in formulation.

Duration of exposure

From responses to a questionnaire sent to formulators, workers are potentially exposed to 2-butoxyethanol for an average of 3 hours/week (range 0.1-20). For most formulators, 2-butoxyethanol is an ingredient in only some of their products, so exposure is not continuous on a daily or weekly basis. From 74 responses to the questionnaire, the distribution for potential exposure duration was as follows:

	number	%
less than 1 hour/week	30	41
1 hour	11	15
2 hours	11	14
3-4 hours	8	11
5-8 hours	6	8
greater than 8 hours	8	11

Exposure scenarios

During the formulation of cleaning products, workers may be exposed to 2-butoxyethanol during pre-weighing before mixing, during transfer to the mixing tank, during mixing and during the filling of containers with product. The whole operation is carried out at room temperature.

The potential exposure of workers to 2-butoxyethanol during mixing is variable as the process may be enclosed or relatively open. When the transfer of 2-butoxyethanol to the mixing vessel is carried out in a sealed system, potential exposure will be minimal. However, when the operator adds the raw materials directly by drum to the mixing tank, exposure may be greater due to possible splashing and vapour and/or aerosol generation. Information obtained from the questionnaire indicated that a number of formulators use the latter procedure and that approximately 50% of formulators carry out mixing in open top tanks, with greater potential for exposure.

There is potential for worker exposure during the product filling operation. While workers are potentially exposed to 2-butoxyethanol in a more dilute form than during pre-weighing and transfer to mixing tanks, the frequency and duration of exposure may be greater. The design of the filling operation will influence exposure. For example, if the packing line is enclosed at the point of filling, then inhalational exposure will be reduced. If filling is an automatic operation with containers pneumatically filled, then exposure is likely to be lower.

As operators are generally involved in both mixing and filling, the estimates of exposure are for the formulation process as a whole. Considering the process and the tasks during formulation where exposure may occur, inhalational exposure is assumed

to be continuous and dermal exposure intermittent for the purpose of calculating exposures.

Product concentrations for exposure estimates

For many of the cleaning products, a concentration range was available rather than the exact concentration of 2-butoxyethanol (see section 7.3). On the MSDS, the ranges commonly used are < 10%, 10-30%, 30-60%, and > 60%, so the concentrations selected for the exposure estimates were 10, 30 and 60%. Moreover, 10% is the concentration cut-off for 2-butoxyethanol for listing as a poison under the SUSDP (see section 12.4). Of the cleaning products surveyed in this report (section 7.3), 68% contain <10% 2-butoxyethanol, with only 3-4% containing >30%, of which 1% contain > 60% 2-butoxyethanol.

8.4.2 Exposure to vapour during formulation

The use of atmospheric concentrations for the estimation of worker exposure to 2-butoxyethanol vapours and aerosols during formulation is hampered by lack of data. No atmospheric monitoring results were available for the formulation of cleaning products containing 2-butoxyethanol.

Taking into account the air monitoring data set out in Table 5 for cleaning activities using high concentrations of 2-butoxyethanol (Vincent 1993; Salisbury and Bennett 1987), and noting the potential exposure to 100% 2-butoxyethanol (during pre-weighing and transfer), the atmospheric concentration during the formulation of a product containing 30-60% 2-butoxyethanol would not be expected to exceed 10 ppm (49 mg/m^3) TWA. This assumption is supported to some extent by the only data available for formulation, albeit formulation of varnishes containing 2-butoxyethanol (Angerer et al 1990; Sohnlein 1993). The maximum TWA air concentration for workers in the varnish production plant was 8.1 ppm (39.7 mg/m^3), although the 2-butoxyethanol content in the product(s) was not stated.

Atmospheric concentrations up to 1.2 ppm (5.9 mg/m^3) TWA have been reported during use of a 10-14% cleaning product (Vincent 1993). Taking into account that exposure to the product is less likely during formulation than during cleaning, but that some potential exposure to 100% 2-butoxyethanol exists, atmospheric concentration during the formulation of a product containing 10% 2-butoxyethanol would not be expected to exceed 2 ppm (9.8 mg/m^3).

As vapour estimates are based on monitoring data, they would also account for exposure to aerosols.

Exposure estimates

Assuming that the exposure to 2-butoxyethanol during formulation may occur on a single day each week (see *Duration of exposure* above), exposure estimates have been calculated for 3 hours and 8 hours exposure on a single day. The calculations are detailed in Appendix 3, section 2.2.

For the various scenarios, the estimates for exposure to 2-butoxyethanol vapours varied from 0.5 mg/kg/day (for 3 hours exposure during the formulation of a product

containing 10% 2-butoxyethanol) to 6.8 mg/kg/day (for 8 hours exposure during the formulation of a product containing 60% 2-butoxyethanol) [see Appendix 3, Table 1].

8.4.3 Exposure to liquid during formulation

As little data were available for dermal exposure to 2-butoxyethanol, with no data available for dermal exposure to liquid during formulation, exposures were estimated using the formulae in Appendix 3. Skin contact was assumed to be intermittent (contact for 20% of the work period).

As the generation of aerosols is expected to be infrequent during formulation, the contribution to total dose from dermal absorption of aerosols is expected to be minor.

For the various scenarios, the estimates for exposure to liquid 2-butoxyethanol varied from 0.2 mg/kg/day (for 3 hours exposure during the formulation of a product containing 10% 2-butoxyethanol) to 2.7 mg/kg/day (for 8 hours exposure during the formulation of a product containing 60% 2-butoxyethanol) [see Appendix 3, Table 1].

8.4.4 Combined dermal and inhalational exposure during formulation

For the various scenarios, the combined inhalational and dermal estimates for exposure to 2-butoxyethanol varied from 0.7 mg/kg/day (for 3 hours exposure during the formulation of a product containing 10% 2-butoxyethanol) to 9.5 mg/kg/day (for 8 hours exposure during the formulation of a product containing 60% 2-butoxyethanol) [see Appendix 3, Table 1].

The estimates are likely to be over-estimates for most work situations as they assume continuous inhalational exposure over the full work period and skin contact with the liquid formulation for 20% of the time. In practice, inhalational exposure is likely to be considerably lower in some plants, for example, where there is good ventilation and the transfer system is enclosed, and skin contact may be minimal, for example, by use of control measures such as automatic filling and suitable protective clothing. For air monitoring in particular, the data indicates that typical atmospheric concentrations of 2-butoxyethanol are likely to be significantly below the maximum values used in these estimates.

Given that only 3-4% of formulations contain > 30% 2-butoxyethanol, exposure of the majority of workers in formulation would not be expected to exceed 8.2 mg/kg/day. However, given that approximately 70% of formulators spend less than the average of 3 hours per week on the production of cleaning products containing 2-butoxyethanol, and that approximately 70% of cleaning products contain < 10% 2-butoxyethanol, the exposure of most formulation workers in Australia would not be expected to exceed 1.0 mg/kg/day.

8.5 Exposure during use of cleaning products

8.5.1 Potential for exposure

Due to the large number of cleaning products containing 2-butoxyethanol, a large number of workers may be exposed to the chemical. The main groups of workers who handle cleaning products containing 2-butoxyethanol include:

- carpet cleaners;
- contract cleaners;
- food process workers;
- hospital and nursing home workers;
- hospitality industry workers;
- householders;
- laundry cleaners and workers;
- mechanics;
- metal workers;
- school and office cleaners; and
- window cleaners.

Other workers who may use cleaning products containing 2-butoxyethanol include abbatoir workers, bottling plant workers, brewery workers, builders, chemical process workers, fishermen, leather workers, machine operators, miners, printers, oil rig workers, painters, panel beaters and transport workers.

The largest user-group is in the contract cleaning industry, where products containing 2-butoxyethanol are used widely. In Australia, it is estimated that there are at least 5400 contract cleaning companies, employing approximately 65,000 cleaners. In a survey of the occupational and health performance of the cleaning services industry (Foley 1995), it was estimated that approximately 80% of the cleaners worked part-time, with 25 hours estimated as their average working week. The above estimates do not include other large groups of workers such as liquor and hospitality workers, mechanics and house cleaners.

Exposure to 2-butoxyethanol during cleaning will be extremely variable, due to differences in frequency and duration, strength of solution used, method of application and precautions taken during use.

Dilution of cleaning products

The strength of solution used in the cleaning process is generally low as the product is usually diluted substantially before use, for example, most surface cleaners specify a dilution ratio in the range 1:3 to 1:100, depending on the application and the soil loading. A large proportion (68%) of cleaning products contain less than 10% 2-butoxyethanol, so the final strength of solution is often less than 1%. In a random survey of 20 general surface cleaning products containing < 10% 2-butoxyethanol, the dilution ratio ranged from 1:1 to 1:250, with most ratios in the 1:5 to 1:100 range. Some typical examples were:

- neat to 1:5 degreasing, cleaning ovens and equipment;
- 1:3 stripping floor wax;

- 1:10 cleaning hard surfaces with a heavy soil loading;
- 1:20 washing floors;
- 1:40 high volume foam cleaner;
- 1:100 light duty general cleaning;
- 1:160 pressure washing and steam cleaning.

Some products are sold as high level concentrates (> 50% 2-butoxyethanol) which must be diluted with large volumes of water before use. In some cases, products are diluted with hot water (up to 80°C). A list of cleaning products with their 2-butoxyethanol concentration can be found in Appendix 1.

Exposure during dilution

Dilution is often carried out daily at the beginning of the shift. While the dilution procedure is usually of short duration, the potential exposure may be greater due to use of higher concentrations of 2-butoxyethanol and the possibility of splashing. Higher exposures may also occur if the product is diluted with hot water as vapour concentrations may be higher and skin absorption facilitated. If dilution is carried out in a confined space or poorly ventilated area, exposure may be increased.

Exposure during application of cleaning solution

A number of different methods are used to apply the cleaning solution, for example, washing, wiping, mopping and spraying. Approximately half of the cleaning products are used in spray form, and a small number (12) are marketed in aerosol spray cans or trigger packs. This method of application will potentially increase both dermal and inhalational exposure as the atmospheric concentration of 2-butoxyethanol will be higher and dermal contact will be increased. The potential for exposure may also be increased where heat is applied during cleaning, for example, cleaning ovens and hot-plates.

Duration of exposure

For the calculation of exposure estimates, daily exposure times of 5 and 8 hours were used. As stated above, the average weekly working time in Australia for the largest group potentially exposed, contract cleaners, is 25 hours (average 5 h/day) as most work part-time (e.g. school and office cleaners).

As cleaners could possibly use cleaning products containing 2-butoxyethanol for the complete shift, for example, washing cars or cleaning floors, exposure was regarded as continuous for the purposes of calculating exposure estimates.

Product concentrations for exposure estimates

As the product is diluted substantially in most cases before use as a cleaning solution, often to strengths well below 1% 2-butoxyethanol, the concentrations selected for the calculation of exposure estimates were 0.1% as well as 1, 10, and 30%.

8.5.2 Exposure to vapour during cleaning

In the only local data available for cleaning operations, school cleaners using a solution containing approximately 0.25% 2-butoxyethanol were monitored, with the

atmospheric concentrations below the detection limit of 0.7 ppm (3.4 mg/m^3). As this data did not cover the range of 2-butoxyethanol concentrations that may be used during cleaning, overseas monitoring data were considered to be more suitable for the calculation of exposure estimates for cleaning solutions containing higher concentrations of 2-butoxyethanol.

In the monitoring data available (see Table 5), TWA air concentrations up to 9.7 ppm (47.5 mg/m^3) were obtained for print machine operators using a cleaning solvent containing 10-50% 2-butoxyethanol (Salisbury and Bennett 1987) and up to 7.3 ppm (35.8 mg/m^3) for workers cleaning car windows with a 21.2% solution applied as a spray (Vincent 1993). Based on this data, the 2-butoxyethanol air concentration selected for worst-case estimates for a 30% cleaning solution was 10 ppm (49 mg/m^3) TWA.

For cleaning solutions containing $\leq$ 1% 2-butoxyethanol, the atmospheric concentrations were generally below the limit of detection, however, a personal monitoring reading of 1.6 ppm (7.8 mg/m^3) was obtained during floor scrubbing with a 0.3% solution (Apol and Johnson 1979). Consequently, an air concentration of 2 ppm (9.8 mg/m^3) was selected for 0.1 and 1% cleaning solutions.

The only results available for a solution approximating 10% are < 2 ppm, however, based on the readings available for 0.3% and 21.2% solutions (Vincent 1993; Apol and Johnson 1979), a 2-butoxyethanol air concentration of 4 ppm (19.6 mg/m^3) was selected for exposure estimates for a 10% solution.

Exposure estimates

For the various scenarios, the estimates for exposure to 2-butoxyethanol vapours varied from 0.9 mg/kg/day (for 5 hours exposure during the use of a solution containing 0.1% 2-butoxyethanol) to 6.8 mg/kg/day (for 8 hours exposure during the use of a solution containing 30% 2-butoxyethanol). The calculations for the estimates are detailed in Appendix 3, Table 2.

8.5.3 Exposure to liquid during cleaning

As little data were available for dermal exposure to 2-butoxyethanol, exposures were estimated using the formulae in Appendix 3. The calculations for the estimates are detailed in Appendix 3, section 2.3.

Where cleaning solutions are applied in liquid or spray form, a skin surface area of 1000 cm^2 was considered to be reasonable when estimating dermal exposure to 2-butoxyethanol in liquid or aerosol form, taking into account that the duration of exposure is taken to be continuous throughout the work shift.

For the various scenarios, the estimates for exposure to liquid 2-butoxyethanol varied from 0.01 mg/kg/day (for 5 hours exposure during the use of a solution containing 0.1% 2-butoxyethanol) to 6.9 mg/kg/day (for 8 hours exposure during the use of a solution containing 30% 2-butoxyethanol) [see Appendix 3, Table 2].

8.5.4 Combined dermal and inhalational exposure during cleaning

For the various scenarios, the combined inhalational and dermal daily dose estimates for exposure to 2-butoxyethanol varied from 0.9 mg/kg/day (for 5 hours exposure during the use of a solution containing 0.1% 2-butoxyethanol) to 13.7 mg/kg/day (for 8 hours exposure during the use of a solution containing 30% 2-butoxyethanol) [see Appendix 3, Table 2].

These estimates are likely to be over-estimates of exposure in most work situations as they assume continuous skin contact with the cleaning solution and exposure to vapour over the full 5 or 8 hour period. In practice, some protective clothing may be worn and methods may be in place to minimise skin contact. Also, in many cleaning operations, use of 2-butoxyethanol cleaning products is more likely to be intermittent than continuous. In addition, good ventilation may be available.

Given that approximately 70% of cleaning products contain < 10% 2-butoxyethanol, and that most are diluted to a working strength below 1%, the combined exposure for most cleaners would not be expected to exceed 1.6 mg/kg/day. Moreover, many cleaners work part-time, particularly in the contract cleaning industry, so exposure of most part-time cleaners would not be expected to exceed 1.0 mg/kg/day.

8.6 Conclusions

Workers may be exposed to 2-butoxyethanol during its manufacture and during the formulation and use of cleaning products containing the chemical. Exposure may be short-term, for example, during spray application of a cleaning solution, or prolonged, for example, washing cars throughout a shift.

For 2-butoxyethanol in cleaning products, good quality monitoring data were limited, particularly for formulation. The atmospheric monitoring data available are TWA measurements, although some short-term monitoring, for example, 15 minutes, was conducted during specific cleaning operations. Very little data for dermal exposure were available. Using the available data as much as possible, estimates considered to be 'feasible' worst-case estimates were calculated for the exposure of workers to 2-butoxyethanol during manufacture, formulation and cleaning (see Appendix 3). The exposure estimates are summarised in Table 6. Typical estimates are for the exposure of the majority of workers to 2-butoxyethanol.

Table 6 - Summary of Exposure Estimates (mg/kg/day)

	Exposure estimates - worst-case	Exposure estimates - typical
manufacture	1.4	< 1
formulation	9.5	unknown
cleaning	13.7	< 1

Note: For formulation, scenarios for products containing up to 60% 2-butoxyethanol were considered. For cleaning, scenarios for products containing up to 30% 2- butoxyethanol were considered. The typical exposure estimate for cleaning assumes that most cleaning solutions contain < 1% 2-butoxyethanol.

Estimates should be recalculated for scenarios not accounted for in this exposure assessment, for example, 12-hour shifts, very heavy workload (elevated respiratory rate) and extensive dermal exposure (skin surface area exposed greater than 1,000 cm^2). Exposures higher than usual may also result during the use of heat and/or the use of non-aqueous cleaning solvents. It should also be noted that in some circumstances dermal exposure may be facilitated, for example when skin is damaged or when products are diluted with hot water.

EXAMPLES OF USE OF CLEANING SOLUTIONS

CONTAINING 2-BUTOXYETHANOL

Examples of use of cleaning solutions containing 2-butoxyethanol: photo 1 - Spraying and wiping

Examples of use of cleaning solutions containing 2-butoxyethanol: photo 2 - Carpet cleaning

Examples of use of cleaning solutions containing 2-butoxyethanol: photo 3 - Floor cleaning by machine

Examples of use of cleaning solutions containing 2-butoxyethanol: photo 4 - Dilution of cleaning solution

Examples of use of cleaning solutions containing 2-butoxyethanol: photo 5 - Mopping floor

Examples of use of cleaning solutions containing 2-butoxyethanol: photo 6 - Floor and surface cleaning

2-Butoxyethanol is manufactured at only one plant in Australia. The process is enclosed and regular air monitoring is conducted. Exposure is low, with worker exposures not expected to exceed 1.4 mg/kg/day. This estimate is based on data for non-routine operations such as maintenance and drum filling. As the manufacturing process is enclosed, exposure during routine process work would be much lower. Due to the nature of the process and the control measures in place at the plant, typical exposures are expected to be well below the exposure estimates.

Worker exposure to 2-butoxyethanol during formulation is expected to be quite variable due to differences in process conditions (for example, whether the process is enclosed or relatively open) and the duration of exposure (for example, some formulators produce cleaning products containing 2-butoxyethanol infrequently or in small quantities). From the assessment of exposure, exposures are not expected to exceed 9.5 mg/kg/day, however, for most formulation workers, exposures would be much lower at 1.0 mg/kg/day. Due to the lack of measured data for formulation, and the variation in engineering controls, it is not feasible to quote typical exposures. Exposures in plants where the process is enclosed are expected to be much lower than the exposure estimates.

A large number of cleaning products containing 2-butoxyethanol are marketed in Australia, with thousands of workers potentially exposed to the chemical. Worker exposure varies considerably due to factors such as the type of work, method of application, exposure time and concentration of 2-butoxyethanol in the cleaning solution. Exposure, particularly inhalational exposure, will be increased during spray application or during other operations which may generate vapours or aerosols. From the assessment of exposure, exposures are not expected to exceed 13.7 mg/kg/day, however, for most workers using cleaning products, exposures would be 1.6 mg/kg/day. Using the average atmospheric levels available from monitoring data (see Table 5), typical exposures during the use of most cleaning solutions containing (<1%) 2-butoxyethanol would be less than 1 mg/kg/day.

The exposure assessment has shown that the dermal exposure component of total worker exposure to 2-butoxyethanol may contribute up to 50% of the total exposure (inhalation plus dermal), especially with prolonged (5-8 hours) use of cleaning products containing 10% or more 2-butoxyethanol.

9. Kinetics and metabolism

9.1 General

The toxicokinetics of 2-butoxyethanol have been well investigated in laboratory animals, particularly the F344 rat, and some studies have been conducted on human volunteers. The results of many of the studies have been reported in the open literature, including summaries by ECETOC (1994) and Johanson (1988).

In order to optimise the extrapolation of data from one species to another, pharmacokinetic models have been developed.

9.2 Absorption

9.2.1 Animal studies

Dermal

A number of studies have been conducted in experimental animals to measure the absorption rate of 2-butoxyethanol through the skin, including measurements using various strengths of aqueous solution.

In a study in male and female Wistar rats (Bartnik et al 1987), 200 mg/kg of radiolabelled 2-butoxyethanol (undiluted) was applied to the skin under a perforated glass capsule for 48h. Of the applied dose, 29% was absorbed in males within 48h and 25% in females. The maximum radioactivity in blood and plasma occurred after 2h. As the study was conducted under nonocclusive conditions, some 2-butoxyethanol may have evaporated.

In an occlusive study in ten female guinea pigs using undiluted 2-butoxyethanol (Johanson and Fermstrom 1986), the mean absorption rate obtained was 1.77 mg/cm^2/h (range 0.35-3.3), measured by analysing blood samples at intervals up to 2h after application. In a later study by the same authors using aqueous solutions of 2-butoxyethanol (5-80%) and undiluted 2-butoxyethanol (Johanson and Fernstrom 1988), higher absorption rates were obtained for the aqueous solutions (range 0.52-0.73 mg/cm^2/h) than for the undiluted chemical (0.27 mg/cm^2/h). Only 2 guinea pigs per concentration were used (except for 40% solution - 4 animals). Following this initial exposure, all animals (14) were then exposed to 100% 2-butoxyethanol for 2h and a mean uptake rate of 0.94 mg/cm^2/h (range 0.45-2.9) was obtained.

Although the mean absorption rates varied between studies and the individual rates varied within a study, it was clearly demonstrated that 2-butoxyethanol is significantly absorbed through the skin of the guinea pig, that uptake is rapid, and that absorption is high from aqueous solution.

Inhalational

In a study in male Sprague-Dawley rats (Johanson 1994), the mean uptake rate for continuous exposure to 20 or 100 ppm of 2-butoxyethanol for periods up to 12 days was 1.53 mg/h (3.5 mg/kg/h) and 7.73 mg/h (17.8 mg/kg/h) respectively. The rate

was independent of duration of exposure. No clinical signs of toxicity were observed during exposure. By interpolation, the absorption rate for 25 ppm would be 4.4 mg/kg/h.

9.2.2 *In vitro* studies

A number of *in vitro* studies have been conducted in skin samples from various species, including human tissue, to measure the skin absorption of 2-butoxyethanol.

A series of tests was conducted using both undiluted 2-butoxyethanol and lower strength aqueous solutions (Bartnik et al 1987). The results are tabled below.

Table 7 - *In Vitro* Skin Absorption of 2-Butoxyethanol

Species	Concentration (2-BE %)	Dose* (mg/cm^2)	% of Dose Absorbed/ Absorption Rate ($mg/cm^2/h$)					
			1hour		6hours		16 hours	
			%	rate	%	rate	%	
Rat	100	5.4	19.4	1.05	66.7	0.60	94.3	0.32
	10	0.60	62.7	0.38	80.9	0.081	85.1	0.032
		0.10	43.3	0.043				
	3.5	0.21	45.6	0.096	79.0	0.028	88.4	0.012
Pig	100	5.4			11.2	0.10		
	10	0.60	21.1	0.13	36.9	0.037		
		0.10	17.7	0.018				
	3.5	0.21			47.5	0.017		
Human	10	0.10	17.3	0.017				

** applied dose expressed in terms of 2-butoxyethanol weight*

The results indicated that absorption through rat skin is high and rapid. Absorption through pig and human skin was lower but significant. The % dose absorbed from aqueous solutions was higher than for undiluted 2-butoxyethanol, but the applied dose was much lower. The effects on the rate of skin absorption of 2-butoxyethanol by two ingredients typical of those normally used in cleaning product formulations were also evaluated (separately) in rat and pig skin. The addition of 5% of isopropanol and 5% linear sodium dodecylbenzene sulfate to 3.5% and 10% aqueous 2-butoxyethanol solutions did not significantly affect the skin absorption rate of 2-butoxyethanol.

In human skin tissue measurements, undiluted 2-butoxyethanol was allowed to permeate for 8 hours across a hydrated section of abdominal membrane held in a glass diffusion cell. Dugard et al (1984) obtained a mean absorption rate of 0.20 $mg/cm^2/h$ (range 0.14-0.35). The unpublished data (Scott and Mawdsley 1982) were available for assessment. Barber et al (1991) obtained a higher rate of 1.19 $mg/cm^2/h$ (range 0.57-1.91) for tests in which the damage ratio was acceptable. [Note that the damage ratio is the ratio of permeability constants before and after exposure, with a high ratio indicative of irreversible damage to the skin specimen. In four of Barber's results, the damage ratio was regarded as being unacceptably high (range 6-13), whereas the

corresponding range in Dugard's experiments was 0.8-3.3.] As the series of tests by Barber et al was characterised by wide variability in the results, including a wide variation in the damage ratios of the skin specimens used, the reliability of the study is questionable.

Dugard compared the absorption rates of a number of different glycol ethers and other solvents, with the results summarised in Table 8 (Dugard et al 1982, 1984).

Table 8 - *In Vitro* Skin Absorption Rates of Glycol Ethers and Other Solvents

Chemical	Rate ($mg/cm^2/h$)
2-methoxyethanol	2.82
2-ethoxyethanol	0.80
2-butoxyethanol	0.20
2-(2-methoxyethoxy) ethanol	0.21
2-(2-ethoxyethoxy) ethanol	0.125
2-(2-butoxyethoxy) ethanol	0.035
1-methoxypropan-2-ol	1.17
2-ethoxyethyl acetate	0.80
toluene	0.70
aniline	0.66
chlorobenzene	1.1

The results showed that the absorption rates of the lower homologues, 2-methoxyethanol and 2-ethoxyethanol, were considerably higher than that of 2-butoxyethanol. The absorption rates of the diethylene glycol ethers were considerably lower than the corresponding monoethylene ether.

9.2.3 Human studies

In a human study (Johanson et al 1988), five male volunteers were exposed to 2-butoxyethanol by immersing four fingers of one hand in the chemical (undiluted) for 2h. None of the volunteers was occupationally exposed to solvents and all were non-smokers and consumed little or no alcohol. The mean dermal absorption rate (geometric mean) from 12 measurements was 0.142 $mg/cm^2/h$, with the individual results quite variable (range 0.05 - 0.68 $mg/cm^2/h$). The uptake rate was about 5-10 times lower than that obtained for guinea pigs, but similar to the human *in vitro* result obtained by Dugard et al and consistent with general findings that the permeability of guinea pig skin is greater than human skin. For most of the measurements in the study, there was little or no delay in detecting 2-butoxyethanol in the bloodstream, with the concentration in blood continuing to increase after exposure in most cases, possibly due to a depot effect. The effect of 2-butoxyethanol on the skin of the volunteers was not severe, with visible changes including decreased finger volume and skinfold thickness and a wrinkled appearance which was most obvious at 2-4h after exposure.

In a study carried out in an inhalational chamber (Johanson et al 1986), seven male volunteers were exposed to 20 ppm of 2-butoxyethanol for 2h during light exercise at 50 watts (mean breathing rate 22.6 L/min. or 1.36 m^3/h). By analysing expired air samples at regular intervals during the study, the mean respiratory absorption rate was estimated as 71.6 mg/h (range 54.7-97.1), equivalent to 57.3% of the inspired amount. The uptake was rapid and remained relatively constant during exposure. No adverse health effects were experienced by the volunteers during the experiment.

In a later study by the same authors (Johanson and Boman 1991), the absorption rate of 2-butoxyethanol vapours was measured by exposing 4 male volunteers to 50 ppm for 2h, firstly by inhalation (mouth only), and then by skin only (the volunteers wore shorts and an air respirator). The absorption rates were calculated by measuring the 2-butoxyethanol concentration in blood sampled from the fingers, using the finger-prick method, at regular intervals during exposure. The effect of raised temperature and relative humidity was measured by repeating the experiment at least two weeks later. At ambient temperature (23°C), the inhalational absorption rate was 70.2 mg/h (range 58.9-78.1) whereas the dermal absorption rate was 227 mg/h (range 61.8-348). The results suggest that dermal uptake accounts for approximately 75% of the total uptake during whole-body exposure to 2-butoxyethanol vapours. The average absorption rates at raised temperature and humidity were higher, although the difference was not statistically significant; breathing rates were slightly higher but heart rates were about the same. The respiratory absorption rate was similar to that obtained in the earlier inhalational study conducted at a lower concentration (20 ppm) (Johanson et al 1986) probably due to the lower mean breathing rate (8.8 L/min.) compared with the increased respiration (during light exercise at 50 watts) in the earlier experiment. This result indicated that respiratory uptake is increased under a workload.

In a recent repeat of this study in another laboratory (Corley et al 1995), where six male volunteers exposed one arm to 50 ppm 2-butoxyethanol for two hours, the dermal absorption of vapours was no more than 21% of the total uptake. Blood was sampled from the exposed arm using the finger-prick method and from the unexposed arm using a catheter. The results indicated that sampling via the finger-prick method was not representative of systemic blood concentrations of 2-butoxyethanol. Full details of this study were not available.

In an inhalational study in male volunteers (Van Vlem 1987), reported by NIOSH (1990), 67-78% of the inspired amount was absorbed during exposure to 12.6 or 25.2 ppm, either at rest or during light exercise at 30 watts. The volunteers wore face masks during the four hour exposure. The mean absorption rate for the 25.2 ppm test at rest was 31 mg/h; the breathing rate was not stated. At 12.6 ppm, the mean respiratory uptake rate at rest was 15.5 mg/h, but under a 30 watts workload, it was 33 mg/h.

9.3 Distribution

Animal studies have shown that 2-butoxyethanol is rapidly distributed to all tissues via the blood stream.

In a gavage study (Ghanayem et al 1987(b)) in F344 rats treated with a single dose of 125 or 500 mg/kg of ^{14}C-labelled 2-butoxyethanol, ^{14}C radioactivity was detected in the following tissues at 48h after dosing: liver, kidney, spleen, lung, heart, forestomach, glandular stomach, skin, testes, muscle, blood and fat, with the highest levels in the forestomach, then the liver, kidneys, spleen and glandular stomach.

In a dermal study in male Wistar rats (Bartnik et al 1987), ^{14}C-labelled 2-butoxyethanol was distributed widely to all tissues, with the greatest level of radioactivity in the spleen and thymus, followed by the liver.

In an inhalational study (Johanson 1994), male Sprague-Dawley rats were continuously exposed to 20 or 100 ppm 2-butoxyethanol for 12 days. The mean concentrations of 2-butoxyethanol and the principal metabolite BAA in tissues are tabled below.

Table 9 - Distribution of 2-Butoxyethanol and 2-Butoxyacetic acid in the Rat after Exposure to 20 ppm or 100 ppm 2-Butoxyethanol

	2-Butoxyethanol		2-Butoxyacetic acid	
	at 20 ppm	at 100 ppm	at 20 ppm	at 100 ppm
Blood (µmol/L)	15.1	72.3	41.0	179
Muscle (µmol/kg)	9.1	30.4	9.3	36.2
Testis (µmol/kg)	3.9	2.6	14.1	26.7
Liver (µmol/kg)	10.8	83.8	16.4	85.2

9.4 Metabolism

The metabolism of 2-butoxyethanol has been thoroughly studied in experimental animals, particularly in the rat, and the results are well documented in the open literature (ECETOC 1994). The major metabolite identified in both animals and humans is BAA. The main pathways for the metabolism of 2-butoxyethanol in the rat are presented in Figure 1 (from Medinsky et al 1990).

Early metabolism studies in animals indicated that the main metabolic pathway was oxidation of 2-butoxyethanol by the alcohol and aldehyde deydrogenase enzymes to BAA via the aldehyde, 2-butoxyacetaldehyde (BAL). It was postulated (Ghanayem et al 1987 (c)) that minor degradation of BAA to CO_2 occurred by cleavage of the ether bond, oxidation to butyric acid and entry into fatty acid catabolism. In one of the gavage studies conducted under the NTP, the administration of 2-butoxyethanol in young (4-5 weeks) and adult (9-13 weeks) rats resulted in higher proportions of BAA and $^{14}CO_2$ in the younger rats, probably due to more complete metabolism.

Later studies have supported this pathway and also the alternative metabolic pathways proposed by Medinsky et al (see Figure 1), which included O-dealkylation of 2-butoxyethanol to ethylene glycol and some further breakdown to CO_2. In later dermal and inhalational studies in the F344 rat, the same metabolites were identified. The inhalational study indicated that there was a relationship between exposure concentration and the metabolic route. Higher relative concentrations of BAA and ethylene glycol were obtained at the lower vapour concentrations, and higher 2-butoxyethanol glucuronide (BEG) at the high doses, possibly due to saturation of the pathways leading to BAA and ethylene glycol (EG).

In a recent gavage study in the F344 rat (Corley et al 1994), BAA was again the major metabolite in urine (approx. 65% of ^{14}C-2-butoxyethanol at dose of 126 mg/kg), with approximate concentrations of 15% and 4% of BEG and ethylene glycol respectively.

In an unpublished *in vitro* study conducted with a number of glycol ethers (Calhoun and Miller 1983), the results indicated that 2-butoxyethanol was a relatively good substrate for alcohol dehydrogenase.

A number of studies in volunteers indicate that 2-butoxyethanol is efficiently metabolised in humans. In the inhalational study where seven male volunteers were exposed to 20 ppm 2-butoxyethanol for two hours (Johanson et al 1986), 41% of the absorbed dose was excreted as BAA in the urine in 24 hours and only 0.03% as 2-butoxyethanol. In reports (NIOSH 1990) of inhalational studies by Van Vlem (1987),

13-27% of the absorbed dose was excreted as BAA in urine and less than 1% eliminated as 2-butoxyethanol.

A monitoring study of lacquerers exposed to 2-butoxyethanol showed that the amino acid conjugate of BAA, N-butoxyacetylglutamine, is an important metabolite of 2-butoxyethanol in humans (Rettenmeier et al 1993). The metabolite has not been observed in animal studies.

Figure 1 - Proposed Metabolic Scheme of 2-Butoxyethanol in Rats
[Adapted from Medinsky et al 1990]

Note: See Abbreviations at beginning of report.

9.5 Elimination and excretion

Numerous studies in experimental animals have shown that the major metabolite 2-butoxyacetic acid (BAA) is rapidly excreted in urine after exposure to 2-butoxyethanol.

In a recent inhalation study in Sprague-Dawley rats (Johanson 1994), a total blood clearance of 2-butoxyethanol of approximately 2.6 L/h/kg was measured. The value was independent of vapour concentration (20 and 100 ppm) and was relatively constant throughout the 12 days of continuous exposure. The mean renal clearance values for BAA were 0.49 L/h/kg (mean excretion rate 0.98 mg/h) for 20 ppm, and 0.58 L/h/kg (5.3 mg/h) for 100 ppm.

In a study of the elimination kinetics of 2-butoxyethanol in perfused rat liver (Johanson 1988), the hepatic blood clearance of 2-butoxyethanol was reported as approximately 2.0 L/h/kg. The elimination rate was clearly dependent on concentration. The addition of 0.1% ethanol drastically reduced the elimination rate, supporting the hypothesis that 2-butoxyethanol is normally oxidised by alcohol dehydrogenase in the liver. This effect of ethanol on the elimination of 2-butoxyethanol from blood was also observed in a study in female Sprague-Dawley rats (Romer et al 1985).

In a 2-hour inhalational study in human volunteers (Johanson et al 1986), the mean elimination half-life of 2-butoxyethanol in the blood was 40 min., with a total blood clearance of 1.2 L/min. and a steady-state volume of distribution of 54 L. The concentration and excretion rate of BAA in urine was variable between subjects, with the respective maxima attained after 5-12h and 2-10h. The mean elimination half-life for BAA in urine after exposure was 5.8h.

In a dermal study in human volunteers (Johanson et al 1988), the half-life obtained for the elimination of 2-butoxyethanol from blood was longer (approx. 80 min.), possibly due to a depot effect in the skin. The BAA concentration in urine reached a

maximum at about 3h after exposure, with a mean half-life of 3.1h. A wide variation in results existed between subjects in the study.

9.6 Pharmacokinetic models

Physiologically-based pharmacokinetic (PBPK) models link information about the toxicokinetics and physicochemical properties of a chemical to the effects of the physiological and biochemical processes. They enable data to be extrapolated across species and similar chemicals to be compared within a species. A number of different models have been proposed for 2-butoxyethanol to enable the extrapolation of the effects observed in one species to another, in particular the effects in the rat to humans. Johanson (1986) proposed a PBPK model for the inhalation of 2-butoxyethanol in humans, but recent developments of the model by Shyr et al (1993) and Corley et al (1994) have incorporated more data, including that from rat studies and other routes of exposure.

The Corley model is a dual 2-butoxyethanol-BAA model developed to incorporate more physiological and biochemical information on BAA, the principal metabolite of 2-butoxyethanol. The model also incorporates the other metabolic pathways identified in metabolism studies (see section 9.4 above). In validation work against a wide variety of test results, including data from rat and human studies and data from different exposure routes, values predicted by the model generally agreed well with experimental data. However, the model predicts a much lower dermal uptake of 2-butoxyethanol vapours than the results obtained in a human study (Johanson and Boman 1991) where the dermal uptake of vapours constituted approximately 75% of the total amount absorbed. From simulations of the data conducted on the assumption that the blood sampled (from the fingers) was venous blood (drained from the skin) rather than arterial blood, the Corley et al (1994) PBPK model predicted that the dermal uptake was much lower at 21% of the total amount absorbed.

Aspects of the model are discussed further in chapters 12, *Hazard Assessment and Classification* and 13, *Risk Characterisation*.

9.7 Summary

2-Butoxyethanol is well absorbed in all species via the inhalational, oral and dermal routes. Studies have shown that 2-butoxyethanol is rapidly absorbed through the skin. Dermal absorption rates from controlled human studies (mean 0.14 mg/cm^2/h, range 0.05 - 0.68 mg/cm^2/h) and in *in vitro* human skin specimens (mean 0.2 mg/cm^2/h; range 0.14 - 0.35 mg/cm^2/h) indicate that the dermal absorption rate is most likely of the order of 0.2 mg/cm^2/h. Higher results were obtained in one *in vitro* study, however, the results were questionable.

Studies in guinea pigs and *in vitro* studies in various species, including humans, showed that 2-butoxyethanol is readily absorbed through the skin from aqueous solution. The guinea pig study indicated that the absorption rate may be higher for aqueous solution than for undiluted 2-butoxyethanol, but there were some inconsistent results within the study. *In vitro* studies indicated a higher percentage absorbed from diluted solutions than undiluted 2-butoxyethanol, but the rate of absorption was lower

for aqueous solution. As skin absorption rate is an important determinant in human risk assessment, additional work is needed to clarify the effect of water on absorption rate. *In vivo* studies have shown that, in experimental animals and humans, dermal absorption can occur in the absence of local effects such as irritation.

An absorption study in volunteers exposed to 2-butoxyethanol vapours indicated that the dermal uptake was approximately 75% of the absorbed dose during whole-body exposure. However, a recent study in volunteers indicated that 75% is likely to be an overestimate due to the inappropriate methodology for blood sampling. This study and predictions from Corley et al's PBPK model indicated that the dermal absorption of vapours is more likely 20% of the dose, which is more consistent with the generally-accepted assumption that dermal uptake of vapours is lower compared with respiratory uptake. The data demonstrated the significant contribution of skin absorption to total body uptake during whole-body exposure to vapours.

Inhalational studies in volunteers at rest and under light exercise showed that the respiratory absorption rate of 2-butoxyethanol was considerably higher under a workload.

Following absorption, 2-butoxyethanol is distributed to all parts of the body. It is efficiently metabolised, mainly to BAA, which is formed by oxidation by alcohol/-aldehyde dehydrogenase. Smaller amounts of the glucuronide and sulfate conjugates and ethylene glycol can be formed by other metabolic pathways. In humans, the amino acid conjugate, N-butoxyacetylglutamine, has also been detected in urine, and suggests an additional detoxification pathway in humans. The metabolites of 2-butoxyethanol are rapidly excreted in urine, with BAA elimination half-lives of 3.1 and 5.8h being obtained in human studies. Studies in animals and humans indicate that the metabolic pathways are similar, although the main detailed studies have only been in the male F344 rat. In human studies, wide variations in absorption and excretion rates between subjects have been found.

10. Effects on experimental animals and *in vitro* test systems

10.1 General

A number of reviews of the health effects of 2-butoxyethanol have been published in recent years. These have included:

- ECETOC Technical Report No.64 (August 1995);
- ECETOC Special Report No.7 (April 1994);
- Chapter 31 of *Patty's Industrial Hygiene and Toxicology, 4th edition*, by Gingell et al (1994);
- the USA Cosmetics Ingredient Review (Cosmetic, Toiletry and Fragrance Association 1994);
- the NIOSH *Criteria for a Recommended Standard* for occupational exposure to 2-butoxyethanol and its acetate (September 1990);
- *'Toxicokinetics of 2-butoxyethanol'* by Johanson (1988);
- HSE Toxicity Review no.10 (1985).

This chapter will summarise data covered by other reviews of the health effects of 2-butoxyethanol, and will report on the assessment of unpublished studies and more recently published work.

10.2 Acute toxicity

10.2.1 Oral

The oral LD_{50} has been determined in a variety of species, with the range of values cited in the open literature (ECETOC 1994; Gingell et al 1994) as follows:

species	sex	LD_{50} (mg/kg)
rat	male	560-3000
	female	530-2800
mouse	male	1230
guinea pig		950-1400
rabbit	male	320-370

Effects observed in animals included congestion and haemorrhage of the lungs, mottled liver, kidney congestion and haemoglobinuria. Clinical observations included narcosis, breathing difficulty, rough haircoat and general lethargy.

A number of unpublished oral rat studies were assessed, with the LD_{50} values tabled below.

sex	LD_{50} (mg/kg)	Observed effects	Reference
male	1746	Haemoglobinuria	(Eastman Kodak 1981(a))
male	2410	Breathing difficulty, bloody saliva; liver, kidney and adrenal discolouration; distended stomach, intestinal blood	(Bushy Run Research Centre 1980(c))
female	1000-2000	Clinical observations include perineal staining, rough hair coat, lethargy, respiratory distress, necrosis of tails.	(Carreon 1981)

These values were within the range of published oral LD_{50} values for the rat. The signs of toxicity were similar to those reported in published data.

In a recent guinea pig study (Shepard 1994 (a)), 5 animals/sex/dose were fed 500, 1000 or 2000 mg/kg 2-butoxyethanol by gavage and the LD_{50} was calculated to be 1414 mg/kg. Clinical signs indicating that 2-butoxyethanol was irritating to the stomach were confirmed at necropsy, with necrosis and haemorrhage in the gastric mucosa observed. No signs of haematotoxicity were seen in the study.

10.2.2 Dermal

The dermal LD_{50} has been determined in the rabbit and the guinea pig, with the range of values cited in the open literature (ECETOC 1994) for the rabbit being 100-610 mg/kg. LD_{50} values obtained for the guinea pig were 210 and 270 mg/kg for intact and abraded skin respectively (Roudabush et al 1965).

Where information was available, early deaths were due to narcosis or respiratory failure, and later deaths to kidney damage. Effects observed at necropsy in rabbit studies included severe congestion of the kidneys, spleen, liver and lungs. Haemoglobinuria was noted in the rabbits and, in a study by Carpenter (1956), an increased osmotic fragility of red blood cells was observed at 500 mg/kg one hour after a 3 minute contact period. In a study in female rabbits (Duprat and Gradiski 1979), haemoglobinuric nephrosis was noted in all animals which died, and kidney lesions were observed in surviving animals above 90 mg/kg.

The LD_{50} values obtained in unpublished studies in the rabbit were as follows: male 567 mg/kg, female 636 mg/kg (Bushy Run 1980(c) and (b)). These values are consistent with rabbit LD_{50}s reported in the open literature (see above). Summaries only of both studies were available. Four animals at two doses only were used. The effects observed at necropsy were similar to those seen in other acute studies, viz. discoloured liver, kidneys, adrenals and intestines, and bloated stomach. Haemoglobinuria was observed in animals at both doses. Nystagmus was seen in two high dose females some hours after exposure.

In a comparative study of nine glycol ethers in male New Zealand white rabbits (Eastman Kodak 1981 (b)), an LD_{50} of 435 mg/kg was obtained for 2-butoxyethanol. The protocol was similar to OECD TG402. The effects observed at necropsy included discoloured (dark) kidneys and stomach, pale liver, and haemoglobinuria. In the study, members of the mono-ethylene glycol ethers were more toxic than the corresponding members of the diethylene glycol ethers and, for both groups, toxicity increased with molecular weight. In the same study, it was noted in skin irritation tests that some guinea pigs survived a dose of 4.5 g/kg for 24 hours (see subsection 10.3.1, *Skin Irritation*).

In a recent guinea pig study (Shepard 1994 (b)), no deaths were recorded at the single limit dose of 2000 mg/kg. No clinical signs of toxicity were observed during the study and no effects on organs were noted at necropsy.

There appears to be a wide variability in the dermal LD_{50} values for guinea pigs. The LD_{50} value of the Shephard study (1994(b)) is approximately ten-fold higher than the LD_{50} obtained by Roudabush et al (1965) but is more consistent with the data from an Eastman Kodak (1981(b)) study in which some animals survived doses of 4.5 g/kg. The Roudabush study was conducted in accordance with standard US testing protocol of the time, however the methodology differs in some aspects from OECD Guideline 402, such as choice of treatment site and degree of occlusion. Based on this information, the results of the Roudabush study are considered questionable.

10.2.3 Inhalation

The inhalational LC_{50} has been determined in a variety of species, with the following values cited in the open literature (ECETOC 1994):

species	sex	LC_{50} in ppm (mg/L) exposure	Duration
rat	male	486 (2.41)	4 hours

	female	450 (2.21)	4 hours
mouse		700 (3.4)	7 hours
guinea pig		1300 (6.4)	7 hours

The main effects observed were spleen and kidney damage and haemoglobinuria. In range-finding inhalational studies by Carpenter (1956), increased osmotic fragility of red blood cells was noted in female rats exposed to 62 ppm (0.30 mg/L) for four hours, with older rats more susceptible to this effect than young rats.

The full study for the four-hour LC_{50} rat study cited above (Snellings and Evancheck 1980) was available for assessment and the experimental details have been well reported in the literature. During exposure, a loss of co-ordination, breathing difficulty and blood around the urogenital area were observed at the two highest doses, 523 and 867 ppm. Tail lesions and a marked decrease in body weight were noted in survivors at 523 ppm. Gross pathology of the animals that died revealed enlarged, discoloured kidneys and blood in the urine. No significant gross lesions were observed in survivors at necropsy.

In a range-finding study in six guinea pigs (Carpenter 1956), the animals were exposed to a single dose of concentrated vapour (approx. 930 ppm or 4.5 mg/L 2-butoxyethanol) for four hours. One animal died and no haemoglobinuria was observed.

In a recent guinea pig study (Nachreiner 1994), no mortality or clinical signs of toxicity resulted when male and female animals were exposed (whole body) to 633 or 691 ppm 2-butoxyethanol respectively (3.1 or 3.4 mg/L), but the duration of exposure was 1 hour instead of the usual 4 hours.

10.2.4 Intraperitoneal injection

The rat LD_{50} by intraperitoneal injection cited in the open literature (Carpenter 1956) is 550 mg/kg.

In an unpublished study, the comparative LD_{50}s in female Sprague-Dawley rats were determined for two brands of 2-butoxyethanol, n-Butyl Oxitol® and Dowanol EB® (Norris and Pernell 1972). Groups of four animals/dose were injected with a single dose of 200, 252, 316, 398 or 500 mg/kg body weight. The respective LD_{50} values for n-Butyl Oxitol® and Dowanol EB® were 252 mg/kg (confidence limits 203-312) and 317 mg/kg (241-417). Haemoglobinuria and a bloody nasal discharge were observed in all animals. In surviving animals at the two highest doses, tremors were noted at 22 hours after injection. Body weight gains seemed normal in surviving animals after the two-week post-exposure period, but there were no controls in the study.

10.2.5 Intravenous injection

A number of intravenous injection studies were conducted by Carpenter (1956), with an LD_{50} for the rat of 340-380 mg/kg, for the mouse 1100 mg/kg, and for the rabbit

280-500 mg/kg. It was reported that 2-butoxyethanol solutions greater than 3% resulted in haemolysis of red blood cells in the rat when administered intravenously.

10.2.6 Summary

2-Butoxyethanol has a moderate acute toxicity by all exposure routes in a variety of species. The acute dermal toxicity indicates significant absorption through the skin. Narcosis and respiratory distress are the main causes of death, and congestion and damage to the kidneys, liver, lungs and spleen are often observed at necropsy. Haemoglobinuria, due to haemolysis of the red blood cells, has been reported in most acute studies.

10.3 Irritation

10.3.1 Skin irritation

Few reports of skin irritation studies are available in the open literature. 2-Butoxyethanol is generally reported as a mild to moderate skin irritant in the rabbit (ECETOC 1994; Gingell et al 1994; Tyler 1984) but, due to lack of test detail and protocol deficiencies, the results do not clearly establish its skin irritant potential.

In a recently published study in New Zealand albino rabbits (Zissu 1995), the skin irritancy of five glycol ethers and their acetates was determined using the EEC method (similar to OECD Test Guideline 404). Individual data were not reported for the three animals used per substance in the study, but 2-butoxyethanol and isopropoxyethanol were described as 'irritant', and 2-methoxyethanol, 2-ethoxyethanol, 1-methoxy-2-propanol and all the acetates were described as 'non-irritant'.

Several unpublished rabbit studies with undiluted 2-butoxyethanol were available for assessment.

In a study (Rohm and Hass 1983) conducted by a method similar to OECD TG 404, 0.5 mL of 2-butoxyethanol was applied to the clipped intact skin of six male New Zealand White rabbits for four hours under a patch. Skin reactions were scored at five hours (one hour after patch removal), one day, three days and seven days. The results were variable, with severe and persistent erythema with eschar and severe oedema observed in three rabbits and very slight oedema and erythema observed in the others. No oedema was observed in any rabbit after 7 days. Under the conditions of the study, 2-butoxyethanol was irritating to the skin of rabbits.

In a study in five rabbits little or no irritation was observed, but only 0.01 mL was administered and the skin was uncovered during exposure (Bushy Run Research Centre, 1980(c)).

In a study in one rabbit, 0.5 mL was applied to the clipped intact skin under an occlusive wrap for a series of ten applications over 14 days (Carreon 1981). Slight erythema resulted immediately, with slight oedema after the seventh application. No firm conclusion can be drawn from this study on a single rabbit.

In a comparative study of nine glycol ethers in rabbits and guinea pigs (Eastman Kodak 1981(b)), undiluted material was applied under an occlusive dressing for 24 hours at the dose where enough animals survived to make an evaluation. 2-Butoxyethanol was reported to be a moderate irritant in the rabbit (dose of 0.3 g/kg bw), and a strong irritant in the guinea pig (at higher dose of 4.5 g/kg bw). The methyl, ethyl and propyl monoethylene glycol ethers, their corresponding diethylene glycol ethers, and diethylene glycol monobutyl ether were reported to be slight irritants in both species, while ethylene glycol mono-2-ethylhexyl ether was reported as a moderate irritant.

10.3.2 Eye irritation

The information available in the open literature indicates that 2-butoxyethanol is an eye irritant (Jacobs 1992; Kennah et al 1989). This was confirmed in the assessment of the following two unpublished rabbit studies.

In a study in five rabbits, 0.005 mL of undiluted 2-butoxyethanol caused severe corneal injury and iritis, 0.5 mL of a 15% aqueous solution caused moderate corneal injury, and no effects were observed with 0.5 mL of a 5% solution (Bushy Run 1980(c)). An internal protocol was used and individual results for each animal were not reported.

In a study in a single rabbit, the instillation of 0.1 mL of undiluted 2-butoxyethanol resulted in severe conjunctivitis, iritis and corneal opacity, with irritation still obvious 21 days after exposure (Carreon 1981).

10.3.3 Respiratory irritation

In an Alarie test in male mice, the RD_{50} (concentration which produces a 50% decrease in respiratory rate) for 2-butoxyethanol was estimated to be 2825 ppm (Kane et al 1980). The animals were exposed to vapour concentrations up to approximately 1100 ppm, so the value was obtained by extrapolation. Under the conditions of the test, 2-butoxyethanol was a weak irritant to the upper respiratory tract.

10.3.4 Summary

In liquid form, 2-butoxyethanol is a severe eye irritant. The evidence for skin irritation is less clear, with a number of studies producing variable results. In the best quality study, the skin reactions were variable between animals. On balance, 2-butoxyethanol is a mild to moderate skin irritant in test animals. 2-Butoxyethanol was a weak irritant to the upper respiratory tract in an Alarie test in male mice.

10.4 Sensitisation

An unpublished Magnusson and Kligman guinea pig maximisation study (Unilever Research 1989), was available for assessment to determine the skin sensitising potential of 2-butoxyethanol. In the induction phase, a group of six male and four female animals was treated intradermally with 0.5% 2-butoxyethanol in 0.9% saline, followed by dermal application of a 25% solution (in 0.9% saline) seven days later under an occlusive wrap. The animals were challenged twice with 10% 2-butoxyethanol, firstly at 13 days after induction, and then a week later. Under the

conditions of the study, 2-butoxyethanol was not a skin sensitiser. Some minor deviations from OECD test guidelines were apparent in the assessment, but overall the study was of good quality. A vehicle control group of four animals /sex was used in the study. In a preliminary occluded patch irritation test designed to determine dose levels for the main study, 25% 2-butoxyethanol was irritating to the skin and a 10% solution was non-irritating.

In a recently published Magnusson and Kligman guinea pig study (Zissu 1995) none of the glycol ethers tested, 2-butoxyethanol, 2-methoxyethanol, 2-ethoxyethanol and isopropoxyethanol, was a skin sensitiser.

10.5 Immunotoxicity

10.5.1 Effect on the proliferation of guinea pig lymphocytes *in vitro*

An unpublished *in vitro* proliferation study was available for assessment using 2-butoxyethanol and its main metabolite 2-butoxyacetic acid (BAA) (Crevel et al 1990). Earlier studies in male rats (Bartnik et al 1987; Ghanayem et al 1987(b); Grant et al 1985) had identified the thymus and spleen as potential target organs.

Cultured lymphoid cells from the guinea pig were exposed (in medium) for 48 hours to 2-butoxyethanol or BAA in the presence of a mitogen (phytohaemagglutinin (PHA) at 2.5-10 µg/mL or concanavalin A (Con A) at 5-20 µg/mL) or an antigen (tuberculin at 25-100 µg/mL). After preliminary lymphocyte toxicity tests, the 2-butoxyethanol doses for the main study were set at 0.4, 2.0 and 10mM and the BAA doses set at 0.2, 1.0 and 5.0mM. Control cells were treated with the same doses of mitogen or antigen without exposure to 2-butoxyethanol or BAA.

For 2-butoxyethanol, no significant effects on lymphocyte proliferation were observed at 0.4 and 2.0mM apart from slight reductions at the two highest PHA doses. At the cytotoxic dose of 10mM, a significant reduction in proliferative capacity resulted, particularly for PHA and tuberculin. No significant effects were observed for 2-butoxyacetic acid at any dose tested.

10.5.2 Other studies

In a drinking water study in Sprague-Dawley rats, the immune system was a sensitive target for 2-methoxyethanol but not for 2-butoxyethanol (Exon et al 1991). The immune function parameters measured included natural killer cell cytotoxic response, specific antibody production, and splenocyte production of interferon and interleukin-2.

In a gavage study in male Fischer 344 rats, 2-butoxyethanol and 2-ethoxyethanol had no effect on the immune response, as measured by the antibody response to trinitrophenyl-lipopolysaccharide (TNP-LPS) (Smialowicz et al 1992). In contrast, 2-methoxyethanol suppressed the response to TNP-LPS.

10.6 Repeated dose toxicity

10.6.1 Oral

NTP studies in rats and mice

A series of drinking water studies were conducted in F344/N rats and $B6C3F_1$ mice under the National Toxicology Program (NTP) in the USA (NTP 1993). The target doses in the two-week studies were 100, 150, 250, 400 and 650 mg/kg/day, and for the 13-week studies 750, 1500, 3000, 4500 and 6000 ppm daily. The main results of the studies are tabled below with the mean actual doses. Haematological effects were studied in detail only in the 13-week rat study.

The 13-week drinking water study in rats focussed on the haematological effects of 2-butoxyethanol. Haematology parameters were measured at one, three and 13 weeks, with anaemia present in females at all doses and in the males at the three highest doses. The detailed haematological results were as follows:

- decreased red blood cell count in females at all doses, and in males at higher doses;
- reduced haemoglobin concentration at the higher doses;
- increased mean cell volume (MCV) and mean cell haemoglobin (MCH) at the higher doses (most severe at week one);
- decreased platelet count at higher doses at weeks three and 13 (more obvious in females);
- marked increase in leucocyte count at the two highest doses (week one only);
- increased reticulocyte count at the higher doses (week one only); and
- mildly increased bone marrow cellularity at the two highest doses.

These results indicate that the haemolytic effects are related to erythrocyte toxicity and not bone marrow toxicity.

Table 10 - NTP Repeated Dose Oral Studies

Species	Duration	Dose and Results
Rat (5m,5f)	2-week	m: 0, 73, 108, 174, 242, 346 mg/kg/d f: 0, 77, 102, 152, 203, 265 mg/kg/d • reduced body weight gain at high dose (f) • slight decrease in thymus weight at high dose (f) • dose-related reduction in water consumption
Rat (10m,10f)	13-week	m: 0, 69, 129, 281, 367, 452 mg/kg/d f: 0, 82, 151, 304, 363, 470 mg/kg/d • reduced final body weight at 2 highest doses • anaemia - m: mild, at 281 mg/kg/d and above; f: mild to moderate, at all doses • reduced thymus weight at high dose in m & f and also at 367 mg/kg/d in males

		• atrophy of uterus at 2 highest doses • histopathology - lesions of the liver (hepato-cellular degeneration at 2 highest doses), spleen and bone marrow (hyperplasia at 2 highest doses)
Mouse (5m,5f)	2-week	m: 0, 93, 148, 210, 370, 627 mg/kg/d f: 0, 150, 237, 406, 673, 1364 mg/kg/d • dehydration (m & f) at 2 highest doses • decreased thymus weight (m) at 370, 627 mg/kg/d
Mouse (10m,10f)	13-week	m: 0, 118, 223, 553, 676, 694 mg/kg/d f: 0, 185, 370, 676, 861, 1306 mg/kg/d • reduced body weight gain at 3 highest doses • no treatment-related gross or microscopic lesions

(Note: m = male, f = female)

In the two-week rat study, the only tissues examined microscopically were the testis and epididymis from the lower dose groups and controls; no adverse effects were observed. No microscopic evaluation of tissues was conducted in the two-week mouse study.

In the 13-week rat study, no significant adverse effects on the reproductive organs and glands were observed in animals treated with 2-butoxyethanol. The size of the uterus was reduced in female rats at the two highest doses, with thickening of the muscular wall and uterine mucosa observed, but this was probably an effect secondary to the significant reduction in body weight gain at these two doses. Concurrent studies with 2-methoxy- and 2-ethoxyethanol resulted in testicular atrophy in the male rats. Additional reproductive tissue evaluations were conducted on ten animals/dose for the three highest doses and the controls. Relative testis weights were normal, and the slight reductions in epididymis weight at the two highest doses were consistent with body weight reductions at these doses. A small but statistically significant reduction in sperm concentration was observed at all three doses but the reduction was not dose-dependent and there were no other changes in sperm morphology parameters. In oestrous cycle measurements at the three doses, the total cycle length was not significantly changed but there were differences in the length of the various stages of the cycle.

In the corresponding 13-week study in male and female mice, no adverse effects on reproductive organs or fertility parameters were observed with 2-butoxyethanol, but testicular degeneration was observed with both 2-methoxy- and 2-ethoxyethanol. In additional reproductive tissue evaluations conducted in the 13-week study on ten animals/dose at the three highest doses, slight decreases in sperm motility and testis weight were noted, but the changes were not dose-dependent and not regarded as biologically significant.

Under the conditions of the 13-week studies, the NOAEL for haematological effects in male rats was 129 mg/kg/day, but the corresponding NOAEL for females was not reached as slight anaemia was observed at the lowest dose (LOAEL 82 mg/kg/day). No significant adverse effects were observed in the corresponding mouse study but no haematology was conducted.

Six-week oral study in male rats

A six-week gavage study in male rats was conducted by administering 2-butoxyethanol on 5 days/week to groups of ten male CD rats at the following doses: 0, 222, 443 or 885 mg/kg body weight (Krasavage 1983). The study has been comprehensively reported in the open literature (Krasavage 1986).

Three animals died in the study, two at 885 mg/kg and one at 443 mg/kg. The main toxic effect was on the red blood cell, with a dose-dependent decrease in haemoglobin concentration and red blood cell count and a decrease in mean corpuscular haemoglobin concentration (MCHC) at the two higher doses. There was a dose-dependent increase in MCH at all doses and in MCV at the two higher doses. Haemoglobinuria was observed in animals at all doses, particularly at the two higher doses, and particularly after the first two days. Other significant effects observed included increased absolute spleen weight at the two higher doses and increased relative liver weight at all doses. No adverse effects were observed on the testes, thymus, white blood cells or bone marrow.

Under the conditions of the study, no NOAEL could be established. The LOAEL for haematotoxicity was 222 mg/kg/day.

10.6.2 Dermal

Nine-day repeated dermal application in rabbits

The repeated dose dermal toxicity of 2-butoxyethanol was evaluated by application to the skin of New Zealand White rabbits on nine days over an 11-day period, followed by a 14-day observation period (Bushy Run 1980(b)). A summary of the study has been reported in the open literature (Tyler 1984), and the full study was available for assessment.

In a preliminary study, a dose of 0.625 mL/day 2-butoxyethanol (approx. 225 mg/kg/day) was applied under an occlusive wrap to the backs of four male and two female rabbits for six hours on nine days. Local dermal necrosis was observed in all animals by the fourth day. Histologic examination of the kidneys at necropsy revealed changes consistent with the late stages of haemoglobinuric nephrosis.

In the definitive study, five rabbits/sex/dose were similarly treated with 1 mL/day of undiluted 2-butoxyethanol or 5%, 25% or 50% aqueous solutions. A similar group of controls was treated with distilled water. At necropsy, only the kidneys were examined microscopically. The main results are tabled below.

% 2-BE	Dose (mg/kg/day)	Results
100	360	• Severe necrosis on all animals and accompanied by oedema and erythema by day six; • Haemoglobinuria on day two;

		• Haematologic changes including reduced haemoglobin and red blood cell count, and increased MCH; • Reduced body weight in females; • Thickening of the skin in males; • Colour change of the kidneys in 3/5 females.
50	180	• Necrosis on 1/5 males and 4/5 females; • Haemoglobinuria in one female on day five, in all animals by day nine.
25	90	• Erythema.
5	18	• Slight erythema.

Severe necrosis at the higher doses may have increased the rate of skin absorption. Haematological parameters returned to normal by the end of the 14-day post-exposure observation period.

90-Day dermal toxicity study in rabbits

Based on the results of the 9-day study (Bushy Run Research Centre 1980(b)), see 10.6.2 above) the subchronic dermal toxicity of 2-butoxyethanol and aqueous dilutions of the chemical was evaluated by application to the skin of New Zealand White rabbits for six hours a day, five days a week over 13 weeks (WIL Research Laboratories 1983). A summary of the study has been reported in the open literature (Tyler 1984), and the full study was available for assessment. Ten rabbits/sex/dose were similarly treated with 1 mL/day of 2.8%, 14.3% or 42.8% aqueous solutions, equivalent to 10, 50 and 150 mg/kg body weight respectively. A similar group of controls was treated with distilled water. Haematological and clinical chemistry parameters were measured at weeks 4 and 12 during the study and a comprehensive histopathological examination was conducted on all animals at necropsy. There were no significant findings so, under the conditions of the study, the NOAEL was 150 mg/kg.

Slight erythema was noted intermittently in all animals, including the controls, at and around the dosed area.

10.6.3 Inhalational

Nine-day inhalational rat study

In a nine-day dynamic inhalational study (Longo and Dodd 1981), groups of eight male and eight female Fischer 344 rats were exposed (whole body) to 2-butoxyethanol vapours at 0, 20, 86 or 245 ppm. A second group of animals (8m,7f) exposed to 245 ppm and a second control group (8m, 8f) were observed for 14 days after exposure to test the reversibility of any treatment-related changes. The procedure used was similar to that of OECD Test Guideline 412. The study has been

summarised in the open literature (Dodd et al 1983), and the full study was available for assessment. The main results were as follows:

Dose (ppm)	Results
245	Marked haematological effects;
	Haemoglobinuria in males and females after first 2 exposures only;
	Relative increase in liver weight;
	Discolouration of lungs, respiratory difficulty;
	Body weight decrease, recoverable after post-exposure period;
	Abnormal righting reflex in one female, and no pupil response in another.
86	Less marked haematological effects;
	Relative increase in liver weight (females only).
20	No significant effects.

The dose-related changes in blood parameters were the most significant results of the study. Haematological effects included decreases in erythrocyte count, haemoglobin and MCHC, and increases in MCV, nucleated red blood cells, reticulocytes and, in males only, lymphocytes. A significant recovery was observed after 14 days in the satellite group exposed to 245 ppm, but the decrease in erythrocyte count and the increases in MCV and haemoglobin were still apparent. At necropsy, no treatment-related macroscopic changes were observed.

90-Day inhalational rat study

In a 90-day inhalational study (Snellings et al 1981), groups of 16 male and 16 female Fischer 344 rats were exposed (whole body) to 2-butoxyethanol vapours at 0, 5.0, 24.6 or 77.0 ppm. Ten animals/sex/dose were exposed for six hours/day for 13 weeks (five days/week), while the other six rats/sex/dose were sacrificed after six weeks for blood analysis. The procedure was similar to OECD Test Guideline 413. The study has been summarised in the open literature (Dodd et al 1983), and the full study was available for assessment.

The main findings of the study were the haematological effects observed in the rats exposed to 77 ppm, particularly the females. The haematological effects were much less marked at 13 weeks. These effects were as follows:

- Six weeks exposure: Statistically significant decreases in haemoglobin, red blood cell (RBC) count (f) and haematocrit (f); increase in MCH (f).

- 13 weeks: Statistically significant decrease in RBC count (m,f) and increase in MCH (f); small but not statistically significant decreases in haemoglobin and haematocrit, and increase in white blood cells (m).

There was no sign of blood in the urine, and the nervous system changes noted at higher doses in the nine-day study (see 10.6.3 above) were not observed in this study. No effect on red blood cell osmotic fragility was observed. At necropsy, no significant gross or microscopic lesions were observed, and there were no significant effects on the lungs, liver, kidney or testes. Under the conditions of the study, the NOAEL was 24.6 ppm.

Four-day studies in rats, guinea pigs and dogs

In an unpublished study, two male Beagle dogs, six male guinea pigs and eight male rats were exposed to 57-58 ppm of 2-butoxyethanol vapours for seven hours/day over four consecutive days (Norris and Pernell 1972). The study was intended as a preliminary study only and no controls were used. One guinea pig died of respiratory failure during the study but there were no other deaths and no significant clinical observations. At necropsy on the guinea pigs and rats two weeks after exposure, no treatment-related gross pathological changes were observed.

The results of a similar unpublished study were incorporated into the report of the above study. The animals were exposed to 100 ppm of a competitor's brand of 2-butoxyethanol for seven hours/day for four days. Haemoglobinuria was observed in the rats after the first exposure only, female guinea pigs died after the second day, and one of the dogs displayed unusual behaviour after the second exposure. Full experimental details of both studies were not available.

Other studies

In a series of studies reported by Carpenter (1956), rats, mice, guinea pigs, dogs and monkeys were exposed to 2-butoxyethanol vapours at concentrations up to 494 ppm for periods up to 90 days. Haemoglobinuria and/or increased red blood cell fragility were observed in all species except the guinea pig, with the animals generally returning to normal overnight after exposure ceased. Increased relative liver and kidney weights were noted at 107 ppm and above in the rats and increased relative kidney weight at 203 ppm and above in guinea pigs. In preliminary range-finding tests in rats, the older animals were more susceptible to the haemolytic effects. Haematological observations in the studies are listed in Table 11 in section 10.7.1.

In a behavioural study of nine industrial solvents, female rats were exposed by inhalation to 50, 100, 200 or 400 ppm 2-butoxyethanol for four hours/day, five days/week for ten exposure days (Golberg et al 1964). Behavioural effects were measured using a conditioned avoidance-escape test. No effect on growth-rate or behavioural performance occurred but transient haemoglobinuria was observed at 200 and 400 ppm.

10.6.4 Summary

The main effect seen in repeated dose studies by all exposure routes is anaemia due to haemolysis of the red blood cells. Haemolytic effects included decreased RBC count and haematocrit, decreased MCHC and increased MCV and RBC osmotic fragility.

Several studies demonstrated that the haematological effects caused by repeated exposure to low doses of 2-butoxyethanol were transient, occurring only during the first days of exposure (Dodd 1983, Carpenter 1956, Werner 1943). There is some evidence of haemopoiesis occurring, such as spleen hyperplasia, as a response to the haemolytic effects.

The repeated dose studies indicated that there are species differences in the susceptibility to the haemolytic effects of 2-butoxyethanol. Rats appear to be the most sensitive species in these animal studies.

Results from the 13-week oral study (NTP 1993) and 90-day inhalation study (Snellings et al, 1981) suggest that female rats may be more sensitive to the haemolytic effects of 2-butoxyethanol.

In some studies, adverse effects on the liver, kidney, spleen and/or thymus were observed at dose levels at or above haematotoxic levels, but these effects are generally regarded as being secondary to haemolysis.

In the 13-week NTP studies, no significant adverse effects on reproductive organs were observed in rats and mice. Slight effects on fertility parameters (slight reduction in sperm concentration and differences in length of stages of oestrous cycle) were noted in rats at haematotoxic levels but no adverse effects on fertility were noted in mice. The results of reproductive toxicity studies are discussed further in section 10.8.

10.7 Haematological studies

10.7.1 Early studies

In early studies by Werner (Werner et al 1943) and Carpenter (1956) in a variety of species, haemoglobinuria was observed in animals exposed to 2-butoxyethanol in both acute and repeated dose studies. The effect was transient as the animals tended to recover overnight between exposures and, in the repeated dose studies, haemoglobinuria was generally seen only after the first few exposures. Some species were more affected than others, for example, haemoglobinuria was observed in rats and mice exposed to 200 ppm 2-butoxyethanol for seven hours, but not in guinea pigs exposed to 665 ppm for eight hours. Haemolysis of the red blood cells was shown to occur, and *in vitro* tests in a number of species (Carpenter 1956) indicated that the major metabolite, BAA, was more haemolytic than 2-butoxyethanol.

In inhalational studies to compare the haemolytic effect of 2-butoxyethanol in humans and rats (Carpenter 1956), an increased RBC fragility was observed when three female rats were exposed to 195 ppm over two periods of four hours, and again when six rats were exposed to 113 ppm for four hours (see section 11.2.1 in *Human Health Effects*).

Results of the main studies by Carpenter (1956) are tabled below.

Table 11 - Haematological Effects in Studies by Carpenter et al

Species	Dose	Effect
rat (f)	62 ppm/4h	Increased osmotic fragility
rabbit (m,f)	125, 197 ppm/7h	Increased osmotic fragility
guinea pig (m)	665 ppm/8h	No effect
rat (m,f)	54-432 ppm/7h, 30d	Increased osmotic fragility (all doses) Haemoglobinuria (203 ppm and above, first two exposures only)
mouse (m)	112-400 ppm/7h, 30,60,90d	Increased osmotic fragility (all doses) Haemoglobinuria (200 ppm, first exposure only; 400 ppm, first three exposures only)
monkey (m,f)	100 ppm/7h, 90d 210 ppm/7h, 30d	Transient increase in osmotic fragility Transient increase in osmotic fragility
guinea pig (m,f)	54-494 ppm/7h, 30d	No effect

Note: (m) = male, (f) = female

10.7.2 Gavage study in Sprague-Dawley rats

An investigation of the biophysical and biochemical mechanisms of the haemolysis induced by 2-butoxyethanol was conducted in a gavage study in male Sprague-Dawley rats (Kurantsin-Mills and Lessin 1990). The animals were given a single dose of 2-butoxyethanol (in water) at 0, 50, 100, 250 or 500 mg/kg body weight, and blood was sampled after 0.5, two and four hours for testing. The full study was obtained for assessment. The main results of the study were as follows:

- The following changes in red blood cell parameters occurred:
  - a significant dose and time-related increase in MCV;
  - a significant dose-related decrease in MCHC;
  - slight increases (without dose-dependence) in haematocrit, haemoglobin density width and red cell density width;
  - slight decreases (without dose-dependence) in haemoglobin and red blood cell count.
- Haemoglobin was detected in the plasma and urine of exposed rats, but the concentrations in plasma were low (<5%) compared to total blood.
- The shape of the red blood cells changed in that they swelled to become spherocytic.
- The median density of red blood cells decreased with dose, consistent with swelling of the cells. The effect was apparent at all time intervals, particularly at 4 hours for the two highest doses.
- Mean adenosine triphosphate (ATP) levels in the red cells from exposed rats were slightly higher than levels in controls, especially for rats dosed at 100-500 mg/kg, but the changes were not statistically significant.
- The lack of any increase in malonylaldehyde (MDA) concentration in blood cells indicated that no increase in lipid peroxidation of the red cell

membrane occurred. Haemolysis can be caused by the peroxidation of unsaturated fatty acids in the membrane of red cells, indicated by the formation of carbonyl compounds such as MDA. In the experiment, MDA levels fell by about 50%, irrespective of the dose, indicating an arrest of the auto-oxidative processes in the red cells by 2-butoxyethanol and/or a metabolite.

- The viscosity of plasma and whole blood from exposed rats was higher than for controls, but the effect was more marked at 50 and 100 mg/kg. The lack of a dose-viscosity relationship was attributed by the authors to shear-induced haemolysis at the higher doses. In a cell deformability test conducted under standard conditions, the red cells from treated rats were more rigid than control rat cells.

In light of the results obtained from other studies, most of the findings were expected, although the ATP depletion reported in *in vitro* studies in blood cells from Fischer 344 rats, which indicated that ATP depletion preceded the haemolysis caused by BAA, was not observed (Ghanayem 1989). In some areas, the study report was lacking in experimental detail, for example, numbers of animals used, and identification of dose and time interval for some parts of the experiment.

10.7.3 Other *in vivo* studies (published)

In a gavage study, F344 rats were administered a single dose of 2-butoxyethanol, the major metabolite BAA or the intermediate 2-butoxyacetaldehyde (Ghanayem et al 1987(c)). By selectively inhibiting the activity of the enzymes ADH and ALDH with pyrazole and cyanamide respectively, it was confirmed that BAA was the primary haemolytic agent.

The effect of age on the toxicity and metabolism of 2-butoxyethanol was examined in a gavage study in F344 rats (Ghanayem et al 1987(a)). Both haematotoxicity and the secondary liver and kidney effects were more severe in the older animals (9-13 weeks) than the younger ones (4-5 weeks).

In gavage studies in rats and guinea pigs, the animals were administered a single dose of 250 mg/kg/d (Ghanayem and Sullivan 1993). Increases in MCV and haematocrit and decreases in red cell count and haemoglobin concentration were observed for the rats, but no significant changes in these parameters were noted in the guinea pigs.

In a gavage study in male F344 rats, the animals were dosed at 0, 500 or 1000 mg/kg bw for four consecutive days (Grant et al 1985). At both doses, haematological changes were observed, including reduced red blood cell count, haematocrit and haemoglobin and increased MCV and MCH. The changes were reversible although, for the high-dose group, the MCV and MCH were still slightly raised after 22 days.

10.7.4 *In vitro* studies in various species (published)

In vitro studies in a variety of species have confirmed that the main metabolite of 2-butoxyethanol, BAA, is the primary haemolytic agent and that there are significant differences in haemolytic activity between species. In studies in human and rat red blood cells (Bartnik et al 1987), 2-butoxyethanol caused haemolysis of rat cells at

175-200 mM and of human cells at 225 mM (for 60 min. incubation). For the same incubation time, BAA caused total haemolysis of rat cells at 7.5 mM and no haemolysis of human cells (maximum concentration 15 mM). For an incubation time of 180 min., BAA caused total haemolysis of rat cells at 3.75 mM and no haemolysis of human cells at the maximum concentration of 15 mM.

In a study in red blood cells from human, rat, dog and rabbit blood, BAA lysed rat cells at 0.05% but cells from the other species were stable up to the maximum concentration of 2% BAA (Hext 1985).

In NTP and other *in vitro* studies in rat red blood cells, BAA was shown to cause swelling of the cells, seen as increased mean cell volume (MCV) and haematocrit, prior to haemolysis (Ghanayem et al 1990; Udden and Patton 1994). In a comparative study in rat and human red blood cells, haemolysis was observed in rat cells exposed for four hours to BAA at the lowest dose (0.5 mM) (Ghanayem 1989). No effects were observed in human cells exposed to 2 mM BAA for four hours, but slight swelling of the cells was noted at 4 mM, and slight but significant haemolysis was observed at 8 mM BAA.

Subsequent NTP studies (Ghanayem and Sullivan 1993) confirmed the effect of BAA *in vitro* in mice (at 1 mM BAA), in rats and the yellow baboon at 2 mM (rats not tested at 1 mM), but no significant effect was observed in the red blood cells of guinea pigs, dogs, cats, domestic pigs and humans after exposure to 2 mM BAA for four hours. Rabbit and hamster cells swelled at 2 mM, but no haemolysis occurred.

In a recent study, red blood cells from humans and Fischer 344 rats were treated with BAA (Udden and Patton 1994). On exposure to 2 mM for four hours, the rat cells exhibited significant haemolysis, preceded by a large decrease in red cell deformability (noted at one hour); whereas no haemolysis or change in deformability occurred in human cells. On exposure to 0.2 mM for six hours, the rat cells exhibited very slight haemolysis and a significant decrease in red cell deformability (noted at four hours).

Following the results of this study (Udden and Patton 1994), the haemolytic resistance of red blood cells from potentially susceptible humans was studied (Udden 1994). The red cells from nine healthy younger adults (5m,4f), nine aged persons (5m,4f), 7 patients with sickle cell disease and three persons with hereditary spherocytosis were treated with 2 mM BAA for four hours. Haemolysis in treated cells was higher than controls for aged adults, but the difference was not statistically significant. The deformability of red cells from persons with sickle cell disease or hereditary spherocytosis was reduced, but BAA had no added effect. No other haemolytic or morphological changes were observed.

An *in vitro* study on several haemopoietic cell lines, either growth-factor-dependent or leukaemic, in mouse, rat and human species concluded that 2-butoxyethanol was a haemopoietic toxin (Ruchaud 1992). However, doubts were publicly raised about the results of the study and the purity of the reagents used. Subsequent experiments repeated by the same laboratory with high grade reagents could not reproduce the

original findings. The authors have since publicly withdrawn all conclusions of the study (Boiron et al 1984).

10.7.5 Summary of haematological studies

Several *in vivo* and *in vitro* studies have been conducted to specifically investigate the haemolytic effects of 2-butoxyethanol. *In vivo* and *in vitro* studies have demonstrated that the metabolite BAA is the primary haemolytic agent.

The *in vitro* studies have confirmed that, as observed in *in vivo* studies, there are significant differences in the susceptibility of various species to the haematotoxicity of 2-butoxyethanol. Red blood cells of rats and mice are the most susceptible, then rabbits and baboons, with dogs, humans, guinea pigs, cats and pigs least susceptible to the haemolytic effects of BAA. *In vitro*, human red blood cells were at least 10 times less sensitive than rat cells to the haemolytic effects of BAA.

In vitro studies confirmed that haemolysis is preceded by swelling, decreased cell deformability and increased osmotic fragility of red blood cells. This suggests that pre-haemolytic changes are due to changes in the cell membrane.

Haematotoxicity in rats appears to be age-related, with the effects more severe in older rats. In vitro studies with erythrocytes of humans with congenital haemolytic disorders and the elderly did not demonstrate an increased sensitivity to BAA.

10.8 Reproductive toxicity

10.8.1 General

Due to the known reproductive toxicity of two of the lower molecular weight glycol ethers, 2-methoxyethanol and 2-ethoxyethanol, a number of studies of good quality have been conducted to estimate the reproductive toxicity of 2-butoxyethanol. The results from animal studies in a variety of species by all routes of exposure show that both 2-methoxyethanol and 2-ethoxyethanol are toxic to the sperm of male animals and cause damage to the testes. Animal studies show that 2-methoxyethanol and, to a lesser extent 2-ethoxyethanol, are teratogenic in a wide variety of species.

Most of the studies carried out with 2-butoxyethanol have been reported in the open literature.

Reproductive toxicity includes the adverse effects on the reproductive ability or capacity of adult males and females and on the growth and development of the offspring (developmental toxicity). Developmental toxicity includes toxicity from conception to sexual maturity, including toxicity to the embryo and foetus. Teratogenicity is the ability to cause structural and functional malformations during embryo development and is therefore a part of developmental toxicity.

10.8.2 Two-generation NTP study in mice

The fertility and reproductive effects of 2-butoxyethanol in drinking water were investigated in mice using the NTP continuous breeding protocol (CBP). The study comprised a continuous breeding phase, a crossover mating trial and a final offspring (F_1) assessment phase (Morrisey et al 1989; Heindel 1990).

Male and female Swiss CD-1 mice received 0, 0.5, 1.0 or 2.0% 2-butoxyethanol (equivalent to daily intakes of 0, 720, 1340 and 2050 mg/kg bw) in their drinking water during a continuous breeding phase with a seven-day pre-mating period and a 98-day cohabitation period. During the cohabitation period, deaths occurred in the female mice: 13/20 in 2% group, 6/20 in 1% dose group, 1/20 in 0.5% dose group and 1/40 in control group. The average body weights in the female 2% dose group were consistently lower than the controls. In the male mice, no deaths occurred but weight loss (1-2% of initial body weight) in the two highest doses and reduced weight gain were noted. Reduced fluid consumption was observed at all dose levels in both sexes. The numbers of fertile pairs from the surviving pairs were 38/39, 19/19, 13/14 and 5/7 at 0, 0.5, 1.0 and 2.0% dose levels, respectively. Significant reduction in reproductive performance occurred at 1 and 2% dose levels as indicated by dose-related decrease in litter sizes, pup viability and live pup weight. A significant reduction (5%) of live pup weight was also observed in the 0.5% dose group without other significant effects.

At the completion of the continuous breeding phase, the F_0 breeding pairs were separated and housed individually and exposure to 2-butoxyethanol continued. When the last litter was weaned, F_0 males and females from the 1% dose group were mated with male and female control animals in a one-week crossover mating study to determine any sex-related reproductive effects of 2-butoxyethanol. Exposure to 2-butoxyethanol was discontinued during the one-week mating period and then reintroduced at 1% dose level (estimated daily intake 1830 mg/kg bw). Control males and females were also mated for comparative purposes. The proportion of successful copulations from the breeding pairs was similar in all groups. However, the number of fertile females was significantly reduced in the group where treated females were mated with control males. Male and female mice from the 1% dose group had significantly lower body weights and increased relative kidney weights. At necropsy, a significant increase in relative liver weight was also observed in the females. No significant differences were observed between the control and treated animals for the weights of reproductive organs, sperm motility, morphology and oestrous cycle length and frequency. In the only histopathological examination carried out on the treated females, no treatment related kidneys lesions were observed. The results suggest that the fertility effects were primarily due to effects on the female mice.

A final phase was conducted to assess the fertility and reproductive effects of 2-butoxyethanol in second generation (F_1) pups. The pups selected were those born after the CBP and when the maternal animals were individually housed. As there were insufficient pups in the 1 and 2% dose groups, only the pups from the 0.5% dose group were used. The F_1 generation pups were nursed, weaned and reared to sexual maturity. After weaning, the mice received 0.5% 2-butoxyethanol in their drinking water (estimated daily intake 950 mg/kg bw). At 74 ± 10 days of age, the F_1 animals from different litters were mated. The animals were necropsied after delivery. No significant fertility and reproductive effects were observed in the F_1 animals as indicated by the proportions of successful copulation and fertile females, litter size, pup viability and live pup weights. Similarly, no treatment-related changes in the weights of reproductive organs, sperm motility, morphology and the oestrous cycle

length and frequency were noted. However, a significant increase in relative kidney weight in the females and a significant increase in relative liver weight in both the males and females were observed.

In summary, significant adverse reproductive effects were observed only at very high dose levels (1340 mg/kg and above) which also caused severe maternal toxicity, including death. Under the conditions of the study, the NOAEL for reproductive toxicity of 2-butoxyethanol can be taken as 720 mg/kg/day as only a very slight decrease in pup weight was observed at this dose.

10.8.3 Other studies

In a 60-day stop-exposure study conducted in association with the 13-week NTP study (NTP 1993), 30 male rats per dose consumed 0, 124, 234 or 443 mg/kg/day in drinking water. After exposure to 2-butoxyethanol for 60 days, testis and epididymis weights were normal, and no microscopic lesions were noted [NOAEL 443 mg/kg/day]. On the other hand, testicular degeneration was observed with 2-methoxy- and 2-ethoxyethanol. In the main 13-week study, minor changes in sperm concentration and oestrous cycle were noted with 2-butoxyethanol (see 10.6.1).

To study the reproductive toxicity of a number of ethylene glycol alkyl ethers, groups of 5 male JCL-ICR mice per dose were administered (by gavage) the ether at doses up to 2000 mg/kg/day for five weeks (Nagano et al 1984). Testicular atrophy was observed for 2-methoxyethanol and 2-ethoxyethanol, but not for 2-butoxyethanol.

In a 21-day drinking water study in Sprague-Dawley rats, testicular atrophy and necrosis and reduced numbers of spermatogenic cells were observed in males exposed to 486 mg/kg/day of 2-methoxyethanol, but no adverse effect on fertility parameters was seen in males exposed to 506 mg/kg/day of 2-butoxyethanol (Exon et al 1991).

In a four-day gavage study in male F344 rats, severe testicular atrophy was observed in the animals fed 2-methoxyethanol at 500 mg/kg but no significant effect on the testis was noted in animals fed 2-butoxyethanol at the same dose (Grant et al 1985).

In a fertility study in male Wistar rats (Foster et al 1987), the administration (by gavage) of a single dose of 2-butoxyacetic acid (BAA) did not result in any testicular damage at the lowest dose of 174 mg/kg. In an *in vitro* test, BAA did not produce any changes in testicular cell populations at 5mM. Simultaneous testing with the acids of methoxyethanol and ethoxyethanol resulted in significant spermatocyte cell loss and damage *in vivo* and *in vitro*.

10.8.4 Developmental toxicity/teratogenicity studies

Oral

In an NTP gavage study (Sleet et al 1989) in Fischer 344 rats, groups of 27-33 animals were dosed with 2-butoxyethanol (in distilled water) during the critical periods of cardiovascular development, with dosage set at 0, 30, 100 or 200 mg/kg/day on gestational days (gd) 9 to 11 (group 1) or at 0, 30, 100 or 300 mg/kg/day on gd 11 to 13 (group 2). Except for the restricted exposure time, the procedure was similar to that of OECD Test Guideline 414, and the study satisfied quality assurance requirements.

Dose-related changes in haematological parameters were observed in the dams of both groups at the two highest doses (100 and 200 mg/kg or 100 and 300 mg/kg). The effects were more obvious in the early days after dosing and the effects included decreases in red blood cell count, haemoglobin, haematocrit and MCHC, and increases in MCV, MCH, reticulocytes and white blood cell count. Other signs of toxicity in the dams included dose-related reductions in body weight gain and food and water consumption. The relative spleen weights were increased at 100 and 200/300 mg/kg, relative kidney weights were increased at 200/300 mg/kg and relative liver weights at 200/300 mg/kg. The NOAEL for maternal toxicity was 30 mg/kg/day.

An increase in non-viable and adversely-affected implants, post-implantation loss and resorptions per litter resulted in the animals at 200 mg/kg/day (group 1 only). In the foetus, a decreased platelet count was noted at 300 mg/kg/day (group 2 only). No foetal malformations, and in particular no cardiovascular malformations, were observed at any dose.

In a gavage study in pregnant CD-1 mice, 2-butoxyethanol was administered at 0-2000 mg/kg/day during gestational days (gd) 8-14 (Wier et al 1987). Mortality resulted at 1500 mg/kg and signs of toxicity (haemolysis) were apparent at 650 mg/kg [NOAEL for maternal toxicity 350 mg/kg/day]. An increased number of resorptions and a reduced number of viable foetuses were observed at 1000 and 1500 mg/kg [NOAEL for embryo- and foetotoxicity 650 mg/kg/day]. In a post-natal study, where the dams were treated with 650 or 1000 mg/kg on gd 8-14, no significant effects on pup growth or survival resulted. In a simultaneous study with 2-ethoxyethanol, developmental toxicity was apparent at doses below maternal toxicity levels.

In a gavage screening test conducted in groups of 50 pregnant CD-1 mice (Schuler et al 1984), including controls, 2-butoxyethanol was maternally toxic at the only dose used, 1180 mg/kg, but no significant changes in offspring resulted.

Dermal

In a study in pregnant Sprague-Dawley rats, 0.12 mL (approx. 1760 mg/kg bw) of undiluted 2-butoxyethanol was applied to the skin four times on one day after early tests with 0.35 mL had resulted in mortality (Hardin et al 1984). Haemoglobinuria was observed at the higher dose, but not with 0.12 mL. No embryotoxic, foetotoxic or teratogenic effects resulted. Simultaneous testing with 0.25 mL of 2-ethoxyethanol confirmed its embryotoxic, foetotoxic and teratogenic effects observed in earlier studies.

Inhalational

Studies by Tyl (Bushy Run 1984) in pregnant Fischer 344 rats and New Zealand White rabbits have been comprehensively reported in the open literature (Tyl et al 1984). The animals were exposed to target concentrations of 0, 25, 50, 100 or 200 ppm [0, 0.12, 0.25, 0.49 or 0.98 mg/L] for 6h/day on gd 6-15 for the rat and gd 6-18 for the rabbit. In the rat, haematological effects, increased relative spleen weight and reduced body weight gain were observed in the dams at and above 100 ppm [NOAEL for maternal toxicity 50 ppm]. 2-Butoxyethanol was embryotoxic and foetotoxic only at maternally toxic doses [NOAEL for developmental toxicity 50 ppm].

In the rabbit study by Tyl, exposure to 2-butoxyethanol resulted in mortality, increased number of abortions, and reduced uterus and body weight at the highest dose, 200 ppm [NOAEL for maternal toxicity 100 ppm]. No significant dose-dependent haematological changes were observed. 2-Butoxyethanol was not foetotoxic at any dose [NOAEL for foetotoxicity 200 ppm] but a significantly lower number of total and viable implants per litter were noted at the maternally toxic dose [NOAEL for embryotoxicity 100 ppm]. No signs of teratogenicity were observed at any dose for either species [NOAEL for teratogenicity in the rat and rabbit 200 ppm].

In a study in Sprague-Dawley rats, the animals were exposed to 150 or 200 ppm for 7h/day over gd 7-15 (Nelson et al 1984). Haemoglobinuria was noted (on the first day only) in the dams at both doses, but no evidence of embryotoxicity, foetotoxicity or teratogenicity was observed. Simultaneous testing with 2-methoxyethanol indicated that the chemical was embryotoxic, foetotoxic and teratogenic at the lowest dose tested, 50 ppm.

Subcutaneous injection

An unpublished study of the effects of 2-butoxyethanol on the pregnancy of the CD rat by subcutaneous injection was available for assessment (Tesh 1976). Groups of rats were injected subcutaneously with aqueous solutions of 2-butoxyethanol to determine the teratogenicity of the chemical. In the first of two preliminary studies to set the dose range, non-pregnant rats received a single injection with 225-1350 mg/kg; 80% of the high dose animals died, haemoglobinuria was observed and general poor condition of the rats resulted. In the second preliminary study, no effects were observed when a similar group of rats received repeated injections at 23-90 mg/kg/day. Experimental details for the preliminary studies were not available.

In the main study, conducted in accordance with OECD test guideline 414, groups of 20 pregnant CD rats received 0, 45, 90 or 180 mg/kg/day as an aqueous solution on gd 6-15. No mortality resulted and haemoglobinuria and body weight loss were observed in the medium and high dose dams after the first two injections only. No significant pathological findings were noted at necropsy. Pre-implantation loss increased in the medium and high dose dams compared with the controls, but the values were within the laboratory's normal range. Other parameters were normal. In the foetuses, a slight increase in rib effects and a dose-dependent increase in incomplete ossification of cranial bones were observed, but such changes are considered as variations and not malformations (Working and Mattison 1993).

Under the conditions of the study, pre-implantation loss occurred in dams at maternally toxic doses and there were no treatment related signs of teratogenicity.

10.8.5 Summary

In a two-generation reproductive toxicity study, fertility was reduced in mice only at very high doses (> 1000 mg/kg) which were severely toxic to the adults. In comparative studies with glycol ethers, 2-butoxyethanol did not cause testicular degeneration. Lower molecular weight homologues, 2-methoxyethanol and 2-ethoxyethanol, both caused testicular degeneration in these studies.

No significant adverse effects on reproductive organs were observed in rats and mice in the 13-week drinking water studies (NTP 1993). Slight effects on fertility parameters were observed in rats at haematotoxic levels.

In other reproductive studies, developmental effects were observed only at maternally toxic doses. No evidence of teratogenicity was observed in any studies, again in contrast to 2-methoxyethanol and 2-ethoxyethanol.

10.9 Genotoxicity

10.9.1 *In vitro* assays

Three-test battery of studies

The full studies of a battery of tests designed to evaluate the genotoxicity of 2-butoxyethanol were available for assessment (Bushy Run 1980(a)).

In a Chinese hamster ovary (CHO) cell point mutation assay, 2-butoxyethanol did not significantly increase the frequency of mutations with or without S9 metabolic activation. The cells were exposed for five hours at doses in the range 140-9000 µg/mL. At the highest dose, 2-butoxyethanol was cytotoxic with S9, but non-toxic without S9.

In a sister chromatid exchange (SCE) assay, 2-butoxyethanol did not induce SCEs in CHO cells with and without S9 at the doses used in the assay, 63-2250 µg/mL.

In an Unscheduled DNA Synthesis (UDS) assay, rat liver cells were treated with 2-butoxyethanol in the dose range 0.9-900 µg/mL for two hours in the presence of tritiated thymidine. In the determination of UDS activity by measurement of radioactivity in liver cell nuclei, a statistically significant induction of UDS was observed at the two lowest doses, with the maximum effect at 9 µg/mL. The effect was confirmed by analysis of the radioactivity in DNA isolated from the rat cell nuclei, although the maximum effect was seen at 0.9 µg/mL. This assay should be regarded as inconclusive as there was no clear dose-related response and various experimental problems occurred during the study, for example, failure of the positive control in the first of two tests, and discrepancies in radioactivity measurements.

NTP sponsored assays

The results of a series of genotoxicity studies conducted under NTP have been reported (NTP 1993), with much of the experimental detail included.

In a *Salmonella typhimurium* mutation test, 2-butoxyethanol was negative with and without S9 metabolic activation in the strains TA100, 1535, 1537, 97 and 98 at doses up to 1000 µg/plate. The two lower molecular weight homologues, 2-methoxy- and 2-ethoxyethanol, were also negative in this assay.

In assays in CHO cells, 2-butoxyethanol induced cell cycle delay but did not induce SCEs or chromosomal aberrations with and without S9 at concentrations up to 5000 µg/mL.

Reverse mutation assay on 18% 2-butoxyethanol

In a reverse mutation assay conducted on the 3M product T-3722, which contains 18% 2-butoxyethanol, tests with the *Salmonella typhimurium* strains TA1538, 1537,

1535, 100 and 98 were negative with and without S9 at doses up to 5000 µg/plate (SRI International 1985). Other components in the product included isopropyl alcohols (18%) and a fluorochemical salt (27%). The study was conducted in accordance with OECD Test Guideline 471.

Other *in vitro* studies

In a gene mutation assay, 2-butoxyethanol and its intermediate metabolite, 2-butoxyacetaldehyde, were not mutagenic to CHO-AS52 cells at concentrations up to 0.1% v/v (7.6 mM) and 0.2% v/v respectively (Chiewchanwit and Au 1995).

It was recently reported that 2-butoxyethanol gave positive results with *Salmonella typhimurium* strain TA97a at high concentrations (2.2 mg/plate), with and without S9, but it was negative to the strains TA98, TA100 and TA102 (Hoflack et al 1995). The metabolite BAA and the intermediate metabolite BAL were negative to all strains.

Given that 2-butoxyethanol had previously tested negative to the *Salmonella typhimurium* strain TA97 (see above), the result for the structurally similar strain TA 97a was considered unexpected by some workers, so a similar study was conducted in the USA by the CMA (Gollapudi et al 1995). In the repeat assay, 2-butoxyethanol tested negative to the TA97a strain at concentrations up to 10 mg/plate, with and without S9 metabolic activation. In the study, the *Salmonella typhimurium* strain TA100 and the *Escherichia coli* strain WP2*uvr*A also tested negative under similar conditions. The study was conducted in accordance with standard protocols.

In studies in human lymphocytes *in vitro*, 2-butoxyethanol induced SCEs in the cells at 2000 and 3000 ppm, however, a negative response was recorded in a test for chromosomal aberrations at similar concentrations (Villalabos-Petrini et al 1989). The assays were conducted without metabolic activation or positive controls, therefore no firm conclusions can be drawn.

A series of short-term *in vitro* tests (Elias et al, 1996) were carried out with 2-butoxyethanol and its metabolites BAL and BAA in order to detect gene mutations at the HPRT locus in V79 cells; SCEs in V79 cells; chromosomal aberrations in V79 cells and human lymphocytes; micronuclei (MN) *in vitro* in V79 cells; aneugenic effects in V79 cells; morphological transformation of Syrian hamster embryo (SHE) cells; inhibition of intercellular communication between V79 cells.

The results demonstrated that in V79 cells 2-butoxyethanol induced gene mutations and was a weak inducer of SCEs at high doses and aneuploidy at very high doses. 2-Butoxyethanol enhanced the clastogenic effect of methyl methanesulfonate at high doses and at non-cytotoxic doses it induced a dose-dependent inhibitory effect on intercellular communication in the V79 cell system.

10.9.2 *In vivo* studies

In a mouse bone marrow micronucleus test (Elias et al, 1996), there was no induction of micronucleated polychromatic erythrocytes (MPE) following administration of a single intraperitoneal injection of 2-butoxyethanol (doses from 150-1000 mg/kg) or BAA (50-200 mg/kg) at non-toxic to toxic dose ranges. At least 1000 polychromatic erythrocytes per animal were scored. A significant decrease in

the ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) was seen with BAA but not 2-butoxyethanol, indicating that BAA was more toxic to erythropoiesis.

No DNA binding in liver, brain, kidney, spleen and testis was seen in rats or mice (measured using ^{32}P postlabelling) following exposure to 2-butoxyethanol (Keith et al, 1996). An acute dose, 120 mg/kg 2-butoxyethanol was administered to rats (3 treated and 3 control animals), which were killed 24 hours later. Transgenic mice carrying *ras* oncogenes (8 to 24 animals per group) were administered 1500 mg/kg 2-butoxyethanol subcutaneously over 2 weeks (approximately 120 mg/kg/day) and killed at between 5 and 120 days. The transgenic mice killed after 120 days were also examined for tumour formation and no statistical difference from controls was observed.

10.9.3 Summary of data on genotoxicity

2-Butoxyethanol has tested negative in a wide variety of well-conducted *in vitro* assays, including mutation, chromosomal aberration and DNA effect assays. These assays were generally conducted at both cytotoxic and non-cytotoxic doses. 2-Butoxyethanol was a weakly positive inducer of gene mutations, SCEs and aneuploidy in V79 cells at high doses. 2-Butoxyethanol was negative in an *in vivo* mouse micronucleus assay.

Based on the available information, 2-butoxyethanol is probably not genotoxic.

10.10 Carcinogenicity

No studies were available. The NTP commenced a 2-year inhalation study in rats and mice in 1993. 2-Butoxyethanol was originally selected for study along with other glycol ethers because of its high production volume and human exposure, and known acute toxicity.

The International Agency for Research on Cancer (IARC) has had the glycol ethers listed for review since 1993, but no fixed schedule has been set for the work.

10.11 Summary of toxicological data

Table 12 summarises results of all assessed studies, including critical effects together with NOAELs or LOAELs (where established).

Table 12 - Summary of Toxicological Data

Study Type	*Species*	*Result*	*Section*
Acute toxicity			
oral	rat	LD_{50} 530-3000 mg/kg	10.2.1
	mouse (m)	LD_{50} 1230 mg/kg	
	guinea pig	LD_{50} 950-1414 mg/kg	
	rabbit	LD_{50} 320-370 mg/kg	
dermal	rabbit	LD_{50} 100-610 mg/kg	10.2.2
	guinea pig	LD_{50} 210->2000 mg/kg	
inhalation	rat (m,f)	LC_{50} (4h) 486, 450 ppm	10.2.3
	mouse	LC_{50} (7h) 700 ppm	
	guinea pig	LC_{50} (7h) 1300 ppm	
intraperitoneal	rat	LD_{50} 252-317 mg/kg	10.2.4
Irritation			
skin	rabbit	irritant	10.3.1
	guinea pig	irritant	
eye	rabbit	severe irritant	10.3.2
Sensitisation			
skin	guinea pig	non-sensitising	10.4
Immunotoxicity			
	guinea pig (*in vitro*)	no significant effect on proliferation of lymphocytes	10.5.1
Repeated dose			
9-day/2-week			
dermal	rabbit	haematotoxicity (NOAEL 90 mg/kg/d)	10.6.2
inhalation	rat	haematotoxicity (NOAEL 20 ppm)	10.6.3
6-week			
oral (gav)	rat (m)	haematotoxicity (LOAEL 222 mg/kg/d)	10.6.1
90-day/13-week			
oral (dr/w)	rat (m)	haematotoxicity (NOAEL 129 mg/kg/d)	10.6.1
	rat (f)	haematotoxicity (LOAEL 82 mg/kg/d)	10.6.1
dermal	rabbit	haematotoxicity (NOAEL 150 mg/kg/d)	10.6.2
inhalation	rat	haematotoxicity (NOAEL 24.6 ppm)	10.6.3
Reproductive toxicity			
oral (dr/w)	rat (m)	no effect on testis/epididymus	10.8.3
	mouse	effects only at maternally toxic doses (1340 mg/kg bw and above)	10.8.2
Developmental			
oral (gav)	rat	effects only at maternally toxic doses (100 mg/kg/day and above)	10.8.4
dermal	rat	no effects	10.8.4

inhalation	rat	effects only at maternally toxic doses (100 ppm and above)	10.8.4
	rabbit	effects only at maternally toxic dose (200 ppm)	10.8.4
subcutaneous	rat	no significant effects	10.8.4
Genotoxicity			
In vitro			
mutation	*S. typhimurium*	negative	10.9.1
	E. coli	negative	10.9.1
	CHO	negative	10.9.1
	V79	positive at high doses	10.9.1
SCE	CHO	negative	10.9.1
	V79	weakly positive at high doses	10.9.1
	CHO	negative	10.9.1
chromosomal aberrations	CHO	negative	10.9.1
UDS	rat	inconclusive	10.9.1
micronuclei	V79	negative	10.9.1
aneuploidy	V79	positive at very high doses	10.9.1
In vivo			
micronuclei	mouse bone marrow	negative	10.9.2
DNA binding	rat, mouse	negative	10.9.2

Note:m = male; f = female; dr/w = drinking water; gav = gavage.

11. Human health effects

11.1 Case reports

A number of cases of poisoning by ingestion of formulations containing 2-butoxyethanol have been reported in the literature. The results are summarised as follows:

- Deliberate ingestion of 250-500 mL of window cleaner containing 12% 2-butoxyethanol (dose 30-60g 2-butoxyethanol) resulted in deep coma, metabolic acidosis, hypokalaemia, a rise in serum creatinine level and oxalate crystals in the urine. Haemoglobinuria was observed between the third and sixth days (Rambourg-Schepens et al 1988).
- Deliberate ingestion of about 500 mL of window cleaner containing 12.7% 2-butoxyethanol (dose approx. 60g) and 3.2% ethanol resulted in coma, hypotension and metabolic acidosis. A decrease in haemoglobin was noted on the second day and haemoglobinuria occurred. The main metabolite of 2-butoxyethanol, BAA, was detected in urine but no oxaluria was observed (Gijsenbergh et al 1989).
- Deliberate ingestion of 500 mL of household cleaner containing 9.1% 2-butoxyethanol (dose approx. 45g) and 2.5% ethanol resulted in severe respiratory distress, coma, shock and metabolic acidosis. No haematologic effects were observed (Bauer et al 1992).
- Deliberate ingestion of cleaning product containing 22% 2-butoxyethanol resulted in symptoms consistent with metabolic acidosis. No signs of haemolysis were apparent. The estimated dose was 80-106 g 2-butoxyethanol, equivalent to 1.1-1.5 g/kg bw. In a repeat of the incident two weeks later, similar symptoms were observed (Gualtieri 1995).
- 24 cases of ingestion by children (aged 7 months to 9 years) of window/glass cleaners containing 2-butoxyethanol (range 0.5-9.9%) were retrospectively evaluated. Most of the quantities swallowed were small, but one child ingested 30 mL of cleaner containing <10% 2-butoxyethanol and another 300 mL of an 8% solution. No signs of haemolysis, metabolic acidosis or CNS depression were observed in any case (Dean et al 1992).

One case of haemolysis in a cleaner exposed to 2-butoxyethanol has been reported in the literature (*Pesticide and Toxic Chemical News* 1993). It is alleged that a carpet cleaner using a solution containing an unknown concentration of 2-butoxyethanol experienced dizziness, blurred vision and red urine towards the end of his eight hour shift a number of times. Some uncertainties surround the case, including lack of exposure details and lack of verification by medical professionals. The US EPA took

no action in response to the incident, nor have they been able to find any similar incidents involving 2-butoxyethanol.

11.2 Controlled studies

11.2.1 Inhalational

Three experiments were conducted by Carpenter (1956) on human volunteers, with the results reported in the open literature. The main results of the three tests were as follows:

- When two men were exposed to 113 ppm for four hours, no effect on RBC fragility was observed. The men suffered nasal and eye irritation, nasal discharge and a nasty taste in the mouth. At 4-6 hours after exposure, one man was still unwell.
- When two men and one woman were exposed to 195 ppm for two four-hour periods, the RBC fragility was unaffected. BAA was excreted in the urine of the woman and one male, but only a trace was detected in the second male. Symptoms included irritation of the eyes, nose and throat, unpleasant taste, and headache.
- When two men and two women were exposed to 100 ppm for eight hours, BAA was excreted in all volunteers and no RBC fragility was observed. Symptoms noted were headache and nausea.

In studies in volunteers exposed to 20 or 50 ppm for two hours (Johanson et al 1986; Johanson and Boman 1991), it was demonstrated that 2-butoxyethanol vapours were rapidly absorbed into the bloodstream (see 9.2.3). No adverse health effects were reported.

11.2.2 Dermal

In a study in five volunteers carried out by immersing two or four fingers in undiluted 2-butoxyethanol for two hours (Johanson et al 1988), the results of urine analysis for BAA indicated that the chemical is rapidly absorbed through the skin. The fingers of the volunteers became stiff and wrinkled but no signs of irritation were observed.

The skin sensitisation potential of 2-butoxyethanol was evaluated in a repeated insult patch test carried out on 200 volunteers (TKL Research 1992). The results have recently been reported in the open literature (Greenspan et al 1995). In the induction phase, 0.2 mL of a 10% aqueous solution was applied under a patch for 24 hours to the backs of the subjects for a total of nine times over a three-week period. The sites were evaluated for skin reaction after each application. A slight redness (without swelling) was observed in four subjects after the first application but, by the eighth application, 40 subjects exhibited slight erythema and in another 14, erythema was more definite. The challenge phase was conducted two weeks later, with 10% 2-butoxyethanol applied to previously unexposed sites, with slight erythema noted in only seven subjects after 48 hours and 12 subjects after 72 hours. Under the conditions of the study, 2-butoxyethanol was not a skin sensitiser.

11.3 Occupational studies

In a silkscreening operation in Virginia, USA, workers exposed to undiluted 2-butoxyethanol reported irritation and discomfort (Kullman 1987). In the subsequent inspection of the workplace, atmospheric concentrations of 2-butoxyethanol in the range 13-169 ppm were obtained.

No epidemiological studies were available. In France, studies in workers exposed to glycol ethers, including 2-butoxyethanol, are underway to identify any adverse health effects, including haematotoxicity, associated with exposure.

11.4 Other information

Information was obtained from one of the formulators about cleaners using floor strippers containing high levels of 2-butoxyethanol. The effects noted included eye irritation and drowsiness when the ventilation was poor. Some reddening of the skin and contact dermatitis occurred when the proper safety gloves were not worn.

In New South Wales, several school cleaners reported eye and throat irritation, headache and nausea while using cleaning products solutions, including products containing 2-butoxyethanol. In most cases, the solutions were being used in spray form. Skin irritation was reported by two of the 12 cleaners who responded to a call for information.

Information was also received from cleaners previously exposed to 2-butoxyethanol during their work, which included floor stripping and heavy duty cleaning. Symptoms reported by the cleaners included eye and respiratory irritation, headache, nausea, sleepiness, dizziness and confusion. One worker reported anaemia as a result of exposure.

Individual details of the above cases are summarised in Appendix 4. No monitoring of the cleaners or the workplace was conducted and no medical examination or follow-up of the cleaners was carried out as part of the assessment.

11.5 Summary

Exposure to 2-butoxyethanol vapours may result in irritation of the eyes, nose and throat, headache and nausea. In liquid form (including aqueous solution), 2-butoxyethanol is readily absorbed through the skin, and the results of controlled studies in volunteers have indicated that 2-butoxyethanol vapours are also absorbed via the skin. A few cases of skin irritation have been reported by cleaners using products containing 2-butoxyethanol, but controlled studies in volunteers with 2-butoxyethanol have resulted in slight or no skin irritation. In a patch test in volunteers, 2-butoxyethanol was not a skin sensitiser but slight skin irritation was observed after several applications.

Haemoglobinuria has been observed in humans who have ingested large quantities (30-60g) of 2-butoxyethanol. The ingestion of large quantities of 2-butoxyethanol may also result in severe respiratory difficulty, shock and coma. One unsubstantiated case of haemolysis in a worker exposed to cleaning solutions containing 2-butoxyethanol has been reported in the literature.

12. Hazard assessment and classification

This chapter integrates data on physicochemical hazards, kinetics and metabolism, and health hazards identified from human studies and from experimental animal and *in vitro* testing. The potential hazards to human health from exposure to 2-butoxyethanol can then be characterised and the appropriate hazard classification determined.

Workplace substances are classified as hazardous to health if they meet the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC 1994(a)), and hazardous in terms of physicochemical properties if they satisfy the definitions in the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) (Federal Office of Road Safety 1992).

For transport by road and rail, substances are classified as dangerous goods according to the criteria in the ADG Code, for example, the criteria for corrosivity, acute toxicity, and physicochemical properties such as flammability.

The classification recommended for 2-butoxyethanol is incorporated in the following assessment of health and physicochemical hazards.

12.1 Physicochemical hazards

2-Butoxyethanol is a liquid of low volatility with a flash point of 62°C.

***Classification**:*

2-Butoxyethanol does not meet the ADG Code criteria for any classes pertaining to physicochemical properties, for example, flammability, oxidising properties.

12.2 Kinetics and metabolism

The results of animal and human studies show that 2-butoxyethanol is readily absorbed by all routes. Studies also indicate that 2-butoxyethanol is readily absorbed through the skin from aqueous solution and that skin absorption of vapours may occur. In animal studies conducted by all routes of exposure, 2-butoxyethanol is rapidly distributed to all tissues via the bloodstream. Studies indicate that it is qualitatively metabolised in a similar manner in both animals and humans, the main metabolite being 2-butoxyacetic acid (BAA), which is rapidly excreted in the urine. In humans, significant amounts of the BAA glutamine conjugate have also been measured in urine following exposure to 2-butoxyethanol and suggest an additional detoxification pathway in humans (see chapter 9, *Kinetics and Metabolism*).

12.3 Health hazards

12.3.1 Acute effects

In animal studies, 2-butoxyethanol can be lethal in all species tested by all exposure routes, with the main cause of death being narcosis or respiratory distress. In acute studies, oral LD_{50} in rats ranged from 530 to 3000 mg/kg, dermal LD_{50} in rabbits ranged from 100-610 mg/kg and inhalational LC_{50} in rats ranged from 2.2 to 2.4 mg/L (4h).

No deaths have been reported from cases of deliberate and accidental ingestion of 2-butoxyethanol in humans, but some of the victims lapsed into coma and experienced symptoms such as metabolic acidosis, shock and respiratory distress. Haemoglobinuria was observed in two cases (at the higher doses). In humans, headache and nausea have also been reported.

Classification:

From the LD_{50} and LC_{50} values obtained from animal testing, 2-butoxyethanol meets the Approved Criteria for classification as 'harmful' by inhalation (risk phrase R20), skin contact (R21) and ingestion (R22).

From the results of human case reports and acute toxicity testing in animals, 2-butoxyethanol does not meet the Approved Criteria for classification for non-lethal irreversible effects after a single exposure.

For classification under the ADG Code, the human data are insufficient for classification purposes so, on the basis of animal data for acute dermal and inhalational toxicity (LD_{50} and LC_{50} values), 2-butoxyethanol meets the criteria for classification as a Class 6.1 substance in Packaging Group III (see section 12.4 for further information).

12.3.2 Irritant effects

A number of skin irritation studies in experimental animal studies provided variable results. On balance, 2-butoxyethanol was irritating to the skin of rabbits. On the other hand, studies in human volunteers resulted in slight or no irritation. Isolated cases of skin reddening and dermatitis have been reported in workers using cleaning products on a regular basis, however, as the products contain many ingredients, the irritant effects cannot be solely attributed to 2-butoxyethanol. In general, occupational case studies have not identified skin irritancy as a significant effect in exposed persons.

2-Butoxyethanol has been shown to be a severe eye irritant in both animals and humans.

Occupational case reports have identified respiratory irritation as a potential health effect in humans. In controlled human studies (Carpenter 1956), nose and throat irritation was observed at 113 ppm but not at 100 or 50 ppm. In an Alarie test in male mice, 2-butoxyethanol was a weak sensory irritant (Kane et al 1980).

Classification:

From human evidence and the results of animal studies, 2-butoxyethanol meets the Approved Criteria for classification as an 'eye irritant' (risk phrase R36).

From human evidence in both controlled studies and occupational case reports, 2-butoxyethanol meets the Approved Criteria for classification as a 'respiratory irritant' (R37).

Primarily on the basis of human evidence from controlled studies in volunteers and occupational case reports, and noting the variable results obtained in animal studies, 2-butoxyethanol does not meet the Approved Criteria for classification as a skin irritant.

12.3.3 Sensitisation

Skin sensitisation studies in animals and humans have been negative. There is no evidence that 2-butoxyethanol is a respiratory sensitiser.

Classification:

From the results of human and animal studies, 2-butoxyethanol does not meet the Approved Criteria for classification as a sensitiser.

12.3.4 Immunotoxicity

Studies in rats and *in vitro* studies in guinea pig lymphocytes did not reveal any significant effect on the immune response. There have been no reports of any effect of 2-butoxyethanol on the immune system of humans.

12.3.5 Effects after repeated or prolonged exposure

Haemolytic effects

The main effect observed in both acute and repeated-dose animal toxicity studies is haemolysis of the red blood cells. The principal agent of haemolysis is the major metabolite of 2-butoxyethanol, 2-butoxyacetic acid (BAA). In general, the haematological effects observed at lower doses in repeated-dose studies were transient in nature as they tended to be noticeable during the first few days of exposure only. This feature is attributed to the replacement of older more susceptible red blood cells with younger more resistant cells. Several studies have shown that haemolysis is preceded by an increased osmotic fragility or swelling of the red blood cell, indicating an effect by BAA on the cell membrane, that is, erythrocyte toxicity. There is also limited evidence to show that the haemolytic effects are not related to bone marrow toxicity.

Most animal studies have been conducted in the F344 rat. From inhalational studies in the rat, the NOAEL obtained for haematological effects in a 90-day study was 24.6 ppm. Assuming 100% absorption, an average rat weight of 215g, and a respiratory rate of 0.16 m^3/day (NIOSH 1990), this represents an absorbed dose of:

$$\frac{121\ mg/m^3 \times 0.16\ m^3/day \times 6h}{0.215\ kg \times 24h} = 22.5\ mg/kg/day.$$

In a nine-day study by the same laboratory, the NOAEL obtained for haematological effects was similar at 20 ppm (Longo and Dodd 1981).

In a 90-day dermal study in rabbits, the NOAEL for all effects was 150 mg/kg/day, the highest dose tested (WIL Research Laboratories 1983). In a 90-day drinking water study in rats, the NOAEL for haematological effects in males was 129 mg/kg/day but, in females, a NOAEL was not obtained (LOAEL 82 mg/kg/day) (NTP 1993).

Therefore, the lowest reliable NOAEL from animal studies is 24.6 ppm (121 mg/m^3) in the rat.

Numerous *in vivo* and *in vitro* studies have demonstrated a considerable variance between species in susceptibility to the haemolytic effect of 2-butoxyethanol, with rats and mice the most susceptible, rabbits less susceptible, and guinea pigs and humans the least susceptible. The effect has been well characterised in the rat, with consistent results obtained by different laboratories.

To highlight the differences in effect between species, particularly the rat and humans, the results of key *in vivo* (inhalational) and *in vitro* haematological studies are tabled below. The studies were designed to measure haemolysis and prehaemolytic effects such as swelling and changes in osmotic fragility.

Several *in vitro* studies have demonstrated that human red blood cells are at least ten times less sensitive to haemolysis by BAA than rat cells.

Table 13 - Summary of *In Vivo* Haematological Studies (Inhalational)

Study	***Species***	***Dose/Duration***	***Haemolytic Effect***
Carpenter (1956)	rat	62 ppm/4h	Increased RBC fragility
		54-432 ppm/7h, 30d	Increased fragility (all doses) Haemoglobinuria (≥ 203 ppm)
		113 ppm/4h	Increased fragility
	mouse	112-400 ppm/7h, 30-90d	Increased fragility (all doses) Haemoglobinuria (≥ 200 ppm)
	rabbit	125, 197 ppm/7h	Increased fragility (both doses)
	guinea pig	665 ppm/8h	No effect
	human	113 ppm/4h	No effect
		195 ppm/8h	No effect
Longo and Dodd (1981)	rat	20 ppm/6h, 9d	No effect
		86 ppm/6h, 9d	Haemolysis
Snellings (1981)	rat	25 ppm/6h, 90d	No effect
		77 ppm/6h, 90d	Haemolysis
Johanson (1994)	rat	20 ppm/12d	No haemolysis
		100 ppm/12d	No haemolysis

Table 14 - Summary of *In Vitro* Haematological Studies

Study	*Species*	*Exposure Duration*	*Dose (mM BAA)*	*Effect*
Bartnik (1987)	rat	1h	7.5	Haemolysis
	human	1h	15	No effect
	rat	3h	3.75	Haemolysis
	human	3h	5	No effect
Ghanayem (1989)	rat	4h	0.5	Haemolysis
	human	4h	2	No effect
			4	Slight swelling
			8	Slight haemolysis
Ghanayem and Sullivan(1993)	rat	4h	2	Haemolysis
	rabbit		2	Swelling
	human		2	No effect
Udden and Patton (1994)	rat	6h	0.2	Slight haemolysis preceded by swelling
		4h	2	Significant haemolysis preceded by swelling

Haemolytic effects have been reported in humans in two cases following ingestion of large amounts of cleaning solution containing 30-60g of 2-butoxyethanol. No confirmed cases of haematotoxicity have been reported in persons exposed to 2-butoxyethanol in an occupational setting. There has been one unconfirmed report of a carpet cleaner having red urine following exposure to 2-butoxyethanol. In three controlled studies in volunteers, exposure to 100-195 ppm 2-butoxyethanol for 4-8h did not alter the osmotic fragility of red blood cells (see Table 13 and sections 11.1 and 11.2).

Animal studies indicated that younger rats were less susceptible to the haemolytic effects of 2-butoxyethanol than older ones (see section 10.7). However, an *in vitro* study showed that the red blood cells from aged persons and young adults were not significantly affected in the presence of 2 mM BAA (Udden 1994). The study also indicated that the red blood cells of persons with hereditary blood disorders (sickle cell anaemia and spherocytosis), individuals who are likely to be more susceptible to haemolysis, were not significantly affected in the presence of 2 mM BAA (see 10.7.4).

Toxicokinetic studies have shown that, in rats and humans, 2-butoxyethanol is readily absorbed via inhalation and dermal routes (and oral route in rats) and widely distributed in the rat following absorption. Evidence indicates that the dermal absorption rate in humans for 2-butoxyethanol is approximately 0.2 mg/cm^2/h, although there appears to be a high degree of interindividual variation. Studies have demonstrated that 2-butoxyethanol is extensively and rapidly metabolised by a similar oxidative pathway in rats and humans, with BAA the major metabolite. The major route of elimination is in the urine, with the major metabolite BAA being rapidly excreted in both species. It has been shown that human interindividual rates of

elimination vary (Johanson et al 1986; 1988). Conjugation of BAA with glutamine in humans may provide an additional detoxification pathway.

In summary, the evidence from controlled and case studies in humans, *in vitro* studies in animal and human red blood cells, *in vivo* studies in animals and toxicokinetic data indicates that humans are less sensitive to the haemolytic effect of 2-butoxyethanol than rats, and there is some *in vitro* evidence to indicate that they may be considerably less sensitive.

This conclusion is supported by the physiologically-based pharmacokinetic model developed by Corley et al (1994), which successfully estimated the disposition of 2-butoxyethanol and BAA under a variety of exposure scenarios. Based on data from absorption studies indicating that 2-butoxyethanol was more readily absorbed from aqueous solution (see Chapter 9, *Kinetics and Metabolism*), and assuming that 10% of body area was exposed (approximately 2000 cm^2), Corley et al's model predicted as a worst-case scenario that the skin absorption of undiluted 2-butoxyethanol over 6h would lead to a BAA blood concentration of 0.37 mM, and that absorption of a 40% solution would result in 1.3 mM BAA. These values are below the BAA concentration (2 mM) at which no haemolysis was observed in human *in vitro* measurements and well below the concentration at which haemolysis has been observed in human cells *in vitro* (8 mM BAA).

Other effects from repeated or prolonged exposure

In repeated dose studies in animals, changes to the liver, kidney, spleen and thymus occurred in some cases, but these effects were seen at or above haematotoxic doses and are generally regarded as being secondary to haemolysis. The NOAEL for liver degeneration in a 13-week oral rat study was 281 mg/kg/day (NTP 1993). The NOAEL for all effects in a 90-day dermal study in rabbits was 150 mg/kg/day (WIL Research Laboratories 1983).

Severe effects in humans from repeated or prolonged exposure have not been reported in the literature.

Classification:

The lowest reliable NOAEL from repeated (inhalation) exposure to 2-butoxyethanol is 24.6 ppm (0.12 mg/L). The haematotoxic effects observed at lower doses in animal studies are transient in nature, with affected animals recovering from these effects after the first few exposures. Severe secondary effects were observed in animals only at high doses. Therefore, 2-butoxyethanol does not meet the Approved Criteria for classification on the basis of severe effects after prolonged or repeated exposure.

12.3.6 Reproductive effects

No reports of reproductive effects in humans have been reported in the literature.

The reproductive effects of 2-butoxyethanol have been widely studied in animals by all routes of exposure, with the results indicating that 2-butoxyethanol does not affect fertility or developmental toxicity below doses which are severely toxic to the adults.

No evidence of teratogenicity was observed in any of the studies.

Classification:

From the results of animal studies, 2-butoxyethanol does not meet the Approved Criteria for teratogenicity nor the EC criteria for developmental toxicity and fertility effects (Commission of the European Communities 1993).

12.3.7 Genotoxicity

2-Butoxyethanol has tested negative in a wide range of well-conducted *in vitro* assays, including gene mutation, chromosomal aberration and DNA effect assays. Weakly positive responses in gene mutation, SCE and aneuploidy assays with V79 cells have been observed with very high doses of 2-butoxyethanol in one study.

2-Butoxyethanol was negative in an *in vivo* mouse micronuclei assay.

Classification:

From the results of *in vitro* studies, 2-butoxyethanol does not meet the Approved Criteria for mutagenicity.

12.3.8 Carcinogenicity

No 2-year carcinogenicity studies were available. An NTP study is underway.

Classification:

Due to the lack of data, 2-butoxyethanol cannot be classified for carcinogenicity.

12.4 Classification summary

Approved Criteria for Classifying Hazardous Substances

Under the Approved Criteria, the appropriate classification for 2-butoxyethanol is:

- R20/21/22 Harmful by inhalation, in contact with skin, and if swallowed
- R36 Irritating to eyes.
- R37 Irritating to respiratory system.

This is the same as currently specified on the *List of Designated Hazardous Substances* (the List) except for the risk phrase R36. The concentration cut-offs on the List for 2-butoxyethanol are 12.5% for R20/21/22 and 20% for R37. A cut-off of 20% would also apply for R36. Due to its acute toxicity, a concentration cut-off of 12.5%, lower than the usual 25% cut-off for R20/21/22, was considered appropriate by the EEC.

Poisons Schedule

2-Butoxyethanol itself is not listed on the Poisons Schedule (SUSDP), but it falls within the scope of ethylene glycol monoalkyl ethers, which are listed on Schedule 6 for preparations containing more than 10% glycol ether. Schedule 6 entries are 'poisons that must be available to the public but are of a more hazardous or poisonous

nature than those classified in Schedule 5'. As the health effects of ethylene glycol monoalkyl ethers vary considerably, a separate listing for 2-butoxyethanol on the Poisons Schedule would be more appropriate.

Dangerous goods classification

The results of this assessment indicate that 2-butoxyethanol meets the criteria in the ADG Code for Class 6.1(b) substances, Packaging Group III (as currently listed in the fifth edition of the Code). However, 2-butoxyethanol was delisted by the UN Committee of Experts on the Transport of Dangerous Goods at its November 1994 meeting (United Nations 1995). The relevant Australian authority (the Competent Authorities Sub-Committee to the Advisory Committee on the Transport of Dangerous Goods) has endorsed the decision by recommending that 2-butoxyethanol should not be listed in the next edition of the ADG Code. In the meantime, the authority has issued a generic exemption for the movement of 2-butoxyethanol throughout Australia, provided that it is not marked as a dangerous good (Federal Office of Road Safety 1995).

The criteria for assigning substances to Dangerous Goods Class 6.1 are outlined in section 2.3.9 of the ADG Code (5th edition; Federal Office of Road Safety 1992). Toxic substances are assigned to Class 6.1 on the basis of human experience or, in the absence of human experience, data obtained from animal experiments. The criteria state that account should be taken of human experience in instances of accidental poisoning and of special properties possessed by the substance. For liquid substances assigned on the basis of data from animal experiments, the criteria are tabled in Table 2.2 in the ADG Code, viz.:

- oral LD_{50} (rat) $\leq$ 500 mg/kg
- dermal LD_{50} (rabbit) $\leq$ 1000 mg/kg
- inhalational LC_{50} (rat) (4h). $\leq$ 10 mg/L (one hour) or 5 mg/L

Initially, it was proposed to the UN that 2-butoxyethanol be reclassified, to class 9 (Miscellaneous), rather than be delisted. The proposal was based on the following argument:

- case reports of accidental poisoning in children did not result in medical emergencies, and three attempted suicides were unsuccessful;
- rat and mouse data are not relevant to human toxicity because the main effect in rats and mice, haemolysis of the red blood cells, is not seen in some other species including humans and guinea-pigs;
- acute toxicity data for the guinea-pig were outside the Dangerous Goods Code criteria for a class 6.1 substance, viz.

LD_{50} (oral)	1400 mg/kg (criterion 500 mg/kg)
LD_{50} (dermal)	>2000 mg/kg (1000 mg/kg)
LC_{50} (inhalation)	>3.9 mg/L (10 mg/L); and

- 2-butoxyethanol should be in class 9 because it may cause irritation and nausea.

The human experience alone is considered insufficient for classification purposes. In four cases of poisoning by ingestion, where the amount of 2-butoxyethanol swallowed ranged from 30 to 106g, the victims survived, but only after lapsing into coma and experiencing symptoms such as respiratory distress, metabolic acidosis and shock. In two of the four cases, haemoglobinuria was observed. In case reports of children swallowing small amounts of cleaning products containing 2-butoxyethanol, no adverse effects were observed.

The animal data relevant to the ADG criteria are:

- oral LD_{50} (rat) 530-3000 mg/kg
- dermal LD_{50} (rabbit) 100-610 mg/kg
- inhalational LC_{50} (rat) 2.2-2.4 mg/L (4h).

In consideration of the animal data for acute toxicity, the results of this assessment indicate that 2-butoxyethanol meets the criteria for dermal toxicity (rabbit LD_{50}) and inhalational toxicity (rat LC_{50}). As noted in the UN proposal to delist 2-butoxyethanol, there is a view held by some that the rat and mouse data, including acute toxicity data, are not relevant to humans. This assessment has found that humans are less sensitive to the haemolytic effects seen in rats following repeated exposure, and therefore the rat is not the most appropriate animal model for repeated exposure. However, in acute studies in animals the main cause of death appears to be narcosis or respiratory distress. Therefore, the results for acute toxicity studies in rats and mice should be considered in the classification for 2-butoxyethanol under the ADG Code.

Conclusion

The classification of 2-butoxyethanol outlined above highlights the difficulties created by the existence of different schemes with different criteria. At present, 2-butoxyethanol is a hazardous substance in the workplace at concentrations above 12.5%, it is a poisonous substance to the public at concentrations above 10%, but under the ADG Code, it is not a dangerous good. All classifications have been made on the basis of the health effects.

Also, 2-butoxyethanol is classified as 'harmful' by all 3 routes under the EC regulations and the Approved Criteria. The criteria for inhalational toxicity under the Approved Criteria are the same as under the ADG Code (5 mg/L, 4 hours). The delisting of 2-butoxyethanol has created an inconsistency between the two classification systems.

This problem reinforces the need for harmonised classification systems, and at least the need for consistency in criteria between the different systems.

12.5 Comparison of glycol ethers

Due to the widespread use of ethylene glycol ethers and some concern about the adverse health effects of some members of the group, a number of reviews of the health effects of the ethylene glycol ethers as a class have been conducted in recent years (see section 2.2). Comparative studies have been conducted for many of the toxicological endpoints, for example, repeated dose and genotoxicity studies in NTP Technical Report No.26 (NTP 1993).

From the reviews, it is evident that although the ethylene glycol ethers share some toxicological properties, individual members differ for other properties. The following conclusions have been made about the ethylene glycol ethers as a class:

- They are absorbed through the skin, however, in general, the absorption rate decreases with increasing molecular weight;
- Their acute toxicity is low to moderate (with animal LD_{50} and LC_{50} values for 2-butoxyethanol generally lower than for other ethylene glycol ethers);
- The reproductive and developmental toxicity decreases with increasing alkyl chain length. Only some ethylene glycol ethers, for example, the short chain compounds 2-methoxyethanol and 2-ethoxyethanol, have been shown to be reproductive and developmental toxicants. 2-Butoxyethanol does not exhibit this property;
- Some cause haemolytic effects in animals, for example, 2-butoxyethanol, but others have been shown not to cause these effects;
- They are in general slight irritants;
- They do not appear to be sensitisers;
- They do not appear to be genotoxic.

Comparison of the health effects of glycol ethers should be treated with some caution as many members of the class have not been tested extensively.

In 1993, the US EPA reviewed the human health effects of the glycol ethers (US EPA 1993). In trying to redefine the glycol ethers on their list of toxic substances, the EPA stated that high molecular weight glycol ethers (surfactants) are of low concern for human health and do not meet their toxicity criteria. They also concluded that, while the toxic effects of the glycol ethers varied considerably in type and severity and that human health effects generally decreased with an increase in molecular weight, there was insufficient data at present to establish a size or molecular weight to indicate which other glycol ethers are of low concern.

2-Butoxyethanol exhibits some of the general characteristics of ethylene glycol ethers. However, animal data have demonstrated that 2-butoxyethanol is more acutely toxic than most glycol ethers, is readily absorbed through the skin, does not cause reproductive and developmental effects, but does cause haemolysis in some species. Humans appear to be less sensitive than most animal species to the haemolytic effects of 2-butoxyethanol.

13. Risk characterisation (occupational)

In this section, the results of the hazard and occupational exposure assessments have been integrated to characterise the risk of adverse health effects in workers exposed to 2-butoxyethanol.

13.1 Methodology

The risk to human health from exposure to 2-butoxyethanol has been characterised by using methodology commonly used in international assessments (UK Govt 1993; OECD 1993; European Commission 1994).

For critical effects caused by repeated or prolonged exposure, the risk characterisation is made using the following procedure:

1. Identification of the critical health effect(s).

2. If appropriate and available, then identification of the most reliable NOAEL for the critical effect(s).

3. Where appropriate, comparison of the NOAEL with the estimated human dose

to give a margin of safety, that is:

$$\text{margin of safety} = \frac{\text{NOAEL}}{\text{estimated human dose (EHD)}}$$

4. Characterisation of risk, by judging whether the margin of safety indicates

a concern.

The process of characterising risk requires the consideration of a number of parameters, including the human population exposed, the nature and severity of the effect, interspecies and intraspecies variability, and completeness and quality of the database (including exposure data).

For acute effects, the risk characterisation process considers likely exposure patterns to assess whether single exposures are high enough to indicate a health concern.

13.2 Critical health effects

13.2.1 Acute effects

The critical effects identified for acute inhalational exposure to 2-butoxyethanol are irritation of the eyes and respiratory system. In controlled studies, nasal and eye

irritation was reported in humans after exposure to 113 ppm but not after exposure to 20, 50 or 100 ppm. Eye and throat irritation have been reported in workers using cleaning products containing 2-butoxyethanol but the atmospheric concentrations of 2-butoxyethanol and other ingredients were not known.

Headache and nausea have been reported in controlled studies at 100 ppm and above and by cleaners using cleaning products which have included those containing 2-butoxyethanol.

Haemoglobinuria was reported in animals in acute toxicity studies by all exposure routes, however, haemolytic effects have only been observed in humans after the ingestion of large doses (30-60g) 2-butoxyethanol. The haemolytic effects of 2-butoxyethanol are discussed further in the next subsection.

13.2.2 Effects of repeated exposure

No long-term studies of human populations were available in the scientific literature.

In animal studies, the critical effect of 2-butoxyethanol is haemolysis of the red blood cells. Other systemic effects such as liver damage are generally regarded as secondary to haemolysis. The lowest reliable NOAEL for haematotoxicity in a 90-day inhalation rat study is 24.6 ppm for the rat (Snellings et al 1981), which is equivalent to a daily dose of 22.5 mg/kg/day (see 12.3.5).

Consideration of the haemolytic effect of 2-butoxyethanol in animals indicates that the effect is more of an acute effect than a chronic effect. In repeated dose studies, the effect is transient at low doses, with haematological effects generally noticeable only during the first few days of exposure. The NOAEL for a 9-day inhalational rat study, 20 ppm (Longo and Dodd 1981), is similar to the 90-day NOAEL.

As discussed in section 12.3.5, there is sufficient evidence from controlled and case studies in humans, animal *in vivo* studies, and *in vitro* studies in animals and human cells to conclude that humans are less sensitive to the haemolytic effect of 2-butoxyethanol than rats. This conclusion is supported by predictions from Corley et al's PBPK model (1994).

Animal studies indicated that older rats were more susceptible to haemolysis than younger ones, however, at the concentrations tested, human *in vitro* studies did not confirm this in humans (Udden 1994). The *in vitro* studies also indicated that the red blood cells of persons with some hereditary blood disorders (sickle cell anaemia and spherocytosis) were not significantly affected under the study conditions.

13.3 Occupational health and safety risks

13.3.1 Risk from physicochemical hazards

2-Butoxyethanol is a combustible liquid with flammability limits 1.1-12.7%. However, as 2-butoxyethanol has a low volatility, the risk of fire is low and the risk of explosion minimal. Most cleaning products are aqueous, so there will be no fire risk during their use and little risk during formulation. However, a small number are hydrocarbon or alcohol-based so, for these products, there may be some risk of fire.

2-Butoxyethanol undergoes the reactions typical of glycol ethers, for example, reaction with oxidising agents and alkalis. However, in the formulation and use of cleaning products containing the chemical, the risk of harm to health or safety due to chemical reaction is very low.

13.3.2 Margin of safety

The margin of safety (MOS) provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOS increases, the risk of the adverse health effect occurring decreases. The MOS is normally used for repeated dose systemic effects, where an animal NOAEL can be established.

Historically, the MOS was used to compare therapeutically effective drug doses with doses which caused adverse health effects. More recently, the MOS process has been used to establish acceptable human exposures such as acceptable daily intakes (ADIs) for food additives and in setting occupational exposure limits. In these processes, the animal NOAEL is divided by uncertainty (safety or modifying) factors which take into account the human population exposed, the nature and severity of the effect, inter- and intraspecies differences, and uncertainties in the process, for example, the exposure database. A safety factor of 100 is often used in setting ADIs. It is generally recommended, however, that default safety factors wherever possible be replaced by those supported by experimental or epidemiological data.

The approach in this assessment has been to follow international practice and compare the estimated human dose (EHD) with the animal NOAEL. It is generally considered that when the EHD is greater than the NOAEL, the substance is of concern regarding the human population exposed. Where the EHD is less than the NOAEL, consideration of the MOS is required in deciding whether exposure to the substance is a concern. Expert judgment is required to weigh up these considerations on a case by case basis, taking into account the human population exposed, the nature and severity of the effect, the inter- and intraspecies variability, and the completeness and quality of the database.

For the critical health effect, haemolysis, the margins of safety (MOS) were calculated for the various estimated human dose exposure scenarios using the formula given in section 13.1, viz.:

$$\text{margin of safety} = \frac{22.5 \text{ mg/kg/day}}{\text{estimated human dose (EHD) in mg/kg/day}}$$

The EHD for each scenario is given in Appendix 3, with the summary in chapter 8, *Occupational Exposure*. The MOS for each scenario is tabled below.

Table 15 - Margins of Safety

Concentration of 2-BE	Margin of safety

Manufacture		8 hours/day
100% 2-butoxyethanol		16
Formulation		
	3 hours/day	8 hours/day
10% 2-butoxyethanol	32	11.8
30% 2-butoxyethanol	7.3	2.7
60% 2-butoxyethanol	6.3	2.4
Cleaning		
	5 hours/day	8 hours/day
0.1% 2-butoxyethanol	25	16
1% 2-butoxyethanol	22.5	14
10% 2-butoxyethanol	7.3	4.5
30% 2-butoxyethanol	2.6	1.6

In the context of characterising the risks during manufacture of 2-butoxyethanol and the formulation and use of cleaning products containing the chemical, the MOS are discussed below in 13.3.4, 13.3.5 and 13.3.6.

13.3.3 Uncertainties in the risk characterisation

Uncertainties arise in any risk assessment process due to matters such as inadequate information, assumptions made during the process, and variability in experimental conditions. Examples of uncertainties inherent in the assessment of health risk for 2-butoxyethanol are listed below in Table 16. These uncertainties need to be kept in mind when discussing the implications of any margin of safety, particularly when deciding if a calculated exposure is of concern. Given that the risk characterisation in this assessment simply aims at identifying scenarios of possible concern, it is not considered necessary to carry out a quantitative uncertainty analysis.

Table 16 - Uncertainties in Risk Characterisation

Area of uncertainty	Specific concerns
Inadequate information	Lack of representative exposure data. Lack of dermal exposure data. Inadequate data to differentiate between the various methods of application during cleaning.
Assumptions in assessment process	Assumption of a linear correlation between estimated human dose and variables such as atmospheric concentration and exposure time. Assumptions in rate and extent of dermal absorption of vapours and liquid. Use of standard constants for breathing rate, body weight and bioavailability.
Experimental conditions	Selection of doses used in the critical study. Variability in results between laboratories. Precision and accuracy of constants and variables used in the assessment, for example atmospheric monitoring data.

13.3.4 Risk during manufacture of 2-butoxyethanol

The manufacture of 2-butoxyethanol is an enclosed process so typical worker exposure is very low. Single exposures may occur during activities such as plant maintenance and drum filling, however, as the highest inhalational exposure reported is low (1.8 ppm TWA) and effective control measures are in place, the risk of irritant effects is low. The calculated MOS (for haemolytic effects) is 16, with a high degree of confidence in the estimate due to sufficient reliable data. Therefore the risk of haemolytic effects in workers exposed to 2-butoxyethanol during manufacture is minimal.

13.3.5 Risk during formulation of cleaning products

Acute effects

The determination of the risk of acute adverse health effects such as eye and respiratory irritation, headache and nausea during formulation was hampered by lack of data.

Firstly, no atmospheric monitoring data were available for the formulation of cleaning products containing 2-butoxyethanol. In particular, short-term measurements which may have provided some insight into peak 2-butoxyethanol concentrations during specific operations were not available. As a result, values available for varnish production and cleaning operations were used in the exposure calculations for formulation. This may lead to overestimates as inhalational exposure during formulation would be expected to be lower than during cleaning, due to the less dispersive use of 2-butoxyethanol during formulation.

In addition, information obtained from formulators indicated that there was a wide variation in process conditions, for example, some plants have the filling operation enclosed whereas others have an open system.

Vapour concentrations from single exposures are unlikely to be high enough to result in respiratory or eye irritation under routine operating conditions where the process is well-controlled, for example, transfer to the mixing tank is sealed or the filling station on the packing line is enclosed. However, approximately 50% of formulators use open tanks and, in some cases, 2-butoxyethanol is added directly to the tank from a drum above the tank, and splashing may occur. The filling operation may also be open.

In the absence of definitive inhalational exposure data during formulation, it is considered that there is a risk of acute effects during some operations in open plant systems and other work situations where aerosols may be generated or where high vapour concentrations may occur, for example, during the handling of spills, during maintenance, or if heat is applied.

Haemolysis

The risk of haemolysis from exposure is very dependent on factors such as the severity of the effect in humans, the duration of exposure during a work shift, and the concentration of 2-butoxyethanol in the products formulated. MOS ranging from 2.4 to 32 were calculated for the various exposure scenarios (see Table 15). MOS for the

various individual operations during formulation, for example, adding 2-butoxyethanol to the mixing tank, were not estimated as most operators perform a variety of tasks during a normal work period. The scenarios with the lowest MOS are those concerned with exposure during the formulation of cleaning products containing a high concentration of 2-butoxyethanol. For the higher concentrations of 2-butoxyethanol in formulations (30-60%), the MOS was 2-3, however, only 3-4% of formulations contain > 30% 2-butoxyethanol. Approximately 70% contain < 10% 2-butoxyethanol; in these circumstances, the MOS was 11.8 for an 8-hour scenario. Also, the exposure duration for approximately 70% of formulation workers is less than 3 hours/week, so the MOS for many work situations is > 7.3 and for most situations > 32.

In assessing the risk of haemolysis in formulation workers exposed to 2-butoxyethanol, the MOS for each scenario needs to be considered in conjunction with parameters such as severity of the effect, intra- and interspecies differences and uncertainties in the risk assessment process.

A number of uncertainties were inherent in the assessment of risk from exposure to 2-butoxyethanol during formulation (see Table 16). In particular, the exposure assessment for formulation was hampered by lack of data for both inhalational and dermal exposure. Inhalational exposure may have been overestimated as a consequence of assuming exposure to vapours is continuous and of selecting values from air monitoring data for cleaning operations. During formulation, use of 2-butoxyethanol is less dispersive when compared with cleaning, and exposure to vapours is likely to be more sporadic. Similarly, the assumed skin contact time of 20% of exposure duration (intermittent exposure) and skin surface exposed (a hand and a forearm) are also likely to be overestimations as direct handling of 2-butoxyethanol during formulation is likely to be occasional, evaporation of 2-butoxyethanol may occur, and skin protective equipment such as gloves may be worn.

There is a degree of uncertainty regarding the rate of skin absorption. By using the rate of 0.2 mg/cm^2/h (see Appendix 3) dermal exposure may have underestimated. *In vitro* and *in vivo* studies indicate that skin permeability to 2-butoxyethanol differs considerably between subjects (see chapter 9, *Kinetics and Metabolism*). If for example, the estimates are recalculated using the highest skin absorption rate (0.68 mg/cm2/h) observed in human volunteers (Johanson et al 1988), the estimates of dermal exposure would be 3 to 4 times higher. The impact on total exposure and the MOS would not be as great. The smallest MOS would be 2.0 and 1.4 for 8 hour exposure during formulation of 30% and 60% 2-butoxyethanol products, respectively.

Variability between subjects was also observed in inhalational absorption studies, so some degree of uncertainty exists for the value used for bioavailability in vapour exposure estimates. Similarly, the proportion of 2-butoxyethanol vapours dermally absorbed would be expected to vary between subjects. Also, higher absorption under a workload may result in a slight underestimate in the daily dose.

Importantly, when considering species differences, humans are less susceptible than rats to the critical effect of 2-butoxyethanol, haemolysis. In addition, this effect is considered to be transient at lower doses. Therefore, considering the range of MOS

calculated, the uncertainties involved, and the species difference, the risk of haemolytic effects in workers exposed to 2-butoxyethanol during formulation is considered to be minimal.

Other ingredients

Many of the cleaning products which contain 2-butoxyethanol also contain other hazardous ingredients, for example, rust removers may contain phosphoric acid. As the overall health risk to workers may be increased by the presence of the other ingredients, formulators need to consider all ingredients when assessing the health risk of cleaning products containing 2-butoxyethanol.

13.3.6 Risk during use of cleaning products

Acute effects

The determination of the risk of acute adverse health effects such as eye and respiratory irritation, headache and nausea during formulation was hampered by a shortage of data. Some atmospheric monitoring data was available for the use of cleaning solutions containing 2-butoxyethanol, however, TWA measurements were made rather than peak measurements during specific cleaning operations. There are a number of different methods of applying cleaning solutions, for example, mopping, scrubbing, and spraying, and a wide variety of working conditions.

Cleaning products containing 2-butoxyethanol are often used in workplaces where control measures are poor, for example, proper ventilation and protective equipment may not be used during use in schools, offices, workshops and homes. Moreover, supervision in the use of the products may be only occasional, for example, contract cleaners working by themselves or in small groups, and specific training in the proper use of the products and associated protective measures may be inadequate. In Australia, most of the reports of adverse health effects such as eye and respiratory irritation, headache and nausea have originated from workers such as school and office cleaners.

Many of the cleaning products are deliberately used in spray form. The resultant periodic generation of aerosols leads to a greater risk of respiratory and eye irritant effects, particularly in workplaces with little or no effective ventilation. Most of the reports of irritation, headache and nausea in cleaners have been associated with the use of cleaning products in spray form.

Vapour concentrations from single exposures are unlikely to be high enough to result in respiratory or eye irritation under most routine operating conditions where the cleaning operation is well-controlled, for example, when dilute solutions are used with good ventilation. However, irritant effects and/or headache and nausea may be experienced in work situations where aerosols are generated or where high vapour concentrations occur, for example, during spray use, if heat is applied, or during the use of cleaning solutions containing high concentrations of 2-butoxyethanol. Most cleaning products are diluted before use, however, in some work situations, the product is used neat or diluted only marginally, for example, degreasing, oven cleaning, floor stripping (see section 8.5).

Similarly, irritant effects may arise during the dilution of solutions as aerosols may be generated during mixing, particularly if dilution is carried out in confined spaces without adequate ventilation. The application of heat, either during dilution or use, and the incidence of spills and maintenance work may also increase the risk of acute effects. It is important to note that skin absorption can and does occur in the absence of local effects such as irritation.

Haemolysis

The risk of haemolysis in workers using cleaning solutions is very dependent on factors such as the severity of the effect in humans, the duration of exposure, and the concentration of 2-butoxyethanol in the cleaning products used. MOS ranging from 1.6 to 25 were calculated for the various exposure scenarios (see Table 15).

The lowest MOS for 8-hour use of a cleaning solution 30% 2-butoxyethanol is 1.6, so the work situations of greatest concern occur when cleaning solutions containing high concentrations are used, often undiluted, for long periods, for example, floor stripping, washing cars.

Approximately 70% of cleaning products contain < 10% 2-butoxyethanol. For the use of cleaning solutions containing 10% 2-butoxyethanol (undiluted) over 8 hours, the MOS is 4.5. However, most cleaning solutions are diluted substantially before use to a working strength below 1%; the MOS for this scenario is 14 for 8 hours exposure.

In the cleaning services industry, most cleaners work part-time, with the average working day 5 hours; the respective MOS for these scenarios for exposure to 1% and 10% solutions are 22.5 and 7.3. A large proportion of school and office cleaners work part-time and information indicates that they use dilute solutions, generally containing < 1% 2-butoxyethanol. As the typical daily dose for a worker using cleaning products containing 2-butoxyethanol over 8 hours was > 1.6 mg/kg/day, the MOS for such a scenario would be > 14. For a typical part-time work scenario (5 hours exposure), the MOS is > 22.5.

A number of uncertainties exist in the assessment of risk from exposure to 2-butoxyethanol during cleaning operations (see Table 16). In particular, the exposure assessment was hampered by the lack of data, especially dermal exposure data. Inhalational exposure may have been overestimated as a consequence of selecting maximum values from air monitoring studies. Similarly, dermal exposure may have been overestimated by assuming worker exposure to be continuous, and not allowing for other factors that might limit exposure, such as evaporation of 2-butoxyethanol from skin surface and the use of protective gloves.

There is a degree of uncertainty regarding the rate of skin absorption. By using the rate of 0.2 mg/cm^2/h (see Appendix 3), dermal exposure may have been underestimated. If for example, the estimates are recalculated using the highest skin absorption rate (0.68 mg/cm^2/h) observed in human volunteers (Johanson et al 1988), the estimates of dermal exposure would be 3 to 4 times higher. The impact on total exposure and the MOS would not be as great. The smallest MOS would be 1.2 and 0.74 for 5 and 8 hour exposure during use of cleaning solutions containing 30% 2-butoxyethanol respectively, and 2.1 for 8 hour exposure to 10% solutions.

Other uncertainties inherent in the process included the influence of workload and the variability in working conditions. Some cleaning operations are carried out under a workload higher than normal, for example, washing cars, and may lead to increased absorption. Poor working conditions, for example, poor ventilation or lack of proper protective equipment, may also lead to increased absorption.

Importantly, when considering species differences, humans are less susceptible than rats to the critical effect of 2-butoxyethanol, haemolysis. In addition, this effect is considered to be transient at lower doses. Therefore, considering the uncertainties involved, and the species difference, the risk of haemolytic effects in workers exposed to 2-butoxyethanol during cleaning for the various scenarios considered, that is, use of cleaning solutions containing less than 30% 2-butoxyethanol, is considered to be minimal.

Exposure estimates for use of cleaning solutions containing 30% 2-butoxyethanol indicate that there is a concern in situations where there is prolonged exposure, particularly dermal exposure, to solutions containing high concentrations (30% or more) of 2-butoxyethanol.

Other ingredients

As for formulators, employers of cleaners and other workers carrying out cleaning operations using solutions containing 2-butoxyethanol also need to consider the health risk posed by other ingredients in cleaning solutions when assessing the overall health risk as other ingredients may increase the risk.

13.4 Areas of concern

From the risk assessment, there may be concern for the health of workers in some work situations where exposure to 2-butoxyethanol may occur. Although little short-term exposure data were available, sufficient information was available to conclude that there may be a risk of eye and respiratory irritant effects, headache and nausea when high vapour and/or aerosol concentrations of 2-butoxyethanol occur during acute exposures. As 2-butoxyethanol is relatively non-volatile, these situations will most likely occur only during the deliberate volatilisation of 2-butoxyethanol, for example, spraying or heating, or when work practices are poor, for example, poor ventilation. Consequently, there is concern for the health of workers, in relation to the irritant effects and headache and nausea, in the following situations:

- use of products in spray form without adequate ventilation;
- use of heat during dilution or application without adequate ventilation;
- generation of aerosols;
- handling of spills if the proper procedures are not followed; and
- maintenance when the proper precautions are not taken.

From the risk assessment, it is unlikely that these effects will occur during manufacture, but they may arise during formulation and cleaning.

Characterisation of the risk of the critical adverse health effect, haemolysis, in workers potentially exposed to 2-butoxyethanol was hampered by a number of uncertainties in the risk assessment process, particularly the lack of exposure data (especially dermal exposure). A number of assumptions were needed to enable an assessment of risk, however, for the scenarios considered, it is considered that the risk of haemolysis in workers is minimal.

Based on the risk assessment of cleaning solutions containing 30% 2-butoxyethanol, there is a concern in situations where there is prolonged exposure (particularly dermal exposure) to solutions containing 30% or more of 2-butoxyethanol.

Although short-term repeated dose studies (up to 13 weeks exposure) provide some information, it should be noted that the chronic effects of 2-butoxyethanol are largely unknown. An NTP 2-year study in rats and mice is currently underway and will provide some information on chronic effects of 2-butoxyethanol.

14. Risk management

The risks to occupational health and safety posed by the manufacture of 2-butoxyethanol and its formulation and use in cleaning products were identified and evaluated in the previous chapter, *Risk Characterisation*. Areas of concern, that is, where the risk to human health may be unacceptable, were established. This chapter focuses on the management of those risks, with emphasis on the areas of concern. In general, many of the strategies are applicable to other uses of 2-butoxyethanol and to the management of potential risks to the environment and to the health and safety of the public at large.

The key elements of risk management described in this chapter for 2-butoxyethanol include:

- control measures;
- hazard communication, including training and education;
- monitoring; and
- regulatory controls.

This chapter includes an assessment of the strategies currently employed and/or recommended to manage health and safety risks associated with the formulation and use of cleaning products containing 2-butoxyethanol. It includes an assessment of the MSDS and labels submitted by formulators in response to the questionnaire sent to them during the assessment period, and a review of the regulatory controls currently in place for 2-butoxyethanol.

14.1 Control measures

According to the *National Model Regulations for the Control of Workplace Hazardous Substances*, exposure to hazardous substances should be prevented or, where that is not practicable, adequately controlled so as to minimise risks to health. A *National Code of Practice for the Control of Workplace Hazardous Substances* provides further guidance in the from of a hierarchy of controls, which should be considered to assist with this control, namely:

- elimination;
- substitution;
- isolation;
- engineering controls;
- administrative controls;
- safe work practices; and

- personal protective equipment.

In relation to 2-butoxyethanol, particular care needs to be given to control measures to minimise inhalational and dermal exposure.

14.1.1 Elimination

Elimination means the elimination of chemicals from a process, such as the use of a physical process instead of a chemical process in cleaning. Elimination should be the first option considered when minimising risks to health. However, in situations where it is considered that a chemical process for cleaning is necessary then the second control option to be considered is substitution.

14.1.2 Substitution

Substitution includes substituting a less hazardous substance, the same substance in a less hazardous form or the same substance in a less hazardous process. Substitutes for 2-butoxyethanol need to be thoroughly tested and, in general, they should demonstrate a lower toxicity, irritancy and potential for skin absorption in humans.

Information on solvent substitution is available on the Internet, for example, the Solvent Alternatives Guide (SAGE) and the Hazardous Solvent Substitution Data System (HSSDS).

In some workplaces, the application of cleaning products in spray form has been substituted with a procedure less likely to generate vapours or aerosols, for example, applying the solution as a liquid stream onto the surface to be cleaned.

14.1.3 Isolation

The manufacture of 2-butoxyethanol is an enclosed process operated from a remote control room so, during normal operation, workers are isolated from contact with 2-butoxyethanol. Similarly, 2-butoxyethanol is transferred to road tankers and sealed storage vessels via an enclosed system.

In some formulation plants, the process has been enclosed to a large extent to minimise exposure. In some plants, 2-butoxyethanol is transferred via a manifold into the bottom of the mixing tank filled with water, with the tank covered during mixing. For the filling and packing operation, some formulators have enclosed the packing line at the point of filling to minimise exposure and contain spills. In other cases, the filling process has been automated to isolate workers from the process.

In the end-use of cleaning products containing 2-butoxyethanol, there is far less scope for isolation of the worker as most of the products are applied in an open environment, for example, cleaning offices, homes and schoolrooms. In a few cases, the work area is enclosed, for example, the use of a spray booth or fume cupboard during the cleaning of machinery parts in a workshop.

14.1.4 Engineering controls

At the 2-butoxyethanol manufacturing plant, local exhaust ventilation has been installed to minimise exposure during the drumming-off of 2-butoxyethanol from

storage tanks. In the filling of road tankers, a mass flow meter has been installed to prevent overfilling and therefore spillage.

In the formulation and end-use of cleaning products containing 2-butoxyethanol, good ventilation is often used to minimise inhalational exposure to 2-butoxyethanol. This may consist of local exhaust ventilation, dilution ventilation or the use of portable fans.

Several formulators indicated that exhaust fans were installed above the mixing tanks to take any vapours away from the mixing area. In some cases, formulators have added scrubbers to the exhaust system to prevent the escape of 2-butoxyethanol and other contaminants to the atmosphere. On the filling line, some formulators indicated that they had local exhaust ventilation at the point of filling to extract 2-butoxyethanol vapours away from operators on the line. Good mechanical dilution ventilation is required in all work areas in the formulation process and, in at least one plant, the ability to increase the flow rate (number of changes per hour) in the event of spills has been provided. Ventilation needs to be provided in accordance with the relevant Australian standards, in particular AS 1668.2-1991 (Standards Australia 1991).

In the transfer of 2-butoxyethanol to the mixing tank during formulation, mass flow meters can be installed to prevent over-filling and the consequent spillage. In at least one formulation plant, the mixing tank and filling areas have been bunded so that any spills are confined.

In the end-use of cleaning products, the ventilation provided in workplaces is extremely variable. In some applications, such as the use of a metal cleaning product in a mechanical workshop, effective local exhaust ventilation is provided to minimise exposure, particularly if the product is used in spray form. Good general mechanical ventilation is provided in many workplaces, for example, offices and some factories, to ensure an adequate air flow in the vicinity of the worker. However, in a large proportion of work situations, effective mechanical ventilation is not provided or switched on as the work is conducted outside normal working hours and/or in workplaces such as schools and homes not equipped with air-conditioning. Portable fans have been used in some work situations where general mechanical ventilation is not available, for example, in school classrooms, but great care is required in the positioning of the fans to ensure that vapours and aerosols are directed away from exposed persons. Simple measures such as open doors and windows have been shown to be helpful in reducing exposure.

As splashing and vapour and aerosol generation may occur during the dilution of cleaning products before use, exposure to 2-butoxyethanol is likely to be lower where good ventilation has been provided. Where available, the use of local exhaust ventilation for dilution work is even more effective.

The design of containers used for dispensing the cleaning products is important in minimising skin and inhalational exposure. For example, in order to reduce skin contact during the application of cleaning solutions in liquid form, liquid stream containers such as plastic wash bottles are being used by some cleaners to direct the cleaning solution onto the surface instead of pouring the solution on to a cloth or rag.

To reduce inhalational exposure during spray use, the nozzles of spray applicators for cleaning solutions are often designed to ensure that the spray droplets are not too fine.

14.1.5 Administrative controls

To reduce exposure to 2-butoxyethanol, at least one formulator has introduced job rotation, where the operators are rotated from one part of the plant to another, with each operator spending 2-4 hours per shift in a work area with potential exposure to 2-butoxyethanol.

The prohibition of entry to an area which has just been cleaned or treated with a cleaning product containing 2-butoxyethanol has also been used as a means of reducing exposure. For example, in NSW schools, entry to classrooms is restricted until one hour after cleaning.

14.1.6 Safe work practices

Appropriate safe work practices which have been used during the formulation, handling and use of cleaning products containing 2-butoxyethanol include the following:

- minimising spray use;
- if spray is used, spray away from the breathing zone;
- prevention of aerosol generation during mixing and end-use (in spray use, nozzles which produce a fine spray are not suitable);
- addition of 2-butoxyethanol as the last (or near last) ingredient during the mixing process in formulation;
- prevention of splashing, particularly during formulation and dilution;
- avoidance of heat, for example, during mixing in formulation, during dilution of cleaning product before application, and during end-use;
- storage of cleaning solutions in cool, well-ventilated areas;
- proper labelling of containers, including containers used for application of cleaning solution;
- keeping lids on mixing tanks and caps on cleaning solution containers when not in use (to prevent evaporation, splashing and spillage);
- containment of spills during handling, for example, by carrying out dilution in a sink or bunded area;
- prompt clean-up of spills;
- proper cleaning of drums and other containers;
- proper disposal of contaminated containers and equipment no longer required;

- use of proper size funnels in dilution work to prevent spillage and skin contact;
- laundering of contaminated clothing;
- good housekeeping; and
- high standard of personal hygiene.

14.1.7 Personal protective equipment

Where other control measures are not practicable or adequate to control exposure, personal protective equipment is generally used. As 2-butoxyethanol is readily absorbed through the skin, the prevention of skin contact is particularly important.

Protective gloves are generally provided but some are not suitable for solutions containing 2-butoxyethanol. In a survey of different glove materials using the GlovES database, butyl rubber and nitrile rubber were identified as being the most suitable for handling 2-butoxyethanol (Keith et al 1990). NIOSH have also reported that butyl rubber has good resistance to 2-butoxyethanol (NIOSH 1990). In selecting suitable gloves for use with cleaning products, other ingredients in the solutions may need to be considered, for example, high caustic or acid strength.

Covering of the arms and legs is good practice during the handling and use of cleaning products containing 2-butoxyethanol, for example, overalls or long-sleeved shirts and trousers. In formulation plants, overalls are often worn to protect the arms and legs. In some cases, for example, in the handling of large quantities of undiluted or highly concentrated solutions of 2-butoxyethanol, a butyl or nitrile rubber apron is often used to reduce the risk of skin absorption in case of spills or splashing.

Similarly, socks and covered footwear provide good protection for the feet. In an industrial environment where larger quantities of cleaning product may be handled, or where corrosive substances such as sodium hydroxide may be present (for example, during formulation) safety shoes or boots are often worn to provide greater protection.

For eye protection, chemical safety goggles are generally provided when handling large quantities of solution, for example, during filling or emptying drums. In some cases (for example, when splashing may occur) a face-shield has been found to be more suitable. In general, protective eyewear is not worn during cleaning. In some cases, safety spectacles are worn (for example, during spray application or if splashing may occur).

Respiratory protection is not normally required during the formulation or use of cleaning products containing 2-butoxyethanol. In response to the questionnaire, a number of formulators indicated that they provided half-face respirators for their workers, but they generally elected not to wear them as they experienced no discomfort from vapours during normal operations. However, in certain work situations, for example, during the cleanup of large spills, a respirator was worn to reduce exposure. A half-face mask with organic vapour cartridge has been found to be suitable.

14.2 Emergency procedures

In the formulation of cleaning products, the availability of an emergency response plan to deal with unexpected releases of 2-butoxyethanol such as large spills is good practice. Standard emergency procedures are good policy wherever undiluted 2-butoxyethanol or large amounts of concentrated cleaning solution containing the chemical are handled so that exposure is minimised and action to remedy the situation can be taken swiftly.

14.3 Hazard communication

14.3.1 Assessment of Material Safety Data Sheets

Introduction

MSDS are the primary sources of the information needed to handle chemical substances safely. Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994(c)) and corresponding State and Territory legislation, suppliers are obliged to provide MSDS to their customers for all hazardous substances.

In 1994, prospective formulators of cleaning products containing 2-butoxyethanol were requested to reply to a questionnaire and to send a copy of the MSDS and label for each of these products (see section 7.2). The responses to the questionnaire identified 82 formulators and 434 cleaning products containing 2-butoxyethanol (see Appendix 1) and 409 MSDS were submitted. A representative sample was assessed, with the specific objective to qualitatively assess the MSDS in terms of compliance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (MSDS Code) (NOHSC 1994 (d)) and the SUSDP with regard to the provision of adequate information about 2-butoxyethanol. In particular, specific health effects data and safe handling precautions were assessed.

At the time of the survey in 1994, no State or Territory had enacted their legislation for workplace hazardous substances and the revised MSDS Code and Approved Criteria had only been published earlier that year. As a considerable time has elapsed since receipt of the MSDS (late 1994), a random re-sample of MSDS took place in April 1996.

Methodology

A number of approaches have been used to assess MSDS (Lewis et al 1993; Kolp et al 1995). In this assessment, a qualitative evaluation method similar to that proposed by Lewis was used, whereby information in the MSDS was assessed according to the MSDS Code in the four specific information sections: product and ingredient identification, health hazard information, precautions for use and safe handling information.

2-Butoxyethanol is currently on the *List of Designated Hazardous Substances* (the List) as a hazardous substance with a concentration cut-off level of 12.5%. On the SUSDP, it falls within the scope of 'ethylene glycol monoalkyl ethers', which are listed on Schedule 6 for preparations containing more than 10% glycol ether. Therefore, for the purposes of this MSDS review, the products were divided into two

groups, those containing ≥10% 2-butoxyethanol, and those containing <10% 2-butoxyethanol, to broadly distinguish 'hazardous' products for 2-butoxyethanol from those which did not meet the criteria for being 'hazardous'.

MSDS for all 83 products identified as containing ≥10% 2-butoxyethanol were assessed. Of these 83 products, four contained >60% 2-butoxyethanol, five had 30-60%, 56 had 10-<30%, and 18 MSDS listed concentrations which did not fit into these specific proportion ranges. Of the remaining 326 products with MSDS, 64 containing <10% 2-butoxyethanol were selected in a way that covered various formulations and all companies. As a result, a total of 147 MSDS were assessed.

Of 16 companies contacted in the random sample in April 1996, six had not made changes, nine had made changes to some or all of their MSDS and one company no longer used 2-butoxyethanol. In general, the changes were minor. Where appropriate, comment on the changes has been incorporated into the following subsection.

Results and discussion

The results of the assessment are summarised in Table 17.

Table 17 - Findings of MSDS Assessment (1994 Survey)

Aspect	> 10% 2-BE		< 10% 2-BE	
	number	%	number	%
Total	83		64	
Ingredient- (2-BE concentration)				
exact 2-BE concentration stated	17	20	5	8
no 2-BE concentration stated	2	2	5	8
correct proportion ranges used	48	58	40	78
incorrect proportion ranges used	16	19	4	6
Use				
major uses indicated	72	87	61	95
spray use indicated	5	6	12	19
Hazard classification				
statement of hazardous nature	1	1	3	5
SUSDP designation	60	72	n. a.	
Health effects stated				
skin absorption	21	25	7	11
eye irritation	70	84	53	83
skin irritation	63	76	50	78
nose/throat irritation	61	73	10	16
headache/nausea	35	42	21	33
data on chronic effects	16	19	2	3
Exposure standard				
correct value stated	46	55	30	47
skin notation mentioned	14	17	13	20
Engineering controls recommended				

Aspect	> 10% 2-BE		< 10% 2-BE	
	number	%	number	%
'adequate' ventilation	58	70	41	64
'local' ventilation	19	23	7	11
Personal protection recommended				
gloves (non-specific)	65	78	51	80
butyl or nitrile rubber gloves	4	5	1	2
respirator	19	23	10	16
respirator during spray use	11	13	13	20
Safe handling statements				
skin protection for handling spills	2	2	4	6
Emergency telephone no. stated	28	34	27	42

Note: n. a. = not applicable; 2-BE = 2-butoxyethanol

General information

Approximately 90% of the MSDS assessed were in the format recommended in the MSDS Code. Several MSDS, all from one company, did not provide appropriate company details such as Australian address or telephone number. In general, all MSDS stated the company telephone number, but only 37% indicated the specific emergency telephone number.

For the purpose of hazard identification, the MSDS Code now specifies that a 'statement of hazardous nature' be included in the introductory section of a MSDS. The 'statement of hazardous nature' should contain one of the following phrases:

- 'Hazardous according to criteria of Worksafe Australia'; or
- 'Not classified as hazardous according to criteria of Worksafe Australia'.

The former statement should be used on MSDS for all workplace products containing ≥12.5% 2-butoxyethanol. However, it was found on the MSDS of only one of the 83 products containing ≥10% 2-butoxyethanol. Of the 64 products containing <10% 2-butoxyethanol, only three were found to have a statement of hazardous nature. Hence 97% of the total MSDS assessed did not contain any statement of hazardous nature. This omission could be explained by the fact that this statement has only been a requirement in the MSDS Code since March 1994, and that, at the time of the survey, the hazardous substances regulations were not in force in the State and Territory jurisdictions. The 1996 re-sample of MSDS indicated that approximately 50% of MSDS had incorporated a statement of hazardous nature since the original survey.

Product and ingredient identification

The MSDS Code allows specific proportion ranges, namely <10%, 10-<30%, 30-60% and >60%, to be used when stating ingredient concentration so that commercial confidentiality of a formulation can be protected. Of the 147 MSDS assessed, 20% of products containing ≥10% 2-butoxyethanol and 8% of those containing <10% 2-butoxyethanol disclosed the exact concentration of the chemical; this more specific information may often assist end-users in determining the hazards of the product. The

allowable proportion ranges were used in 58% and 78% of the products containing ≥10% and <10% 2-butoxyethanol respectively. Non-standard proportion ranges, for example, 10-60%, <60%, were used in 19% of the products containing ≥10% 2-butoxyethanol.

In addition to the 'statement of hazardous nature', the hazardous nature of a product can also be identified from the SUSDP, where any consumer product containing >10% 2-butoxyethanol should be designated as a schedule 6 poison. Approximately 50% of the products containing ≥10% 2-butoxyethanol had this designation on the MSDS.

The 'Use' subsection is another important feature of a MSDS. Major uses were stated in 87% and 95% of products containing ≥10% and <10% 2-butoxyethanol, respectively. The method of application, however, was not generally stated. Despite spray application being indicated on many labels, use of the product in spray form was mentioned in only 12% (17/147) of the MSDS. As spray use may increase the exposure to 2-butoxyethanol, it is important to indicate 'spray use' on the MSDS where applicable so that proper control measures can be implemented during use of the product. The discrepancy between MSDS and labels in this respect is noteworthy (see 14.3.2.).

In the re-sample of MSDS in April 1996, some of the MSDS which had been updated contained less information about the ingredients than on the original MSDS, for example, no identification or CAS number of ingredients, including 2-butoxyethanol. This occurred only for some products not classified as hazardous.

Health hazard information

Based on the health hazard assessment in this report, this section of the MSDS should include the following information about 2-butoxyethanol:

- acute effects (in humans)
  - eye and respiratory irritation;
  - degreasing action on skin;
  - possibility of headache and nausea;
  - coma and breathing difficulties after ingestion of large doses.
- chronic effects - effects on blood, kidney and liver observed in animal tests.
- ready absorption through skin.

Only 25% of the MSDS for products containing ≥10% 2-butoxyethanol provided information on the skin absorption property. Eye irritation was stated in 84% of these MSDS and nose and throat irritation in 73%.

Skin irritation was mentioned in 76% of MSDS. 2-Butoxyethanol appears to be only a slight skin irritant in humans, but reddening and degreasing of the skin may occur and contact dermatitis may result after repeated or prolonged exposure. The presence of strong skin irritants such as sodium hydroxide and phosphoric acid in many of the cleaning products may bias the results for this part of the assessment.

Headache and nausea were stated in 42% of the MSDS for products containing ≥10% 2-butoxyethanol. Breathing difficulties and coma, which have been observed after the ingestion of high doses of 2-butoxyethanol, were not indicated in any of these MSDS. The effects of 2-butoxyethanol on blood, kidney and liver were stated in the 'chronic effects' subsection in 19% of these MSDS.

Clearly defined first aid instructions with standard statements are available for all scheduled poisons listed in the SUSDP. As 2-butoxyethanol at concentrations >10% is listed as a schedule 6 poison in the SUSDP (under ethylene glycol monoalkyl ethers), standard first aid instructions are available and were used in the 'first aid' subsection of all the MSDS in this assessment.

Precautions for use

According to the MSDS Code, the Australian exposure standard should be used on the MSDS where allocated. The Australian exposure standard for 2-butoxyethanol is 25 ppm TWA (121 mg/m^3) with a 'skin' notation (NOHSC 1995). The numerical value was stated as an Australian (or Worksafe) exposure standard on 52% of the total 147 MSDS, and as an ACGIH 'TLV' (also 25 ppm TWA) on 13% of the MSDS. The 'skin' notation was mentioned on only 18% of MSDS. The remainder had no exposure standard at all.

The MSDS Code specifies that 'engineering controls' and 'personal protection' subsections should address the hazards identified for the substance. Under engineering controls, guidance that good dilution ventilation be maintained was considered adequate. A sole instruction to avoid breathing the vapour, found on a number of MSDS, was considered inadequate.

For personal protection, all MSDS recommended wearing eye protective equipment, that is, goggles or safety glasses, and 82% recommended the wearing of gloves. Butyl and nitrile rubber gloves are considered the most suitable type of gloves for handling 2-butoxyethanol but were specified in only 3% of the MSDS. A respirator was also recommended in about 20% of the MSDS. The use of respirators may be an over-cautious measure when using cleaning products containing 2-butoxyethanol as the only hazardous substance, especially for those products containing <10% 2-butoxyethanol. However, it may be appropriate in some situations where the product is applied in spray form, where heat may be applied, or during the clean-up of large spills. It may also be appropriate for products containing other respiratory irritants, for example, sodium hydroxide, where caustic mists may be generated.

Safe handling information

In general, all cleaning products containing 2-butoxyethanol should be stored in cool, well ventilated areas. About 56% of the 147 MSDS provided some information on

the storage and transport of products containing 2-butoxyethanol. However, over 95% of the MSDS did not indicate the need for skin protection when containing or cleaning up spills.

Summary

The assessment indicated that a high percentage of the MSDS conformed to the format recommended in the MSDS Code. With respect to the content of the MSDS, a number of deficiencies were noted:

- no 'statement of hazardous nature';
- correct proportion ranges not used for ingredients;
- no indication of spray use in the 'use' section when applicable;
- poor indication that 2-butoxyethanol is readily absorbed through the skin;
- lack of information on the effects of prolonged or repeated exposure;
- poor indication of the most suitable types of gloves for handling 2-butoxyethanol;
- lack of information on the need for skin protection when dealing with spills; and
- the full Australian exposure standard not stated.

The most serious deficiencies were those related to the ready absorption of 2-butoxyethanol through the skin from solution. Skin protection is most important in all work situations, particularly during non-routine situations such as the cleanup of spills. Proper indication of the exposure standard, particularly the 'skin' notation, was poor.

The assessment of MSDS was not altered significantly by the re-sample of MSDS in April 1996. The only major change noted was inclusion of a statement of hazardous nature on a large number of updated MSDS.

It was evident from the response to the questionnaire that most formulators had adopted the policy of preparing MSDS for products whether they were classified as hazardous or not. On examination of the re-sampled MSDS, it was noted that, unfortunately, some suppliers had reduced the amount of information on MSDS for non-hazardous products.

A sample MSDS for 2-butoxyethanol, prepared in accordance with the MSDS Code, is provided in this report as Appendix 6. The sample MSDS, prepared from information obtained for the assessment of 2-butoxyethanol, is for guidance purposes only. Under the National Model Regulations, manufacturers and importers have the responsibility to compile their own MSDS and ensure that the information is up-to-date and accurate.

14.3.2 Assessment of labels

Introduction

In 1994, information was received on 434 cleaning products containing 2-butoxyethanol. Labels were supplied for 389 of these products. They were assessed for compliance with some of the labelling requirements of the SUSDP (Australian Health Ministers Advisory Council 1995) and the *National Code of Practice for the Labelling of Workplace Substances* (the Labelling Code) (NOHSC 1994(e)). They were assessed in particular for those requirements relating to safety directions/phrases and risk phrases and ingredient statements relating to 2-butoxyethanol. In addition, labels which specified spraying as a method of application were examined for the presence of any safety statements related to inhalation of vapour or provision of ventilation.

In this assessment of labels, other mandatory requirements of labels were not analysed, for example, directions for use, first aid procedures and information on emergency procedures.

Products for domestic end-use are covered by the SUSDP and need to comply with SUSDP labelling requirements. Under the SUSDP, products containing >10% 2-butoxyethanol are schedule 6 poisons and must be labelled accordingly. After 1993, industrial products were exempted from the SUSDP and should comply with the Labelling Code. Products containing > 12.5% 2- butoxyethanol should be labelled in accordance with the Labelling Code. Products used industrially and domestically need to comply with both codes. For the purposes of this section, 'hazardous' means 'containing >10% 2-butoxyethanol'. The requirements are as follows in Table 18.

Table 18 - Labelling Requirements

	>10%	**>12.5%**	**>20%**
Labelling code - risk phrases		R20/21/22	R20/21/22, R37, R36*
SUSDP safety directions	SD1,4,8	SD1,4,8	SD1,4,8

*Note: * R36 recommended in health hazard assessment (see subsection 12.3.2).*

Key:

R20/21/22	*Harmful by inhalation, in contact with skin and if swallowed*
R37	*Irritating to respiratory system*
R36	*Irritating to eyes*
S24/25	*Avoid contact with skin and eyes*
SD1	*Avoid contact with eyes*
SD4	*Avoid contact with skin*
SD8	*Avoid breathing dust (or) vapour (or) spray mist.*

Under the Labelling Code, information on safe storage, handling and personal protection should be provided on the label by the use of suitable safety phrases. For 2-butoxyethanol, S24/25 are designated on the List as suitable safety phrases, however, others may be used where appropriate. There are no concentration cut-offs specified for safety phrases.

Note that the safety phrases S24 and S25 are the same as SUSDP safety directions SD4 and SD1 respectively.

From information on labels and responses to the questionnaire submitted by the 82 formulators identified during this assessment, 59 indicated that their products were used primarily as workplace substances in industries such as contract cleaning, hospitality, meat processing, automotive, and the metals industries. Only eight formulators indicated that their products were primarily for the domestic market. Most of the labels identified uses for the product that had potential industrial application as well as domestic application, such as floor stripping, carpet cleaning, window cleaning, engine degreasing, vehicle cleaning, oven cleaning, cleaning of food preparation areas and equipment, and disinfection of washrooms.

Compliance with SUSDP

Safety directions

Of the 389 labels, 61 (16%) were for products which contained >10% 2-butoxyethanol. Of the 61 labels, 35 (57%) had all three designated safety directions, 10 (16%) had two of the three (SD1 and SD4), 3 (5%) had one (2 had SD1, one had SD8), while 13 (21%) had none. That is, only 35 of the labels (57%) included a warning of the inhalational hazard (SD8).

Ingredient statements

Labels were checked for compliance with section 2 of the SUSDP, which states that immediate wrappers containing a poison shall be conspicuously labelled with the approved name of the poison and a statement of the quantity or the strength of the poison. Section 5 of the SUSDP states that, in respect of a liquid poison in a liquid preparation, the statement should be expressed as mass or volume of the poison per stated volume of the preparation. The labels were checked for statements concerning the presence and concentration of 2-butoxyethanol or ethylene glycol monoalkyl ether.

Of the 61 labels for hazardous products, 36 (59%) had a statement detailing the exact concentration of 2-butoxyethanol, 6 (10%) had a statement indicating the presence of 2-butoxyethanol without indicating the concentration, and 19 (31%) had no ingredient statement. On 9 of the labels, the generic term ‘ethylene glycol monoalkyl ether’ was used instead of ‘2-butoxyethanol’ or ‘ethylene glycol monobutyl ether’.

Compliance with the National Code of Practice for the Labelling of Workplace Substances (the Labelling Code)

From information on labels and from formulators in their response to the questionnaire, all products containing >10% 2-butoxyethanol could be used industrially. The cut-off for 2-butoxyethanol as a hazardous ingredient in workplace substances is slightly different than in the SUSDP (12.5% rather than 10%) but, for

convenience, all labels for products containing >10% 2-butoxyethanol (61) were assessed for their compliance with the designated risk and safety phrases (or equivalent statements) (see Table 18). Findings included the following:

- None of the 61 labels contained the risk phrase R20 (Harmful by inhalation), however 35 labels (57%) had the safety phrase S23 (Do not breathe gas/fumes/vapour/spray) or the equivalent SUSDP safety direction SD8 (Avoid breathing vapour (or) spray mist);
- None contained the risk phrase R21 (Harmful in contact with skin), however 48 (79%) had the safety phrase S24, which is the same as SUSDP safety direction SD4 (Avoid contact with skin); and
- None contained the risk phrase R22 (Harmful if swallowed), where there is no equivalent SUSDP safety direction.

Summarising, none of the labels contained the risk phrases for acute toxicity (R20/21/22).

Of the 61 products containing >10% 2-butoxyethanol, at least 20 products and possibly another 20 contained ≥20% 2-butoxyethanol, which is the concentration cut-off for the risk phrases R37 (Irritating to respiratory system) and R36 (Irritating to eyes). Findings for the incidence on labels of risk and safety phrases relating to eye and respiratory irritation included the following:

- None contained R37, but 35 of the 61 labels (57%) had the safety phrase S23 (Do not breathe gas/fumes/vapour/spray) or the equivalent SUSDP safety direction SD8 (Avoid breathing vapour (or) spray mist); and
- Only two (3%) had R36 (Irritating to eyes), but 48 (79%) had the safety phrase S25 (Avoid contact with eyes), which is the same as SUSDP safety direction SD1.

Summarising, many labels did not provide proper indication of the irritant effects of 2-butoxyethanol.

The 61 labels for hazardous products were also checked for any statements relating to use of gloves or provision of ventilation. Suitable safety phrases in the Worksafe labelling system for workplace substances are:

- S36/37 Wear suitable protective clothing and gloves
- S51 Use only in well ventilated areas.

These safety phrases are relevant due to the ready skin absorption of 2-butoxyethanol, and the frequent use of cleaning products in spray form. It was found that only six labels (10%) contained S36/37 (or an equivalent statement), and only 14 (23%) contained S51 (or an equivalent statement).

Labels for spray products

The spraying of products containing 2-butoxyethanol increases the potential for exposure to the chemical as the atmospheric concentration of 2-butoxyethanol may be

increased due to aerosol generation. A separate assessment of safety statements on the labels of these products was undertaken in order to determine whether, as a group, any extra emphasis was given to the increased risk associated with spraying.

Of the 389 labels, 163 identified spraying as a method of application. Of these, 73 listed spraying as the only or the major method of application. General purpose surface cleaners and glass/window cleaners were the most represented groups of products amongst the spray products.

Of the 163 labels, 19 were for products containing >10% 2-butoxyethanol. Of these, eight contained a safety phrase (or safety direction) warning against breathing of vapour (S23), five contained a safety phrase (or safety direction) concerning ventilation (S51), and one had both. Of the 144 labels for spray-use products containing ≤10% 2-butoxyethanol, 21 contained S23, seven contained S51, and three had both. Overall, only 45 (28%) of the labels for spray products had one or more of safety phrases S23 or S51 (or equivalent safety directions SD8, SD9 or SD10).

For spray use, a comparison was carried out between labels and MSDS for the products surveyed in the MSDS assessment (see 14.3.1), with the results as tabled below for products containing >10% 2-butoxyethanol and those with ≤10%.

The analysis found that where spray use was indicated on the label of a product, it was rarely mentioned on the MSDS.

Table 19 - Indication of Spray Use on MSDS and Labels

	>10% 2-BE		<10% 2-BE	
	number	%	number	%
Number of MSDS assessed	85		63	
Spray use indicated on label but not MSDS	17	20	17	27
Spray use indicated on MSDS but not label	1	1	2	3

Summary

Most cleaning products containing 2-butoxyethanol are used industrially but, at the time of the survey in 1994, most companies had not yet updated their labels to meet the requirements of the relatively new Labelling Code. Thus a large proportion of the products were still labelled according to SUSDP requirements. However, many of the labels for products containing >10% 2-butoxyethanol did not comply fully with SUSDP requirements. Few of the labels fulfilled the requirements of the Labelling Code, in particular, the assigning of risk phrases which may cover hazards not addressed by the designated SUSDP safety directions (for example, acute toxicity). As no label contained the risk phrase R22 (Harmful if swallowed), it can be assumed that no products containing >12.5% 2-butoxyethanol complied fully with the requirements of the Labelling Code for products that could reasonably be expected to be used in the workplace.

Other deficiencies in the labels included the following:

- Lack of warning of inhalational hazard for 43% of products containing >10% 2-butoxyethanol;
- Omission of the ingredient statement on 31% of products containing >10% 2-butoxyethanol; and
- Indication of presence of 2-butoxyethanol in the formulation but omission of the concentration on 10% of products containing >10% 2-butoxyethanol.

Due to the increased health risk from spray use and the need for good ventilation and skin protection, it would be advisable if more labels contained safety phrases (or safety directions) to cover the following:

- Warning of inhalational hazard for all products which may be used in spray form;
- Need for the use of gloves for skin protection; and
- Need for good ventilation, particularly when products are used in spray form.

As only certain requirements were analysed in this assessment, no comment can be made on compliance with other mandatory requirements, such as first aid and emergency procedures. All labels should be checked against the full requirements of the SUSDP or Labelling Code.

14.3.3 Education and training

Under the *National Model Regulations for the Control of Workplace Hazardous Substances*, employers are obliged to provide training and education for workers potentially exposed to hazardous substances, and their supervisors. In accordance with the regulations, the program must address those areas where there may be a risk to health and safety.

The key elements of an adequate induction and training program are listed in section 10.3 of the *National Code of Practice for the Control of Workplace Hazardous Substances*. For 2-butoxyethanol, the program should address those risks identified under section 13.4 of this report. Specifically, matters which need to be addressed include:

- the health effects of 2-butoxyethanol;
- the skin absorption potential of 2-butoxyethanol, including the fact that it can be absorbed without skin irritation, and that absorption may be greater when the skin is cracked or damaged;
- explanation of MSDS and labels of cleaning products used;

- instruction in the proper handling and use of cleaning solutions containing 2-butoxyethanol, including information about the additional risks posed by spray use and the use of heat; and
- the specific protective equipment to be worn.

The Model Regulations stipulate that training and induction should be appropriate for the workers concerned. The contract cleaning industry in particular comprises many workers from a non-English speaking background, so the program should be suitably designed to accommodate their needs. For example, visual training methods may be more suitable than oral instruction and a fact sheet in another language may be more appropriate than a complex MSDS in English.

In accordance with standard risk management practice, training and education needs for workers should be reviewed on a regular basis.

In Australia, some programs have been instituted to train and educate suppliers, supervisors and workers who may manufacture, supply or use cleaning products containing 2-butoxyethanol. For most of the cleaning products, there are a number of steps between the manufacture and importation of 2-butoxyethanol and final use of the product. For example, the manufacturer may sell 2-butoxyethanol to a formulator who may sell the cleaning product to a reseller who may then sell the product on to the final employer. Education and training are beneficial at all steps in the process to ensure that the proper information about the safe use of the cleaning products is passed on to the employees using the product.

As sole manufacturer of 2-butoxyethanol in Australia, ICI Australia has conducted Detergency Seminars for their customers and other interested parties, for example, union and industry association representatives. The seminars have included information about the health and environmental effects of the glycol ethers and 2-butoxyethanol in particular.

In some cases, formulators have comprehensive education programs in place for employees. For example, S C Johnson Pty Ltd has an active hazard communication program run by a special committee (separate from the OHS committee) which organises regular training in chemical safety matters, reviews MSDS and conducts safety audits. The program incorporates a written manual which has information about labelling and MSDS and instructions for the safe handling of chemicals on the plant.

Some formulators also provide for each of their products a technical bulletin which gives more detailed information than an MSDS about the technical aspects of the product, such as information about the uses, methods of application and any special features of the product.

The Australian Building Services Association (ABSA) has set up a number of training courses for contract cleaning managers and supervisors and the cleaners themselves. The structured training program for cleaners (see Appendix 5) can be used 'in-house', for example, by the qualified trainers of contract cleaning companies. ABSA also has audio visual safety training programs available for use, and conducts seminars and

workshops for members on a variety of topics including occupational health and safety and environmental issues.

In NSW, the relevant union, the LHMU - Miscellaneous Workers Division, has recently developed a system of competency-based training with industry and government representatives for workers in the contract cleaning industry.

At Worksafe Australia, an *Occupational Health and Safety Management Resource Kit for the Contract Cleaning Industry* has been prepared as part of the organisation's Best Practice program for industry (NOHSC 1996). The kit, compiled in consultation with industry, unions and government, is available for companies in the contract cleaning industry. The resource kit is suitable for use by formulators of cleaning products.

Under its Responsible Care program, the Plastics and Chemical Industry Association (PACIA) has established a Code of Practice for Product Stewardship, which commits members to addressing health and safety issues arising at any stage of the life cycle of the product. The program is supported by other members of the chemical industry such as the Australian Chemical Specialties Manufacturers Association (ACSMA). As a means towards fulfilling this commitment, suppliers need to make MSDS and other health and safety information freely available to persons involved in the handling of these products at any stage of the product's life cycle (for example, formulators, distributors and downstream customers).

14.4 Monitoring and regulatory controls

14.4.1 Exposure standard

The current occupational exposure standard for 2-butoxyethanol in Australia is 25 ppm TWA with a 'skin' notation and was adopted from the ACGIH. The ACGIH criteria documentation was issued in 1991. Other occupational exposure limits for 2-butoxyethanol are in Table 20 below.

The current exposure standard is based on the haemolytic effects observed in experimental animals. This assessment has concluded that in animal studies, the lowest NOAEL for haemolytic effects is 25 ppm, based on a Dodd et al (1983) 90-day rat inhalational study. This is the same study on which the current exposure standard is based.

No explicit numerical uncertainty factors appear to have been applied to the NOAEL which has been used as the basis of the current exposure standard. This can be justified as humans are less susceptible than rats to the heamolytic effects of 2-butoxyethanol. This conclusion is based a range of data, including type and severity of the effect, intra- and interspecies differences. The haemolytic effects are considered to be acute and transient. Data indicate that the effect is due to changes to the red blood cell membrane and not bone marrow toxicity. *In vitro* and *in vivo* studies have demonstrated that there are species differences in susceptibility to the effect, with humans less sensitive than rats. For example, in humans exposed to 195 ppm, osmotic fragility (a pre-haemolytic effect) was not found. In addition, *in vitro* studies indicate that human red blood cells are at least 10 times less sensitive than rat

red blood cells to haemolytic effects of BAA (the major metabolite of 2-butoxyethanol and primary haemolytic agent). Therefore, while no explicit factors have been included, there is an implicit uncertainty factor built into the NOAEL and the current exposure standard is considered adequate with respect to haemolytic effects.

Sweden has based their exposure limit primarily on other effects such as irritation and headaches. The Swedish documentation states that these effects have been reported in Swedish workplaces at the previous TLV of 20 ppm. These effects were reported in humans in controlled studies at exposure levels of 100 ppm and above. Workers in Australia (Appendix 4) have also reported these effects when using solutions containing < 10% 2-butoxyethanol, however the atmospheric levels are unknown. However, in controlled studies by Johanson (Johanson et al 1986; Johanson and Boman 1991), no adverse effects were reported when volunteers were exposed to 20 or 50 ppm for 2 hours.

NOHSC should review the occupational exposure standard for 2-butoxyethanol and consider what the basis of the standard should be and use this assessment to prepare updated Australian documentation.

It should be noted that air monitoring may not provide an accurate estimate of total exposure in situations where significant dermal exposure occurs.

Table 20 - Occupational Exposure Limits

Country	Exposure Limit
Belgium	25 ppm TWA (skin)
Denmark	25 ppm TWA (skin)
Finland	25 ppm TWA (skin)
France	25 ppm TWA (skin)
Germany (1990)	20 ppm TWA, 40 ppm STEL (skin), C
Italy	25 ppm TWA (skin)
Japan	50 ppm TWA (skin)
Netherlands	20 ppm TWA, 40 ppm STEL (skin)
New Zealand	25 ppm TWA (skin)
Norway	20 ppm TWA
Sweden	10 ppm TWA^{+}, 20 ppm STEL (skin)
United Kingdom (HSE, 1991)	25 ppm TWA (skin)
USA - ACGIH (1987)	25 ppm TWA (skin)
- NIOSH (1990)	5 ppm TWA*
- OSHA	50 ppm TWA (skin)

Note: *C = Pregnancy group C (no reason to fear risk of damage to the developing embryo when adhering to MAK or BAT values).*

\+ *Based primarily on 'subjective effects of irritation, headache and tiredness'.*

* *Based on NOAEL of 50 ppm (Tyl et al 1984) and uncertainty factor of 10 for intraspecies differences.*

14.4.2 Atmospheric monitoring

Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994 (c)), employers need to carry out an assessment of the workplace for all hazardous substances, with methodology for the assessment provided in the *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* (NOHSC 1994(f)). When the assessment indicates that the risk of inhalational exposure is significant, atmospheric monitoring should be conducted to measure 2-butoxyethanol concentrations in the workplace as a precursor to the introduction of proper control measures to reduce exposure. Monitoring should also be conducted at a later stage to ensure that the measures are effectively controlling atmospheric levels.

Analytical methods for the measurement of 2-butoxyethanol in air are detailed in Chapter 6, *Methods of Detection and Analysis*.

14.4.3 Health surveillance

From information obtained during the assessment, health surveillance is not routinely conducted for workers exposed to 2-butoxyethanol. From published reports in the literature, biological monitoring has been conducted in some work situations (outside Australia) in order to estimate the combined inhalational and dermal exposure to 2-butoxyethanol (see Table 5 in chapter 8, *Occupational Exposure*). Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994 (c)), 2-butoxyethanol is not on Schedule 3 (the list of hazardous substances for which health surveillance is required).

NOHSC characterise biological monitoring as a form of health surveillance and has established a number of points to consider in deciding whether health surveillance is required, viz.:

- Is the substance hazardous to health?
- Is there evidence that the substance is injuring the health of workers, or is there reason to suspect that this could be so, under the anticipated conditions of use?
- Is atmospheric monitoring, without health surveillance, sufficient to evaluate exposure to the substance?
- Are health surveillance techniques available for the substance?
- Would health surveillance be beneficial to those at risk?
- Are the health surveillance methods likely to be acceptable to those at risk?
- Are the health surveillance methods practically and ethically acceptable?

2-Butoxyethanol is a hazardous substance. While there is no evidence of haemolytic effects in workers during its use, there is evidence of acute effects including eye and respiratory irritation, headache and nausea in some work situations involving the use

of cleaning products. As dermal exposure may be significant, and 2-butoxyethanol is readily absorbed through the skin, atmospheric monitoring is not sufficient to evaluate total exposure. While biological monitoring methods are available to estimate total exposure, the benefits of health surveillance to those at risk are considered low. Considerations of whether health surveillance would be acceptable to those at risk, or whether it would be practically or ethically acceptable, are outside the scope of this assessment.

Although routine health surveillance is not recommended, the dermal exposure of workers in Australia is largely unknown. To estimate the health risk to workers, modelling was conducted in this assessment (see chapter 8, *Occupational Exposure*). To assist in the development of risk management strategies for the various work scenarios, a study of workers in the cleaning industry, including biological and atmospheric monitoring, should be conducted to more accurately estimate dermal exposure. The merits of biological monitoring for 2-butoxyethanol are discussed below.

Biological monitoring

Skin contact is one of the main routes of exposure to 2-butoxyethanol and toxicokinetic studies in humans and animals have shown that skin absorption is significant. *In vitro* studies have shown that the skin absorption rate may be higher from aqueous solution, and controlled studies in volunteers have indicated that 2-butoxyethanol vapours can also be absorbed via the skin (see section 9.2). For these reasons, atmospheric monitoring may not provide a realistic indication of total exposure when significant dermal exposure occurs.

Some biological monitoring of workers has been carried out overseas to estimate total exposure, with measurements centred around the determination of BAA in urine at the end of the working shift (see Table 5 in chapter 8, *Occupational Exposure*). In a comprehensive study (Vincent 1993), urinary BAA levels up to 371 mg/g creatinine were obtained for car cleaners using a window cleaner containing 21.2% 2-butoxyethanol (for 5.3 hours). (Based on experimental data, the exposure standard of 25 ppm is equivalent to approximately 250 mg BAA/g creatinine (NIOSH 1990)). The cleaners wore gloves, but short-sleeved shirts were worn. In common with the results of other studies, urinary BAA results in this study did not correlate well with atmospheric 2-butoxyethanol concentrations.

No country or organisation has set a biological exposure index (BEI) based on biological monitoring for 2-butoxyethanol. The ACGIH in the USA are in the process of setting a BEI for 2-butoxyethanol, and some regulatory authorities have recommended that a BEI be set for 2-butoxyethanol (NIOSH 1990). Biological monitoring has also been recommended in a number of scientific papers (Johanson et al 1986; Rettenmeier et al 1993; Sakai et al 1993; Vincent 1993) as a means of more accurately estimating total exposure of individuals to 2-butoxyethanol. The main reasons given for conducting biological monitoring of workers exposed to 2-butoxyethanol have included the following:

- dermal exposure is greater than inhalational exposure in many work situations;

- atmospheric monitoring results do not correlate well with biological monitoring results, so use of the former alone may not give an accurate measure of worker exposure;
- a suitable marker, BAA, is available; and
- biological monitoring more accurately reflects total uptake over a work shift, and takes factors such as workload into account (see subsection 9.2.3).

In biological monitoring conducted to assess total exposure to 2-butoxyethanol, BAA is a suitable marker for the following reasons:

- BAA is not normally found in the urine of humans, but it is found in appreciable quantities in the urine of persons exposed to 2-butoxyethanol;
- BAA has an elimination half-life in humans of three to six hours, so it provides a good indicator of exposure over a normal working shift;
- BAA is the primary haemolytic agent, so its concentration may more accurately reflect potential toxicity; and
- reliable analytical methods for the determination of BAA in urine are available (see section 6.3).

The main argument against using the determination of BAA in urine in biological monitoring for 2-butoxyethanol is the variation in results between individuals exposed to the same amount of 2-butoxyethanol. This is believed to be due to variations in dermal uptake, perhaps due to variations in skin thickness and permeability, and more significantly, to variation in excretion rates. In addition, the presence of conjugated BAA in humans raises the question as to whether the amount of BAA in urine is an accurate reflection of the full extent of BAA exposure (Rettenmeier et al 1993).

15. Public health assessment

15.1 Exposure

The public is unlikely to be exposed to 2-butoxyethanol during its importation, manufacture or formulation into cleaning products in Australia. The manufacturing process is enclosed and unused product is recycled into the process. Small amounts of 2-butoxyethanol may be lost in spills or maintenance. Cleaning products containing 2-butoxyethanol are produced by mixing the components at room temperature in open or covered containers, with minor losses to the atmosphere due to the low vapour pressure of the chemical. Small losses of 2-butoxyethanol may occur in aqueous rinses from mixing containers, which may be disposed into the sewer system.

The public may be exposed to 2-butoxyethanol in a large number of domestic, and some trade formulations, for example, floor strippers. Exposure is mainly by dermal contact, and also by inhalation of vapours.

15.2 Health effects

The health effects of 2-butoxyethanol are described in chapter 10, *Effects on Animals and In Vitro Test Systems* and chapter 11, *Human Health Effects*.

15.3 Health risk to the public

In light of the low concentration of 2-butoxyethanol in most domestic cleaning products containing the chemical and the intermittent use of such products by the public, and provided that normal precautions are taken to avoid skin, eye and inhalational contact, the public health risk posed by cleaning products containing 2-butoxyethanol is expected to be minimal.

16. Environmental assessment

16.1 Environmental exposure

16.1.1 Release

During the synthesis of 2-butoxyethanol at ICI's Matraville plant, release to air is low, due to enclosure of the process and the low volatility of the chemical. Release to water will occur when flushing spills to drain with copious amounts of water. Release to soil is unlikely as the plant is confined to paved areas. Non-purified material or mixed product is recycled back into the process, so there is virtually no disposal of waste product other than through spills or maintenance. Drums used to transport 2-butoxyethanol are usually recycled.

At formulation plants, mixing tanks are often covered and 2-butoxyethanol is usually added last to the mixture, so there is little opportunity for escape of 2-butoxyethanol vapours to atmosphere. In the filling process, 2-butoxyethanol apparently acts as a foam suppressant, further reducing the risk of escape of vapour and liquid.

At one formulation plant visited, any spills in the production area are contained and flushed to drain. Washings are neutralised and filtered before discharge to sewer, but any 2-butoxyethanol would pass straight through. To cater for any spills outside the production area (for example, during storage) spill control stations are set up at the site boundaries. Empty drums are cleaned and sent to drum reconditioners. 2-Butoxyethanol loss was estimated as being minimal.

The predominant practice among product formulators is the disposal of tank rinsings from the cleaning of blending tanks to sewer. For cleaning products, it is estimated that approximately 0.1% of 2-butoxyethanol is lost to the sewer. In the responses to the questionnaire sent to formulators, the vapour emissions from open blending tanks were reported as being low.

Disposal practices for waste 2-butoxyethanol mentioned in the various MSDS for cleaning products include incineration and burying, presumably in landfills.

When surfaces have been cleaned and washed down and any cleaning equipment rinsed off, the resulting wash water containing 2-butoxyethanol is likely to be disposed to sewer.

16.1.2 Fate

2-Butoxyethanol will enter the environment via effluent at formulation sites and via wash water from cleaning operations using the formulated products. The latter is the predominant pathway. Biodegradation studies indicate that 2-butoxyethanol will be readily degraded by micro-organisms present at sewage treatment plants.

Any 2-butoxyethanol that passes through sewage treatment plants and enter receiving waters is likely to remain in the water column until biodegraded by micro-organisms

present in the water. 2-Butoxyethanol half-lives in surface water range from 7 days to four weeks (Howard et al 1991).

Alcohols and ethers are generally resistant to hydrolysis and they do not absorb UV light in the environmentally significant range (>290 nm). Therefore, 2-butoxyethanol is not expected to undergo hydrolysis or direct photolysis in the environment (Howard et al 1993). The complete miscibility of 2-butoxyethanol in water suggests that volatilisation, adsorption and bioconcentration are not important fate processes (Howard et al 1993).

Due to its short atmospheric residence time and lack of direct photochemical activity, 2-butoxyethanol does not fall within the definition of a volatile organic compound (VOC) for the purposes of VOC emission estimates and the contribution of VOCs to photochemical smog.

Calculations using the MacKay level 1 environmental partitioning model indicate that 2-butoxyethanol will partition predominantly into water (84%) and to a lesser extent air (16%), and with less than 0.1% associated with sediment/soil. These results were obtained from the US EPA's ASTER database (US EPA Mid-continent Ecology Division (b)). It should be noted that the Mackay level 1 model is an equilibrium, steady state system, assuming no movement of the chemical between the various environmental compartments, for example, air, water, soil, sediment (Mackay and Paterson 1982).

Incineration of waste 2-butoxyethanol will produce oxides of carbon.

Disposal of waste 2-butoxyethanol to landfills may result in contamination of groundwater. A K_{oc} of 67 for 2-butoxyethanol indicates it will be highly mobile in soil, and it is unlikely to partition from the water column to organic matter contained in sediments and suspended solids (Howard et al 1993). 2-Butoxyethanol has been detected in aquifers underlying a municipal landfill and a hazardous waste site in the US (Howard et al 1993).

Biodegradation test results

The biodegradability of 2-butoxyethanol was evaluated (Microtech Labs, *pers. comm.* 1993) using a test method (ISO 7827) based on the OECD ready biodegradability tests (TG301A and 301E). The test was performed over a 7 day period and the level of organic carbon was measured as an indicator for biodegradation. The inoculum used was mixed activated sludge and secondary effluent, incubated at 20-25^{o}C. 2-Butoxyethanol achieved a biodegradation rate of 77.7% after 3 days and 100% biodegradation by the end of the study. The result indicates that 2-butoxyethanol is readily biodegradable.

An additional study (CEFIC to ICI(UK) *pers. comm.* 1993) was provided for the biodegradation potential of 2-butoxyethanol. The test methods used were the 20-day Biochemical Oxygen Demand (BOD_{20}) and the 28-day Closed Bottle Test (OECD TG 301D). The inoculums used in the BOD_{20} test and 28-day Closed Bottle Test were domestic sewage micro-organisms and a mixture of soil and Hach Polyseed sewage micro-organisms, respectively. The biodegradation rate at the end of the BOD_{20} and 28-day Closed Bottle tests were 75% and 88%, respectively. The results indicate that

2-butoxyethanol is likely to be biodegraded by micro-organisms in sewage treatment plants.

The ASTER ecotoxicity profile of 2-butoxyethanol calculated a BOD half-life from two to 16 days, confirming the ready biodegradability of 2-butoxyethanol. Test results provided by notifiers from additional biodegradation studies (reports not provided but literature references given) confirm the ready biodegradation of 2-butoxyethanol. The studies included ready biodegradability (OECD TG 301E), inherent biodegradability (OECD TG 302B), and 5-day BOD studies.

Bioaccumulation

No bioaccumulation studies were provided. Because 2-butoxyethanol is miscible in water, bioconcentration in aquatic systems is not expected to be an important fate process. Based upon the log K_{ow}, a bioconcentration factor of 0.40 was calculated, which indicates 2-butoxyethanol is unlikely to bioaccumulate in aquatic organisms (Howard et al 1993).

The ASTER ecotoxicity profile for 2-butoxyethanol has provided a calculated value for bioaccumulation in fish. The calculated bioconcentration factor of two indicates that 2-butoxyethanol is unlikely to accumulate in aquatic organisms.

16.1.3 Summary

2-Butoxyethanol will predominantly enter the environment from the disposal of wash water from the cleaning process and also via effluent at sites where it is formulated into cleaning products. 2-Butoxyethanol will be readily degraded by micro-organisms present at sewage treatment plants and in the receiving waters and is unlikely to bioaccumulate.

2-Butoxyethanol disposed to landfill may leach to groundwater due to its expected high mobility in soil and low adsorption potential.

16.2 Environmental effects

The following ecotoxicological study reports have been provided for 2-butoxyethanol.

Table 21 - Results of Ecotoxicological Studies Provided by Notifiers

Test	Species	Result	Reference
Acute toxicity	Fathead minnow	4d LC_{50} = 2137 mg/L	(Bartlett 1979)
Acute toxicity	*Daphnia magna*	2d LC_{50} = 835 mg/L	(Bartlett 1979)
Acute toxicity	Oyster (*Crassotera virginicas*)	4d LC_{50} = 89.4 mg/L	(US EPA 1984)
Acute toxicity	Sheepshead minnow	4d LC_{50} = 116 mg/L	(US EPA 1984)
Acute toxicity	White shrimp (*Panaeus setiferus)*	4d LC_{50} = 130 mg/L	(US EPA 1984)
Growth inhibition	Green algae (*Selenastrum capricornutum)*	7d EC_{50} > 1000 mg/L	(Dill and Minazzo 1988)

Growth inhibition	Bacteria from sewage	16h IC_{50} > 1000 mg/L	(Waggy 1989)

The above results indicate that 2-butoxyethanol is slightly toxic to oysters and practically non-toxic to fish, aquatic invertebrates, algae and sewage micro-organisms. The above studies were conducted according to US EPA toxicity test methods for aquatic organisms.

Test results from other aquatic toxicity studies (reports not provided but literature references given) indicated that 2-butoxyethanol has low toxicity to aquatic organisms. These included a 24h LC_{50} of 1650 mg/L for the goldfish and a 7d LC_{50} of 983 mg/L for the guppy (Verscheuren 1983).

Additional information was obtained from the US EPA's AQUIRE database, which is an aquatic toxicological database containing peer reviewed aquatic toxicity test results (US EPA Mid-continent Ecology Division (a)). A selection of the results is tabled below.

Table 22 - Aquatic Toxicity Results in AQUIRE Database

Test	Species	Result
Growth inhibition	Blue-green algae	$EC_{50} \geq 35$ mg/L
Acute toxicity	*Daphnia magna*	24h EC_{50} = 1815 mg/L
Acute toxicity	Inland silverside	4d LC_{50} = 1250 mg/L
Acute toxicity	Brine shrimp	24h LC_{50} = 1000 mg/L

The results indicate that 2-butoxyethanol is practically non-toxic to fish and aquatic invertebrates, and is slightly toxic to algae.

The ASTER ecotoxicity profile for 2-butoxyethanol has provided calculated QSAR values for the acute and chronic toxicity to fish and aquatic invertebrates, with the results tabled below.

Table 23 - QSAR Results Provided in ASTER Database

Test	Species	Result
Acute toxicity	*Daphnia magna*	2d LC_{50} = 478 mg/L
Acute toxicity	Bluegill sunfish	4d LC_{50} = 782 mg/L
Acute toxicity	Fathead minnow	4dLC_{50} = 1078 mg/L
Acute toxicity	Channel catfish	4d LC_{50} = 463 mg/L
Acute toxicity	Rainbow trout	4d LC_{50} = 532 mg/L
Chronic toxicity	Fathead minnow	32d MATC = 135 mg/L

The above results indicate that 2-butoxyethanol is practically non-toxic to fish and aquatic invertebrates.

16.2.1 Summary

From the studies and test results provided by notifiers and the information gained from the AQUIRE and ASTER databases, 2-butoxyethanol can be classified as being practically non-toxic to fish, aquatic invertebrates and sewage micro-organisms, slightly to practically non-toxic to algae and slightly toxic to oysters.

16.3 Environmental risk

2-Butoxyethanol is unlikely to present a hazard when it enters the environment via effluent at sites where it is formulated into cleaning products and via the disposal of wash water from cleaning operations. 2-Butoxyethanol will be biodegraded by micro-organisms present at sewage treatment plants. Any 2-butoxyethanol that passes through the sewage treatment plant and enters the receiving waters will be further degraded by micro-organisms. 2-Butoxyethanol is of low toxicity to aquatic organisms and is likely to exist at concentrations below that which would be hazardous to the environment.

Approximately 1000 tonnes of 2-butoxyethanol are formulated into cleaning products per annum. Assuming 300 tonnes per year may be used in a metropolitan area, for example, Melbourne, a worst-case situation may occur where 1000 kg enters the sewer per day as a result of the formulation process and from the use of cleaning products. The resultant concentration of 2-butoxyethanol at a sewage treatment plant (500 ML flow per day) would be approximately 2 ppm. Further dilution in the order of 1:5 to 1:25 is likely to occur in the receiving waters. Therefore the expected environmental concentration of 2-butoxyethanol is likely to be in the order of sub-ppm.

These calculations are based on a worst-case scenario and assume no degradation of 2-butoxyethanol by micro-organisms at the sewage treatment plant or in the receiving waters. The calculations give an expected environmental concentration several orders of magnitude below toxic levels for aquatic organisms. Therefore, the risk of 2-butoxyethanol to the environment is expected to be low.

17. Recommendations

The assessment focussed on the use of 2-butoxyethanol in cleaning products. However, many of the recommendations are applicable to the other uses of 2-butoxyethanol.

17.1 Classification

17.1.1 NOHSC hazard classification

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1994(a)) and based on an assessment of health hazards, the recommended classification for 2-butoxyethanol is:

- R20/21/22 Harmful by inhalation, in contact with skin, and if swallowed
- R36 Irritating to eyes
- R37 Irritating to respiratory system.

It is therefore recommended to NOHSC that the risk phrase 'R36 Irritating to eyes' be added to the classification of 2-butoxyethanol on the *List of Designated Hazardous Substances* (NOHSC 1994(b)).

In determining whether a mixture containing 2-butoxyethanol is hazardous, the following concentration cut-offs apply: 12.5% for R20/21/22 and 20% for R36 and R37.

It is recommended that the differences in concentration cut-offs for 2-butoxyethanol be brought to the attention of the National Drugs and Poisons Scheduling Committee (NDPSC) and NOHSC and, notwithstanding policy issues, that consideration be given to harmonising on a cut-off of 10%.

17.1.2 SUSDP listing

At present, 2-butoxyethanol is listed on the SUSDP under 'ethylene glycol monoalkyl ethers', and is often listed on labels as such. However, the health effects of the members of this class of chemicals vary significantly, so it is recommended that the NDPSC consider a separate listing for 2-butoxyethanol.

It is recommended to NDPSC that, during consideration of a separate listing, they reconsider the first aid instructions for 2-butoxyethanol, in particular the standard statement to be used in case of swallowing (see 17.3.2).

17.1.3 Dangerous goods classification

This report confirms that 2-butoxyethanol should be classified as 'harmful' by all three routes of exposure under the EC Directive (on which the Australian Approved Criteria are based). The criteria for acute inhalational toxicity are the same under the

EC Directive and the UN Recommendations on the Transport of Dangerous Goods (and the ADG Code). Therefore, the recent decision by the UN Committee of Experts on the Transport of Dangerous Goods to delist 2-butoxyethanol raises concerns regarding possible differences in the application of the criteria and resulting inconsistencies between EU and UN classifications of 2-butoxyethanol.

17.2 Control measures

2-Butoxyethanol is a hazardous substance which is acutely toxic, readily absorbed through the skin and is an irritant to the eyes and respiratory system. In accordance with the *National Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC 1994(c)) exposure to hazardous substances should be prevented, or where that is not practicable, controlled so as to minimise risks to health. Control measures should be implemented in accordance with the following hierarchy of controls.

In devising effective control measures for cleaning products containing 2-butoxyethanol, suppliers and end-users should also consider the hazards of other ingredients in each product, for example, phosphoric acid in rust removers and sodium or potassium hydroxide in oven cleaners.

In relation to 2-butoxyethanol, particular care needs to be given to control measures to minimise inhalational and dermal exposure. It should be noted that 2-butoxyethanol can be readily absorbed through the skin and absorption can occur in the absence of irritation.

17.2.1 Elimination

To minimise risks to health, elimination should be the first control option considered. Elimination is the removal of all chemicals from the cleaning process, such as by employing a physical cleaning process or process redesign.

17.2.2 Substitution

Where elimination of 2-butoxyethanol from cleaning processes is not practicable, substitution with another chemical or method of application should be considered. Any substitution of 2-butoxyethanol should be with safer alternatives which have been thoroughly tested and have demonstrated a lower toxicity, irritancy and potential for skin absorption in humans.

With a view towards minimising exposure, formulators should consider reducing the 2-butoxyethanol content in cleaning products. Similarly, it is recommended that methods of application be reviewed by suppliers and end-users, for example, substituting spray use with use as a liquid stream and application and dilution of cleaning products without heat.

17.2.3 Engineering controls

Formulation

It is appropriate that formulators take into account the health and safety hazards of all ingredients in the formulation to arrive at a safe process that will minimise exposure to 2-butoxyethanol.

Accordingly, it is recommended that the mixing and transfer process be enclosed and that 2-butoxyethanol be added to the mixing vessel in a safe manner, for example, as one of the last ingredients. The mixing and storage tanks should be covered and exhaust fans installed above them if they are not completely sealed. The mixing area should be bunded so that any spills can be confined.

The packing line at the point of filling should be enclosed as much as possible, with local exhaust ventilation recommended if complete enclosure is not achievable.

Good dilution ventilation in accordance with Australian standards is essential in all production areas, with the ventilation rate capable of being substantially increased in case of emergencies such as spillage. Total loss ventilation is recommended.

Cleaning

In some workplaces, for example, mechanical workshops, local exhaust ventilation can be used, but in most work situations, for example, in the cleaning of schools and offices, this is not practical. In these cases, dilution ventilation should be used as much as possible, for example, air conditioning, portable fans, open windows and doors. Good ventilation is essential during the dilution and mixing of solutions.

17.2.4 Safe work practices

Cleaning products should be formulated and applied in a manner which minimises exposure. Recommended safe working practices include:

- avoidance of splashing and aerosol generation;
- avoidance of heat where possible;
- keeping of lids on tanks and containers;
- prompt clean up of spills;
- storage of products and cleaning solutions in cool, well-ventilated areas;
- use of appropriate personal protective equipment;
- minimisation of spray use during cleaning operations;
- if spray is used, spray away from the breathing zone;
- proper labelling of containers, including those used for diluted product during application;
- prompt rinsing (with cold water) and cleanup of cloths and other equipment used in cleaning, for example, mops, buckets and brushes, followed by safe disposal; and
- use of as little cleaning solution as possible during end-use.

17.2.5 Personal protective equipment

The following personal protective equipment is recommended where occupational exposure to 2- butoxyethanol may occur:

- butyl or nitrile rubber gloves;
- protective clothing which includes protection of the arms, legs and feet; and
- eye protection when aerosols or vapours may be generated, for example, during handling of large quantities, during dilution, when heat is used, or when splashing may occur; eye protection may also be required when the product is applied as a spray.

All personal protective equipment should be in accordance with the relevant Australian standards.

17.3 Hazard communication

17.3.1 MSDS

It is recommended that suppliers amend their MSDS where necessary in order to rectify the deficiencies identified in this assessment.

Deficiencies in MSDS noted in the assessment indicate that attention needs to be paid to the following:

- inclusion of a statement of hazardous nature where appropriate;
- under 'Health Effects', state that 2-butoxyethanol is readily absorbed through the skin;
- under 'Exposure Standard', state the complete Australian exposure standard;
- under 'Engineering Controls', sufficient and appropriate guidance should be provided for the use of cleaning products in spray form, for example, 'Avoid inhalation of vapours or spray', 'Use local exhaust ventilation', or 'Ensure good ventilation, especially during spray use';
- under 'Personal Protection', specify the use of butyl or nitrile rubber gloves; and
- under 'Spills/Disposal', specify the use of the proper gloves, safety eyewear, and protective clothing.

17.3.2 Labels

It is recommended that suppliers amend their labels where necessary in order to rectify the deficiencies identified in this assessment.

The assessment of labels showed that a number of products available to consumers were not labelled with the safety directions required by the SUSDP. Products available to the public which contain more than 10% 2-butoxyethanol must include the following first aid instructions and safety directions on the product label, in accordance with the following labelling standards recommended by the SUSDP for the ethylene glycol monoalkyl ethers (and their acetates).

Safety directions:

- Avoid contact with eyes (SD1).
- Avoid contact with skin (SD4).
- Avoid breathing vapour (SD8).

First aid instructions:

- If poisoning occurs, contact a doctor or Poisons Information Centre.
- If skin contact occurs, remove contaminated clothing and wash skin thoroughly.
- If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

In accordance with SUSDP, the current first aid instruction for ingestion of preparations containing more than 10% 2-butoxyethanol (listed under ethylene glycol monoalkyl ethers) is 'If swallowed, and if more than 15 minutes from a hospital, induce vomiting, preferably using Ipecac Syrup APF.' As 2- butoxyethanol is a respiratory irritant and a large number of cleaning products which contain 2-butoxyethanol also contain substances which may be corrosive, it is recommended that consideration of the specific formulation be made when developing first aid advice. For example, when products are formulated with a corrosive substance, the induction of vomiting would be contra-indicated and the following instruction would be warranted: 'If swallowed, do NOT induce vomiting. Give water to drink.'

The assessment of labels also showed that the labels of cleaning products which are likely to be used in the workplace, and contain 12.5% or more of 2-butoxyethanol, had inadequate labelling, lacking the designated risk phrases or equivalent statements required by the NOHSC National Code of Practice for the Labelling of Workplace Substances (NOHSC 1994(e)). It is therefore recommended that, where necessary, suppliers of products for industrial use amend their labels to conform to the Code. It is also recommended that the following safety phrases be included (if not already covered by equivalent SUSDP safety directions):

- S24/25 Avoid contact with skin and eyes
- S36/37/39 Wear suitable protective clothing, gloves and eye protection.

For all products which may be used in spray form in the workplace, it is recommended that the following safety phrase be included on the label:

- S23 Do not breathe vapour or spray.

17.3.3 Training and education

In accordance with the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994(c)), it is recommended that workers potentially exposed to 2-butoxyethanol be educated about its hazards and be trained in the safe handling of 2-butoxyethanol and cleaning products containing the chemical. Accordingly, it is recommended that suppliers, formulators and employers adequately educate and train their customers and employees. Specifically, matters which need to be addressed include:

- the health effects of 2-butoxyethanol;
- the skin absorption potential of 2-butoxyethanol, including the fact that it can be absorbed without skin irritation, and that absorption will be greater when the skin is cracked or damaged;
- explanation of MSDS and labels of cleaning products used;
- instruction in the proper handling and use of cleaning solutions containing 2-butoxyethanol, including information about the additional risks posed by spray use and the use of heat; and
- the specific protective equipment to be worn.

The training and education of workers who use cleaning products containing 2-butoxyethanol should be in accordance with the elements listed in the *National Code of Practice for the Control of Workplace Substances* (NOHSC 1994(c)), and should include specific information about the hazards of 2-butoxyethanol and the specific precautions required for safe handling.

As many cleaners employed are from a non-English speaking background, it is recommended that practical and audiovisual methods be used as much as possible, and that some written material about the hazards of 2-butoxyethanol and precautions for the safe use of cleaning products containing the chemical be available in languages other than English, for example, a single page facts sheet.

17.4 Exposure standard

It is recommended that NOHSC use this assessment report to prepare updated documentation for the occupational exposure standard. It is also recommended that NOHSC consider whether the basis of the exposure standard should be haemolytic effects or other effects such as irritation, nausea and headache, as overseas regulatory agencies have adopted a lower standard based on these effects.

17.5 Biological monitoring and biological exposure index

It is recommended that NOHSC develop guidelines for biological monitoring (including analytical method, time of sampling, type of specimen, etc.). These guidelines would assist in the further work recommended to investigate skin absorption (see 17.7.2) and provide assistance to medical practitioners investigating possible exposures to 2-butoxyethanol.

In developing guidelines for biological monitoring and following the further study to investigate the extent of skin absorption, NOHSC should consider whether it is appropriate to establish a Biological Exposure Index (BEI).

17.6 Disposal

It is recommended that waste 2-butoxyethanol not be disposed of to landfill because of its high mobility, low abiotic degradation and its demonstrated ability to leach into groundwater from landfills in the USA. Preferred disposal options are incineration, recycling or removal by a licensed reclaimer.

17.7 Health hazards

17.7.1 Case reports

It is recommended that instances of adverse health effects after exposure to 2-butoxyethanol be fully documented and investigated by the employer and that the cases be reported to the Director, Chemicals Notification and Assessment at Worksafe Australia.

17.7.2 Further testing

A number of gaps were identified in the knowledge base regarding the health effects of 2-butoxyethanol, including:

- the mechanism of action of BAA on the red blood cell in various species, in particular, comparative data on the rat (sensitive species), guinea pig (insensitive species), and human (species of concern) to enable better extrapolation from animals to humans;
- clarification of the skin absorption rate of 2-butoxyethanol from various strengths of aqueous solution and comparison with the rate for undiluted 2-butoxyethanol; and
- the extent of dermal exposure for the various work scenarios.

Skin absorption is a significant route of exposure and there is a degree of uncertainty in the estimates of dermal exposure in this assessment. It is therefore recommended that a study be conducted, including biological and atmospheric monitoring, to more thoroughly understand the extent of skin absorption of 2-butoxyethanol for workers in the cleaning industry.

It is noted that a 2-year inhalational study in rats and mice is currently being conducted under the NTP, and an epidemiological study in workers exposed to glycol ethers, including 2-butoxyethanol, is under way in France. These studies will be reviewed when available as a secondary notification.

18. Secondary notification

Under section 65 of the Act, the secondary notification of a chemical may be required if there has been a change in circumstances which warrants a reassessment of any of the hazards of the chemical.

In the case of 2-butoxyethanol, a secondary notification may be required if significant new information about its health and/or environmental effects becomes available, for example, the results of a 2-year inhalational study in rats and mice currently being conducted under the NTP, and the results of an epidemiological study in workers exposed to glycol ethers, including 2-butoxyethanol, in France.

APPENDIX 1

CLEANING PRODUCTS CONTAINING 2-BUTOXYETHANOL

The list of cleaning products includes the main use of the product and the concentration of 2-butoxyethanol in the formulation. The list also denotes whether an MSDS and label was provided for the assessment of 2-butoxyethanol in cleaning products.

The list was compiled from responses to a questionnaire sent to formulators in late 1994. It is not intended to be a comprehensive listing. Formulations may have changed since the preparation of this list.

Appendix 1 - Cleaning products containing 2-butoxyethanol

Product	MSDS	Label	% 2-BE	Formulator	Use
2-534 Acidic Train Wash Detergent	Y	Y	<10%	Applied Chemicals Pty Ltd	Removal of brake dust on railway rolling stock and equipment
3-123 Multi Purpose Detergent	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
3-273 General Purpose Pine Detergent	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
3-275 General Purpose Cleaner/Deodorant	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
3M Brand 001 Glass Cleaner	Y	Y	5-10%	3M Australia Pty Ltd	Glass/window cleaner ; Laminate cleaner
3M Brand Glass and Laminate Cleaner	Y	Y	10-15%	3M Australia Pty Ltd	Glass/window cleaner ; Laminate cleaner
3M Brand Glass and Laminate Cleaner	Y	Y	5-10%	3M Australia Pty Ltd	Glass/window cleaner ; Laminate cleaner
3M Topline Brand Floor Conditioner	Y	Y	10-15%	3M Australia Pty Ltd	Floor stripper
4-415 Hot Tank Emulsion Degreaser	Y	Y	<10%	Applied Chemicals Pty Ltd	Degreaser
4-492 General Purpose Detergent	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
4-500 General Purpose Solvent Degreaser	Y	Y	<10%	Applied Chemicals Pty Ltd	Automotive degreaser
4-852 Alkaline Detergent Degreaser	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
4-855 Multi Purpose Spray Cleaner	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
8-240 Dewatering/Corrosion Preventive	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner/rust preventative
8-370 Concentrated Degreasing Solvent	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
8-480 Specialty Solvent Cleaner	Y	Y	93%	Applied Chemicals Pty Ltd	Ink removal
A.S.L. Cleaner	Y	Y	5%	Demack Enterprises	Surface cleaner - general purpose
Acidiquat-NF cleaner/sanitiser	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner/sanitiser in food industry
Action Plus	Y	Y	<10%	Newland Products Pty Ltd	Laundry detergent
Activ D.O.T	Y	Y	<10%	Peerless Emulsion Products Pty Ltd	Surface cleaner - heavy duty
AD 25-D	Y	N	<10%	Ardelve P/L	Surface cleaner - heavy duty
AD 25-E	Y	N	<10%	Ardelve P/L	Surface cleaner - heavy duty
Agri Chem Sooty Mould Cleaner	Y	Y	<10%	Castle Chemicals Pty Ltd	Removal of sooty mould from citrus fruit
Aim U.V. Wash	Y	Y	<50%	Recochem Inc	U.V ink removal from rollers and presses
Al-U-Clean	Y	Y	<10%	Chemsolve	Aluminium and stainless steel cleaner
Alkaclean	Y	Y	12%	Micelle Chemical Products Pty Ltd	Surface cleaner - general purpose

Product	MSDS	Label	% 2-BE	Formulator	Use
Alkafoam	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - recommended for food processing areas
All Clear	Y	Y	<10%	Chemsolve	Glass/window cleaner
All Purpose Cleaner	Y	Y	10%	Jamac-Safe and Clean Pty Ltd	Surface cleaner - heavy duty
All Purpose Cleaner	Y	Y	<5%	IDL Chemicals Pty Ltd	Surface cleaner - general purpose
All Purpose Stripping Emulsion	Y	Y	20.6%	Peerless Emulsion Products Pty Ltd	Floor stripper
All Surface Cleaner	Y	Y	12%	Micelle Chemical Products Pty Ltd	Surface cleaner - general purpose
Aluwash	Y	Y	<10%	Novamax Technologies (A'Asia) Pty Ltd	Acid etch cleaner for aluminium surfaces
Amdet	Y	N	11.2%	Bunzl Ltd (reseller - products manufactured by JC Allen)	Floor stripper
Ammonia Free Stripper	Y	N	30.5%	Bunzl Ltd (reseller - products manufactured by JC Allen)	Floor stripper
Amsolve	Y	Y	<10%	Agar Chemicals	Carpet stain remover
Anglomoil Degreaser	N	Y	0.5%	Anglo Design Pty Ltd	Surface cleaner - heavy duty
Apple Clean	Y	Y	<10%	Castle Chemicals Pty Ltd	Detergent for removal of fats and greasy soils from apples
Aquafoam	Y	Y	<10%	Ecolab Pty Ltd	Surface cleaner - general purpose
Aquasolve	Y	Y	1-10%	Challenge Chemicals Aust.	Cleaning of metal parts (esp. automotive components) in soak tanks
Assault	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Floor stripper
Automatic Carpet Shampoo	Y	Y	Not stated	Peerless Emulsion Products Pty Ltd	Carpet cleaner
Autowash	Y	Y	<5%	Cleveland Chemical Co. Pty Ltd	Vehicle surface cleaner
Away	Y	Y	<10%	Alliance Technology Pty Ltd	Surface cleaner - general purpose, for use in food processing areas
Betz 407C	Y	N	<10%	Betz Laboratories Pty Ltd	Cooling water cleaner
Blast Off	Y	Y	<10%	Shamrock Chemicals Pty Ltd	Surface cleaner - heavy duty
Blast Off	Y	Y	1-10%	Lustral	Removal of wax from new vehicles
Blue Lazer	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Surface cleaner/disinfectant - washrooms
Break Up	Y	Y	<10%	S.C.Johnson	Surface cleaner - heavy duty
Breakthru	Y	Y	<10%	Castle Chemicals Pty Ltd	Surface cleaner - heavy duty

Product	MSDS	Label	% 2-BE	Formulator	Use
Brill	Y	Y	<7%	BettaChem Chemical Manufacturers	Glass/window cleaner
Brilliant	Y	Y	<10%	Chemsolve	Laundry detergent
Bushland Industrial Multipurpose Cleaner	Y	N	<10%	Campbell Brothers Limited	Surface cleaner
Butron	Y	Y	10-<30%	Ecolab Pty Ltd	Laundry detergent
Carpet Care	Y	Y	Not stated	Alliance Technology Pty Ltd	Carpet cleaner ; Upholstery cleaner
Carpet Prespray	N	Y	Not stated	Demack Enterprises	Carpet cleaner
CC Extractor	Y	Y	1-11%	Challenge Chemicals Aust.	Carpet cleaner
CC Prespray	Y	Y	1-10%	Challenge Chemicals Aust.	Carpet cleaner
CC Solspray	Y	Y	1-10%	Challenge Chemicals Aust.	Carpet cleaner
Cerfa Kleen CST	Y	N	<10%	Houghton Australia Pty Ltd	Surface cleaner
Champ	Y	Y	<10%	Newland Products Pty Ltd	Oven cleaner
Charger	Y	Y	1-10%	Challenge Chemicals Aust.	Laundry detergent
Chemkleen Plus	Y	Y	1.5%	Demack Enterprises	Surface cleaner - general purpose
Clean Easy	Y	Y	"low"	Dari Cleaning Products	Surface cleaner - heavy duty (for floors)
Cleans All	Y	Y	1-10%	Cyndan Chemicals	Surface cleaner - general purpose
Cleanscene	Y	Y	<1%	Cleveland Chemical Co. Pty Ltd	Glass/window cleaner
Clear Vision	Y	Y	Not stated	Young's Motor Products Pty Ltd	Glass/window cleaner ; Windscreen cleaner additive
Clearclean Plus	Y	Y	<10%	S.C.Johnson	Surface cleaner - general purpose
Clearstrip MK II	Y	Y	<10%	S.C.Johnson	Floor stripper
Clearview	Y	Y	<10%	Cleveland Chemical Co. Pty Ltd	Glass/window cleaner
Clockwork	Y	Y	1-10%	Lustral	Surface cleaner - heavy duty ; Oven cleaner
Colorfast	Y	N	10-30%	Cleancare of Australia	Carpet cleaner ; Upholstery cleaner
Commando	Y	Y	<10%	Castle Chemicals Pty Ltd	Carpet cleaner
Complete	Y	Y	<2%	Cleveland Chemical Co. Pty Ltd	Surface cleaner and disinfectant for bathrooms
Continuum	Y	Y	<10%	IDL Chemicals Pty Ltd	Laundry detergent
Corexit 6792ES	Y	Y	<10%	Nalco/Exxon Energy Chemicals Australia Pty Ltd	Corrosion inhibitor
Corexit CL 8561	Y	Y	<10%	Nalco/Exxon Energy Chemicals Australia Pty Ltd	Surface cleaner - general purpose

Product	MSDS	Label	% 2-BE	Formulator	Use
Countdown	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - general purpose
Countdown Blue	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - general purpose
Cross Link Strip	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Floor stripper
Crystal Clear	Y	Y	<10%	Amway of Australia Pty Ltd	Window/glass cleaner
Crystal Clear Chemkleen	Y	Y	Not stated	Crystal Clear (reseller)	Surface cleaner - general purpose ; Fabric cleaner
Crystal Clear Degreaser	Y	Y	Not stated	Crystal Clear (reseller)	Surface cleaner - general purpose
Crystal Clear Stripper	Y	Y	Not stated	Crystal Clear (reseller)	Floor stripper
Crystal Clear Window Cleaner	Y	Y	Not stated	Crystal Clear (reseller)	Glass/window cleaner
CT 13	Y	Y	7%	Castle Chemicals Pty Ltd	Removal of travel wax from new vehicles
D-Rust	Y	Y	<10%	Chemsolve	Rust remover ; Masonry cleaner
Deckhand	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - recommended for boats
Degreaser	Y	Y	Not stated	Demack Enterprises	Surface cleaner - general purpose
Degreaser	N	N	Not stated	Anglo Design Pty Ltd	Surface cleaner - general purpose
Degreaser Detail	Y	Y	<5%	Cleveland Chemical Co. Pty Ltd	Surface cleaner - general purpose ; Engine cleaner
Degreaser STG	Y	Y	<5%	Cleveland Chemical Co. Pty Ltd	Surface cleaner - general purpose ; Engine cleaner
Degreaser, (Hot Plate and Oven Cleaner)	Y	Y	5%	Maxpro Detergents Pty Ltd	Oven cleaner
Degreaser-O3	Y	Y	<5%	Cleveland Chemical Co. Pty Ltd	Surface cleaner - general purpose ; Engine cleaner
Delo	Y	Y	low	Dari Cleaning Products	Oven cleaner
Delvolin LLC	Y	Y	<1.5%	Tulloch & Kapeco Pty Ltd	Laundry detergent
Dewaxer/solvent cleaner	Y	Y	<2%	Micelle Chemical Products Pty Ltd	Surface cleaner / Removal of travel wax from new vehicles
Diverfos F69	Y	Y	<1%	Novamax Technologies (A'Asia) Pty Ltd	Combined cleaner/phosphate powder
Diverfos F69S	Y	Y	<1%	Novamax Technologies (A'Asia) Pty Ltd	Combined cleaner/phosphate powder
Dry Foam	Y	Y	<10%	Castle Chemicals Pty Ltd	Carpet cleaner
Dry Foam	Y	Y	1-10%	Lustral	Carpet cleaner
Dry'N'Wet Spotter	Y	N	<10%	Cleancare of Australia	Carpet cleaner ; Upholstery cleaner
Duroclean 16B	N	Y	Not stated	Novamax Technologies (A'Asia) Pty Ltd	Immersion cleaner for aluminium

Product	MSDS	Label	% 2-BE	Formulator	Use
Duroclean 19A	Y	Y	<5%	Novamax Technologies (A'Asia) Pty Ltd	Spray or immersion cleaner for aluminium
Duroclean 40	Y	Y	<5%	Novamax Technologies (A'Asia) Pty Ltd	Spray or immersion cleaner for aluminium
Easy Solve	Y	Y	20%	Elite Chemicals Pty Ltd	Laundry detergent
Easy-Up	Y	Y	12%	Castle Chemicals Pty Ltd	Floor stripper
Easyclean	Y	Y	<10%	Challenge Chemicals Aust.	Surface cleaner - heavy duty
Eazykleen	Y	Y	Not stated	Dynamic Laboratories	Surface cleaner - heavy duty
ECTA	Y	Y	<10%	Chemsolve	Cleaning of exhaust scrubber tanks of locomotives and personnel carriers used in underground mining operations.
Energen	Y	Y	<10%	Gibson Chemicals Limited	Floor stripper
Energizer	Y	N	10-30%	Cleancare of Australia	Carpet cleaner
Extra Carpet Pre-Spray	Y	Y	"minor %"	Agar Chemicals	Carpet cleaner
Extract	Y	Y	<10%	Castle Chemicals Pty Ltd	Carpet cleaner ; Upholstery cleaner
Extractomax	Y	Y	5%	North Queensland Chemicals and Paints	Carpet cleaner
Farmland Window Cleaner	Y	Y	<10%	Pax Australia Pty Ltd	Glass/window cleaner
Fibretone Carpet Shampoo	Y	Y	3.8%	Peerless Emulsion Products Pty Ltd	Carpet cleaner
First Step	Y	Y	Not stated	The Major Chemical Co. Pty Ltd	Carpet cleaner
Fleet	Y	Y	<10%	Gibson Chemicals Limited	Surface cleaner - general purpose
Flexiclean	Y	Y	<10%	Kempo Manufacturing Company Pty Ltd	Surface cleaner - heavy duty
Floorstar TFR II	Y	Y	18-21%	Peerless Emulsion Products Pty Ltd	Floor stripper
Floorstrip	Y	Y	10-30%	Challenge Chemicals Aust.	Floor stripper
Florstrip	Y	Y	10-60%	Agar Chemicals	Floor stripper
Formula 208B	Y	Y	<5%	Gibson Chemicals Limited	Surface cleaner - general purpose
Formula 217B	Y	Y	1-10%	Gibson Chemicals Limited	Surface cleaner - general purpose
Formula 245	Y	Y	<10%	Newland Products Pty Ltd	Surface cleaner - general purpose
Formula 650S	Y	Y	Not stated	Gibson Chemicals Limited	Electrical equipment and metal solvent cleaner
Formula 951B	Y	Y	<10%	Gibson Chemicals Limited	Surface cleaner for use on aluminium and stainless steel

Product	MSDS	Label	% 2-BE	Formulator	Use
Formula 955B	Y	Y	Not stated	Gibson Chemicals Limited	Aircraft exterior cleaner
Freshline Floor Cleaner and Deodorant	N	Y	Not stated	Nature's Land Products	Floor cleaner
Freshline Window and Mirror Cleaner	N	Y	Not stated	Nature's Land Products	Glass/window cleaner
Fulgeo 213 Heavy Duty	Y	Y	<10%	Industrial Cleansers Pty Ltd	Surface cleaner - heavy duty
Fulgeo Decarboniser	Y	Y	<10%	Industrial Cleansers Pty Ltd	Decarboniser
Fulgeo Graffiti Remover	Y	Y	10-60%	Industrial Cleansers Pty Ltd	Surface cleaner - graffiti remover
Fulgeo K.B.4	Y	Y	<10%	Industrial Cleansers Pty Ltd	Vehicle surface cleaner
Fulgeo Meatworks Multi-Cleanse	Y	Y	<10%	Industrial Cleansers Pty Ltd	Surface cleaner - abbatoir meat hooks, floors, walls, plant, vehicles
Fulgeo Sanitiser	Y	Y	<10%	Industrial Cleansers Pty Ltd	Surface cleaner - general purpose
Fulgeo Unique	Y	Y	<10%	Industrial Cleansers Pty Ltd	Surface cleaner - heavy duty ; Floor stripper
Fulgeo Window Cleaner	Y	Y	<10%	Industrial Cleansers Pty Ltd	Glass/window cleaner
Gemini	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - recommended for meat and food processing establishments
General Purpose Cleaner	Y	Y	16%	Micelle Chemical Products Pty Ltd	Surface cleaner - general purpose
Glance Glass Cleaner	Y	Y	30%	S.C.Johnson	Glass/window cleaner
Glass & Chrome Cleaner	Y	N	5-10%	Castrol Australia Pty Ltd	Glass/window cleaner
Glass Act (3-180)	Y	Y	<10%	Applied Chemicals Pty Ltd	Glass/window cleaner
Glass and Laminate Cleaner (Trigger Pack)	Y	Y	5-10%	3M Australia Pty Ltd	Glass/window cleaner ; Laminate cleaner
Glass Cleaner	Y	Y	Not stated	Young's Motor Products Pty Ltd	Glass/window cleaner
Glaze	Y	Y	1-10%	Challenge Chemicals Aust.	Glass/window cleaner
Greasaway	Y	Y	Not stated	Cleveland Chemical Co. Pty Ltd	Surface cleaner ; Machine parts degreaser
Grease Lightning	Y	Y	1-10%	Lustral	Surface cleaner - general purpose
Greasoff	Y	Y	5-10%	North Queensland Chemicals and Paints	Surface cleaner - heavy duty
Greasol	Y	Y	Not stated	Alliance Technology Pty Ltd	Surface cleaner - heavy duty, for removal of animal or vegetable fats.
Green Lazer	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Surface cleaner/disinfectant - general purpose
Greencare Multipurpose Spray and Window Cleaner	Y	Y	<10% w/w	Harcros Chemicals Limited	Window cleaner / Surface cleaner - general purpose

Product	MSDS	Label	% 2-BE	Formulator	Use
Greencare Prewash Stain Remover	Y	Y	10-30%	Harcros Chemicals Limited	Prewash stain remover
Grenade	Y	Y	10-30%	True Blue Chemicals Pty Ltd	Floor stripper
Grill, BBQ & Hot Plate Cleaner	Y	Y	<10%	Chemwell Products Pty Ltd	Oven cleaner
GSB Fast U V Wash	Y	N	10-60%	GSB Chemicals	Ink and resin removal from silk screens
H.D.C	Y	Y	<10%	Newland Products Pty Ltd	Surface cleaner - heavy duty
Hammer	Y	Y	15.4%	The Major Chemical Co. Pty Ltd	Floor stripper
Hand Clean	Y	Y	Not stated	Young's Motor Products Pty Ltd	Hand cleaner
HD Cleaner	Y	Y	<10%	Challenge Chemicals Aust.	Surface cleaner - heavy duty
Heavy Duty Cleaner No.4	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Surface cleaner - heavy duty
Heavy Duty Soil Lifter	Y	N	10-30%	Cleancare of Australia	Carpet cleaner ; Upholstery cleaner
Hi Shine (3-182)	Y	Y	<10%	Applied Chemicals Pty Ltd	Glass/window cleaner
Hook Guard	Y	Y	<10%	Ecolab Pty Ltd	Temporary rust preventative and lubricant for meat hooks
Hot Shot	Y	Y	<10%	Castle Chemicals Pty Ltd	Oven cleaner
Hulk	Y	Y	1-10%	Lustral	Surface cleaner - general purpose
Hydrakleen	Y	Y	10%	Castle Chemicals Pty Ltd	Surface cleaner - general purpose
Impact	Y	Y	"minor quantity"	Gibson Chemicals Limited	Hand cleaner
Industroclean	Y	Y	<10%	Albright & Wilson (Australia) Limited	Surface cleaner - heavy duty
Industroclean	N	Y	Not stated	Amway of Australia Pty Ltd	Surface cleaner - heavy duty
J Shop 300	Y	Y	<10%	S.C.Johnson	Surface cleaner - general purpose
J Shop 600	Y	Y	<10%	S.C.Johnson	Solvent degreaser
Jack	N	Y	15.3% w/v	Lustral	Floor stripper
Jackpot	Y	Y	<10%	Chemsolve	Surface cleaner - general purpose
JP50	Y	Y	<1.5%	Tulloch & Kapeco Pty Ltd	Laundry detergent
Jupiter	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - general purpose
Just Mop It	Y	Y	<10%	Gibson Chemicals Limited	Floor stripper
Karpet Life	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Carpet shampoo
Kenco Degreaser	N	Y	Not stated	Kenco Car Care Pty Ltd	Surface cleaner - heavy duty

Product	MSDS	Label	% 2-BE	Formulator	Use
Kitchen Degreaser	Y	Y	2%	Chemwell Products Pty Ltd	Surface cleaner - heavy duty, for food preparation areas and processing equipment
Kleebond 24/55	Y	Y	<10%	Novamax Technologies (A'Asia) Pty Ltd	Rust remover
Kleen Etch Plus	Y	Y	<10%	Novamax Technologies (A'Asia) Pty Ltd	Acid etch cleaner for aluminium
Kleen Rite	Y	N	<10%	Cleancare of Australia	Upholstery cleaner
Kleen Rite - Superbase	Y	N	10-30%	Cleancare of Australia	Upholstry cleaner
Kleen Strip	Y	Y	15%	Newland Products Pty Ltd	Floor stripper
Knab Water Soluble Dampener Wash	Y	Y	1-10%	Knab Industries	Ink removal from cotton covers on dampening rollers of offset printing machines
Lab 230	Y	Y	10-30%	Castle Chemicals Pty Ltd	Surface cleaner - heavy duty ; Engine cleaner ; Vehicle exterior cleaner
Lab 563	Y	Y	12%	Castle Chemicals Pty Ltd	Cleaning of exhaust scrubber tanks of locomotives and personnel carriers used in underground mining operations.
Laser Q	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Surface cleaner - heavy duty
Lazer	Y	Y	<10%	Peerless Emulsion Products Pty Ltd	Floor stripper
Lazer Super	Y	Y	20%	Peerless Emulsion Products Pty Ltd	Floor stripper
Lenz	Y	Y	<10%	Castle Chemicals Pty Ltd	Glass/window cleaner
Lift Off Plus	Y	Y	7.5%	Demack Enterprises	Surface cleaner - general purpose
Lift-off	Y	Y	10-30%	S.C.Johnson	Floor stripper
Liqua Steam - Superbase	Y	N	<10%	Cleancare of Australia	Carpet cleaner
Liqua-steam	Y	N	<1%	Cleancare of Australia	Carpet Cleaner
Liquipol L61-FE	Y	Y	<10%	Novamax Technologies (A'Asia) Pty Ltd	Surface cleaner
LL-300	Y	Y	Not stated	Ecolab Pty Ltd	Jeans de-sizing detergent
M1000	Y	Y	<5%	Town & Country Chemicals Pty Ltd	Surface cleaner - general purpose
Machine Tool Cleaner	Y	N	17.6%	Houghton Australia Pty Ltd	Cleaner for metal working machines
Magic Cleaner	Y	Y	2%	Chemwell Products Pty Ltd	Surface cleaner - heavy duty, for kitchen areas.
Major Plus	Y	Y	10-29%	Advanced Chemicals Pty Ltd	Surface cleaner - heavy duty; oven cleaner
Marine Clene	Y	Y	<10%	Septone Products Pty Ltd	Surface cleaner for boats

Product	MSDS	Label	% 2-BE	Formulator	Use
Max Multipurpose Cleaner	Y	Y	5%	Atherton Chemicals Pty Ltd	Surface cleaner - general purpose
Maxi-Strip	Y	Y	1-5%	North Queensland Chemicals and Paints	Floor stripper
Maxiclean	Y	Y	1-5%	North Queensland Chemicals and Paints	Surface cleaner - heavy duty
Meat Hook Derust	Y	Y	Not stated	Peerless Emulsion Products Pty Ltd	Rust remover
Metal Prep	Y	Y	30-60%	Septone Products Pty Ltd	Rust remover
Mirrors & Glass	Y	Y	10-30%	Cyndan Chemicals	Glass/window cleaner ; Floor stripper
Mop N Strip	Y	Y	<10%	Alliance Technology Pty Ltd	Floor stripper
MP1000	Y	Y	<10%	Chemsolve	Surface cleaner - heavy duty
MP2000	Y	Y	<10%	Chemsolve	Surface cleaner - general purpose
Mrs Beeton's Range Cleaner	Y	Y	<10%	Gibson Chemicals Limited	Oven cleaner
Multi Clean	Y	Y	13.7%	Elite Chemicals Pty Ltd	Surface cleaner- general purpose
Multi Purpose Cleaner	Y	Y	2%	Chemwell Products Pty Ltd	Surface cleaner - general purpose
Multi UV Washup	Y	N	<40%	GSB Chemicals	Ink and resin remover
Multikleen	Y	N	6%	Bunzl Ltd (reseller - products manufactured by JC Allen)	Surface cleaner - general purpose
Multikleen	Y	Y	5%	Dynamic Laboratories	Surface cleaner - general purpose
Multisolve	Y	Y	<10%	Town & Country Chemicals Pty Ltd	Surface cleaner - heavy duty
Multistrip	Y	Y	13%	Ecolab Pty Ltd	Floor stripper
N.A.Stripper	Y	N	10-60%	Tasman Chemicals Pty Ltd	Floor stripper
Naturally Clean Chrome and Glass Cleaner	Y	Y	<10%	Benckiser Australia	Glass/window cleaner
NC 160	N	Y	Not stated	Ecolab Pty Ltd	Surface cleaner - general purpose
New Liquid Degreaser	Y	Y	1-10%	Lustral	Surface cleaner - general purpose
New Look	Y	Y	3%	The Major Chemical Co. Pty Ltd	Glass/window cleaner
New Multi Purpose Cleaner	Y	Y	7%	Protect-A-Clean	Surface cleaner - general purpose
No Frills Grime Fighter	Y	Y	<2%	The Phase Corporation of Australia Pty Ltd	Surface cleaner - general purpose
No Frills Prewash	Y	Y	<5%	The Phase Corporation of Australia Pty Ltd	Pre-wash stain remover

Product	MSDS	Label	% 2-BE	Formulator	Use
No Frills Window Cleaner	Y	Y	<1%	The Phase Corporation of Australia Pty Ltd	Glas/window cleaner
No Scrub - No Rinse Stripper	Y	Y	10-30%	S.C.Johnson	Floor stripper
No.1 Marine Metal Cleaner	Y	Y	22.5%	Protect-A-Clean	Rust remover
Nth Power	N	N	Not stated	Cosmic Products	Surface cleaner - general purpose
Nth Power Plus	N	N	Not stated	Cosmic Products	Surface cleaner - general purpose
Nutral Floor Cleaner	Y	N	<1%	Cleancare of Australia	Surface cleaner - general purpose
Oakite Rust Preventative 2	Y	Y	5%	Tak Pty Ltd	Rust preventative
Oasis 111 (Imported)	Y	Y	4%	Ecolab Pty Ltd	Surface cleaner - floors
Oasis 122 (Imported)	Y	Y	<1%	Ecolab Pty Ltd	Floor stripper
Oasis 255 (Imported)	Y	Y	23%	Ecolab Pty Ltd	Glass/window cleaner
Outrite	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Carpet cleaner
Overhaul P.F	Y	Y	Not stated	Cleveland Chemical Co. Pty Ltd	Vehicle surface cleaner
PHA Shift It	N	Y	Not stated	Kenco Car Care Pty Ltd	Surface cleaner - heavy duty; laundry pre-spray
Pile High	Y	Y	<10%	Gibson Chemicals Limited	Carpet cleaner
Plush	Y	Y	<10%	Chemsolve	Carpet cleaner
Polish & Wax Stripper	Y	Y	7%	Chemwell Products Pty Ltd	Floor stripper
Poly-Cot	Y	Y	10-<30%	Ecolab Pty Ltd	Laundry detergent
Polyglaze Auto Glass Cleaner	Y	Y	1-9%	Selleys Chemical Company Pty Ltd	Glass/window cleaner
Polyglaze Foaming Mag Wheel Cleaner	Y	Y	<10%	Selleys Chemical Company Pty Ltd	Cleaner for automotive mag wheels
Polyglaze Mag Wheel Cleaner	Y	Y	1-9%	Selleys Chemical Company Pty Ltd	Cleaner of automotive mag wheels
Polywash Sugar Soap	Y	Y	<10%	Selleys Chemical Company Pty Ltd	Surface cleaner - heavy duty - for use prior to painting and wallpapering
Power	Y	Y	Not stated	Alliance Technology Pty Ltd	Surface cleaner - heavy duty ; Engine cleaner ; Vehicle exterior cleaner
Power Kleen	Y	Y	1-10%	Cyndan Chemicals	Surface cleaner - heavy duty
Power Wash	Y	Y	5%	Cyndan Chemicals	Surface cleaner - general purpose
Prepare	Y	Y	<10%	Elite Chemicals Pty Ltd	Floor stripper
Presto Detergent	Y	Y	<10%	Agar Chemicals	Surface cleaner - general purpose
Print Wash	Y	Y	<10%	Chemsolve	Dampener roller wash

Product	MSDS	Label	% 2-BE	Formulator	Use
Pro-Kleen Floor Stripper	Y	Y	<10%	Peerless Emulsion Products Pty Ltd	Floor stripper
Pro-Kleen Glass Cleaner	Y	Y	<10%	Peerless Emulsion Products Pty Ltd	Glass/window cleaner
Pro-Kleen Spray and Wipe	Y	Y	<10%	Peerless Emulsion Products Pty Ltd	Surface cleaner - general purpose
Pro-Spot	Y	Y	Not stated	Gibson Chemicals Limited	Pre-wash stain remover
Professional Spot Lifter	Y	N	Not stated	Cleancare of Australia	Carpet cleaner
Proof (3-261)	Y	Y	<10%	Applied Chemicals Pty Ltd	Machine glasswashing detergent
Pure Acrylic Stripper	Y	Y	29%	Castle Chemicals Pty Ltd	Floor stripper
Q Fire	Y	N	>60%	Quality Auto Treatment Pty Ltd	Solvent for cleaning petrol and diesel fuel systems
Quik Fill 320 (Imported)	Y	Y	25%	Ecolab Pty Ltd	Floor stripper
Quik Fill 510 (Imported)	Y	Y	13%	Ecolab Pty Ltd	Surface cleaner - general purpose
Quik Fill 520 (Imported)	Y	Y	40%	Ecolab Pty Ltd	Glass/window cleaner
R.39	Y	Y	<10%	B & J Chemicals	Surface cleaner - general purpose
Range Cleaner	Y	Y	10-30%	Shamrock Chemicals Pty Ltd	Oven cleaner
Range Cleaner	Y	Y	<1%	Dominant (Australia) Pty Ltd	Oven cleaner
Rapi-Klenz	Y	Y	5-10%	North Queensland Chemicals and Paints	Surface cleaner - general purpose
Rapid U V Washup	Y	N	10-30%	GSB Chemicals	Ink and resin remover
RC 40	Y	Y	<10%	Demack Enterprises	Carpet cleaner
Red Baron	Y	Y	1-10%	Lustral	Surface cleaner - general purpose
Red Multi Purpose Cleaner	Y	Y	7%	Protect-A-Clean	Surface cleaner - general purpose
Release	Y	N	<1%	Cleancare of Australia	Carpet cleaner
Remove	Y	Y	>10%	Elite Chemicals Pty Ltd	Floor stripper
Render	Y	Y	<10%	Elite Chemicals Pty Ltd	Oven cleaner
Reveal HD Cleaner	Y	Y	<10%	S.C.Johnson	Surface clenaer - heavy duty
Rik LT	Y	Y	"Glycol ethers <10%"	Ecolab Pty Ltd	Floor and wall cleaner for use in cold storage areas
Ripper	Y	Y	25%	Alliance Technology Pty Ltd	Floor stripper
RM 44 Acid Cleaner	Y	Y	Not stated	Peerless Emulsion Products Pty Ltd	Aluminium brightener and stainless steel cleaner
Roto-Brite	Y	N	10-30%	Cleancare of Australia	Carpet cleaner

Product	MSDS	Label	% 2-BE	Formulator	Use
Rugbee Foam Shampoo	Y	Y	<10%	S.C.Johnson	Carpet cleaner
Rugbee Jetstream Plus Liquid Extraction Cleaner	Y	Y	<10%	S.C.Johnson	Carpet Cleaner
Rugbee Soil Release Concentrate	Y	Y	<10%	S.C.Johnson	Carpet cleaner
Rugbee Spotto Heavy Duty Spot and Stain Remover	Y	Y	<10%	S.C.Johnson	Carpet cleaner
Sanclean 400	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Surface cleaner - general purpose
Scene (Aerosol)	Y	Y	<10%	Gibson Chemicals Limited	Glass/window cleaner
Scotchbrite Brand Dri-Strip 303	Y	Y	8-11%	3M Australia Pty Ltd	Floor stripper
Scrub N Shine	Y	Y	Not stated	Alliance Technology Pty Ltd	Floor cleaner and polisher
SD-37 Detergent	Y	Y	20%	Agar Chemicals	Surface cleaner - general purpose ; Floor stripper
SF 100	Y	Y	4%	Demack Enterprises	Surface cleaner - heavy duty ; Engine cleaner
Shift It	Y	Y	15.1%	Lustral	Surface cleaner - general purpose ; Engine cleaner
Shor Kleen	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Surface cleaner - heavy duty
Simplicity	Y	Y	3%	The Major Chemical Co. Pty Ltd	Surface cleaner - for washroom and hard floor
Sirio HD Cleaner	Y	Y	4.75%	Demack Enterprises	Surface cleaner - heavy duty
Slik No.5	Y	N	<10%	Nalco/Exxon Energy Chemicals Australia Pty Ltd	Surface cleaner - general purpose (oil rig equipment)
Slipstream	Y	Y	<10%	Elite Chemicals Pty Ltd	Specialised detergent for use in breweries and bottling plants
Soil Breaker	Y	Y	Not stated	Alliance Technology Pty Ltd	Carpet cleaner ; Upholstery cleaner
Sol Fome	Y	Y	Not stated	Alliance Technology Pty Ltd	Surface cleaner - for use in abattoirs and food processing plants
Solid Regain (Imported)	N	N	Not stated	Ecolab Pty Ltd	Surface cleaner - floors
Solocleaner	Y	Y	<10%	Cleveland Chemical Co. Pty Ltd	Surface cleaner - general purpose
Solspray	Y	Y	"low"	Agar Chemicals	Carpet cleaner ; Hard surface cleaner
Solv Kleen	Y	Y	Not stated	Alliance Technology Pty Ltd	Printers dampener wash
Solv-It	Y	Y	<10%	Elite Chemicals Pty Ltd	Laundry detergent
Solveclean	Y	Y	1-10%	Challenge Chemicals Aust.	Surface cleaner - heavy duty
Solveen	Y	Y	12%	Ecolab Pty Ltd	Laundry detergent

Product	MSDS	Label	% 2-BE	Formulator	Use
Solvex 09WS	Y	Y	<10%	Novamax Technologies (A'Asia) Pty Ltd	Detergent additive for spray phosphating
Solvex 50A	Y	Y	10-30%	Novamax Technologies (A'Asia) Pty Ltd	Detergent additive for phosphating
Solvobreak	Y	Y	12.9%	Castle Chemicals Pty Ltd	Laundry detergent
Sparkle Glass Cleaner	Y	Y	<10%	S.C.Johnson	Glass/window cleaner
Special Linen Solvent	Y	Y	<10%	Kempo Manufacturing Company Pty Ltd	Laundry detergent for tablecloths soiled with spillages of food products containing vegetable oils
Speed	Y	Y	"low"	Agar Chemicals	Surface cleaner - heavy duty ; Floor stripper
Speedkleen	Y	Y	1-5%	North Queensland Chemicals and Paints	Surface cleaner - heavy duty
Spindle Cleaner	N	Y	Not stated	Castrol Australia Pty Ltd	Spindle cleaner - added to water tank on cotton harvesters
Spot Go	Y	Y	30%	Castle Chemicals Pty Ltd	Carpet cleaner ; Upholstery cleaner
Spray and Wipe	Y	Y	<10%	Challenge Chemicals Aust.	Surface cleaner - general purpose
Spray Clean	Y	Y	10-60%	Lustral	Surface cleaner - heavy duty
Spray Kleen	Y	Y	Not stated	Alliance Technology Pty Ltd	Spray burnishing of floors
Spray Kleen Concentrate	Y	Y	Not stated	Alliance Technology Pty Ltd	Spray burnishing of floors
Spray Shine	Y	Y	Not stated	Alliance Technology Pty Ltd	Spray burnishing compound for floors
Spray Wipe	Y	Y	<10%	Shamrock Chemicals Pty Ltd	Surface cleaner - general purpose
Sprayclean	Y	Y	5%	Castle Chemicals Pty Ltd	Surface cleaner - general purpose
Spraycleen	Y	Y	<10%	Town & Country Chemicals Pty Ltd	Surface cleaner - general purpose
Sprayoff Oven Cleaner	Y	Y	Not stated	Cleveland Chemical Co. Pty Ltd	Oven cleaner
Sprint	Y	Y	<10%	Castle Chemicals Pty Ltd	Carpet cleaner ; Upholstery cleaner
Sprite	Y	Y	Not stated	B & J Chemicals	Surface cleaner - general purpose
Squirt	Y	Y	1-10%	Lustral	Surface cleaner - general purpose
Stainless	Y	Y	<2%	Cleveland Chemical Co. Pty Ltd	Surface cleaner and disinfectant for bathrooms and toilets
Stainof	Y	N	Not stated	Cleancare of Australia	Not stated
Status Non Smear Glass Cleaner	Y	Y	4.8%	Peerless Emulsion Products Pty Ltd	Glass/window cleaner

Product	MSDS	Label	% 2-BE	Formulator	Use
Steamate	Y	Y	<10%	Cyndan Chemicals	Cleanser solvent used in steam or cold presssure washers
Step-off Heavy Duty Stripper	Y	Y	10-30%	S.C.Johnson	Floor stripper
Strike	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Surface cleaner - general purpose ; Engine cleaner
Strip	Y	Y	<10%	Chemsolve	Floor stripper
Strip Clean	Y	Y	"medium"	Dari Cleaning Products	Floor stripper
Stripper	Y	Y	7.5%	Demack Enterprises	Floor stripper
Supar	Y	Y	24%	Lustral	Surface cleaner - general purpose ; Print screen/ink cleaner
Super Clear	Y	Y	<10%	Tak Pty Ltd	Glass/window cleaner
Super Kleen	Y	Y	<7%	BettaChem Chemical Manufacturers	Surface cleaner - general purpose
Superb	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Surface cleaner - general purpose
Superclean	Y	Y	<10%	Chemsolve	Surface cleaner - general purpose
Supreme	Y	Y	Not stated	Newland Products Pty Ltd	Surface cleaner - heavy duty, for kitchen and food preparation areas
Supreme (4-490)	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
Surmax CS-555	Y	N	<2%	Swift and Co	General purpose cleaner
SW Supercleaner	Y	Y	10-20%	North Queensland Chemicals and Paints	Surface cleaner - general purpose
Tak Det 12LS	Y	Y	6%	Tak Pty Ltd	Surface cleaner - general purpose
Tak Det 32LS	Y	Y	<10%	Tak Pty Ltd	Surface cleaner - general purpose
Tak Det 5LS	Y	Y	18%	Tak Pty Ltd	Surface cleaner - general purpose
Tak Det 6LS	Y	Y	12%	Tak Pty Ltd	Surface cleaner - general purpose
Tak Det 7L	Y	Y	<10%	Tak Pty Ltd	Ammoniated detergent
Tak Spec 996L	Y	Y	<10%	Tak Pty Ltd	Glass/window cleaner
Take Off	Y	N	0-10%	True Blue Chemicals Pty Ltd	Surface cleaner - general purpose
Take Off	Y	Y	<10%	Shamrock Chemicals Pty Ltd	Surface cleaner - heavy duty
Take Off (4-480)	Y	Y	<10%	Applied Chemicals Pty Ltd	Surface cleaner - general purpose
Techniclean PR	Y	N	10-30%	Castrol Australia Pty Ltd	Paint stripper

Product	MSDS	Label	% 2-BE	Formulator	Use
Terminator	Y	N	Not stated	Whiteley Chemicals Australia Pty Ltd	Floor stripper
Threes	Y	Y	5.3%	The Major Chemical Co. Pty Ltd	Carpet cleaner
TKO Build Up Remover	Y	Y	<10%	Agar Chemicals	Floor stripper
Toilet Bowl and Urinal Cleaner	Y	Y	22.5%	Protect-A-Clean	Toilet bowl and urinal cleaner
Tonizone Glass and Mirror Cleaner	Y	N	<10%	Multi-Fill Pty Ltd	Glass/window cleaner
Top Marks	Y	Y	3.4%	The Major Chemical Co. Pty Ltd	Surface cleaner - general purpose
Top Quartile	Y	Y	10-<30%	Ecolab Pty Ltd	Floor stripper
Touch Up	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Surface cleaner - general purpose
Traffic Zone	Y	Y	<5%	Gibson Chemicals Limited	Heavy duty floor cleaner
Trap Solve	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Grease trap cleaner
Triples	Y	Y	4%	The Major Chemical Co. Pty Ltd	Surface cleaner - general purpose
Trouble Spot	Y	Y	Not stated	Peerless Emulsion Products Pty Ltd	Carpet cleaner
Truck Wash Plus	Y	Y	<10% w/w	Harcros Chemicals Limited	Truck wash
Truckwash	Y	Y	Not stated	Gladstone Chemicals	Vehicle surface cleaner
Truk Wash	Y	Y	1-10%	Dominant (Australia) Pty Ltd	Heavy duty cleaner for trucks and other vehicles
Turco 4258NP	Y	Y	0-10%	Ajax Chemicals	Surface cleaner - aircraft parts
Turco 5884	Y	Y	<10%	Ajax Chemicals	Surface cleaner - heavy duty ; Jet engine compressor washer
Turco 5948 A	Y	Y	<10%	Ajax Chemicals	Aircraft exterior surface cleaner
Turco 5974 BNF	Y	Y	5%	Ajax Chemicals	Surface cleaner
Turco 5975 A	Y	Y	<10%	Ajax Chemicals	Surface cleaner - heavy duty
Turco 6336	Y	Y	<5%	Ajax Chemicals	Not stated
Turco 9128	Y	N	<10%	Ajax Chemicals	Surface cleaner - general purpose
Turco Airtec 19	Y	Y	<10%	Ajax Chemicals	Aircraft exterior surface cleaner
Turco Airtec 22	Y	Y	<10%	Ajax Chemicals	Aircraft exterior surface cleaner
Turco Aquasorb	Y	Y	<10%	Ajax Chemicals	Rust preventative/removal of fingerprints
Turco Cleansolv	Y	Y	<10%	Ajax Chemicals	Electrical and general equipment cleaning solvent
Turco Deodar	Y	Y	<10%	Ajax Chemicals	Toilet deodorant and cleaner

Product	MSDS	Label	% 2-BE	Formulator	Use
Turco Flash	Y	Y	<10%	Ajax Chemicals	Rust remover
Turco HT 301	Y	N	>60%	Ajax Chemicals	Alkaline stripper
Turco Jetclean No. 2	Y	Y	<10%	Ajax Chemicals	Surface cleaner - general purpose, for use in food, transport and metal industries
Turco Metal Glo 6	Y	Y	<10%	Ajax Chemicals	Surface cleaner - aircraft and aluminium surfaces
Turco Meteor	Y	Y	<10%	Ajax Chemicals	Surface cleaner - general purpose
Turco Mulsirex	Y	Y	<10%	Ajax Chemicals	Surface cleaner - general purpose
Turco Odorshield	Y	Y	<10%	Ajax Chemicals	Sanitary deodorant, cleaner and bacteriostat
Turco Rust Converter	Y	Y	1-10%	Ajax Chemicals	Rust remover
Turco Spray & Wipe	Y	Y	<10%	Ajax Chemicals	Surface cleaner - general purpose
Turco Turcosolv Q	Y	Y	Not stated	Ajax Chemicals	Electrical cleaning solvent
Turco WO1	Y	Y	10-30%	Ajax Chemicals	Rust remover
Turcosolv	Y	Y	<10%	Ajax Chemicals	Electrical cleaning solvent
Turcosolv Trsk 54	Y	Y	1-10%	Ajax Chemicals	Electrical cleaning solvent
Twinkle	Y	Y	"medium"	Dari Cleaning Products	Surface cleaner - general purpose
Ultrasolv	Y	Y	<10%	Town & Country Chemicals Pty Ltd	Surface cleaner - heavy duty
Ultrastrip	Y	Y	16.5%	Cleveland Chemical Co. Pty Ltd	Floor stripper
Ultrastrip	Y	Y	"low"	Agar Chemicals	Floor stripper
Use All	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Surface cleaner - general purpose
UV Blanket Roller Wash	Y	N	35%	GSB Chemicals	UV blanket roller wash
Versaclean	Y	Y	<5%	Cleveland Chemical Co. Pty Ltd	Surface cleaner - heavy duty ; Engine cleaner
Vetro	Y	N	"low"	Tasman Chemicals Pty Ltd	Glass/window cleaner
Vision	Y	Y	<1%	Newland Products Pty Ltd	Glass/window cleaner
WDI Degreaser	Y	N	Not stated	KCB Pty Ltd	Engine cleaner
Windex	Y	Y	<10%	S.C.Johnson	Glass/window cleaner
Window and Mirror Cleaner	Y	Y	3%	Chemwell Products Pty Ltd	Glass/window cleaner
Window Cleaner	Y	Y	0-10%	True Blue Chemicals Pty Ltd	Glass/window cleaner
Window Cleaner	Y	Y	5%	Jamac-Safe and Clean Pty Ltd	Glass/window cleaner
Window Cleaner	Y	Y	<10%	Ecolab Pty Ltd	Window cleaner

Product	MSDS	Label	% 2-BE	Formulator	Use
Window Cleaner	Y	Y	10%	Town & Country Chemicals Pty Ltd	Glass/window cleaner
Window Cleaner	Y	Y	<10%	Alliance Technology Pty Ltd	Glass/window cleaner
Window Clear	Y	Y	<10%	B & J Chemicals	Glass/window cleaner
Window Shine	Y	Y	10-30%	Shamrock Chemicals Pty Ltd	Glass/window cleaner
Window Wash	Y	Y	<10%	Agar Chemicals	Glass/window cleaner
Wipe Away Detergent	Y	Y	<10%	Agar Chemicals	Surface cleaner - general purpose
Wipe Clean	Y	N	1%	Sadies Cleaning Products	Surface cleaner - general purpose
Wipe Clean	Y	Y	<10%	Alliance Technology Pty Ltd	Surface cleaner - general purpose
Wipe Clean Concentrate	Y	Y	71%	Alliance Technology Pty Ltd	Surface cleaner - general purpose
Wipe Out	N	Y	<7%	BettaChem Chemical Manufacturers	Surface cleaner - general purpose
ZC2	Y	Y	<10%	Elite Chemicals Pty Ltd	Surface cleaner - heavy duty
Zip 282	Y	Y	<10%	S.C.Johnson	Oven cleaner
Zip Strip	Y	N	Not stated	Whiteley Chemicals Australia Pty Ltd	Floor stripper
Zoom	Y	Y	<10%	Amway of Australia Pty Ltd	Surface cleaner - general purpose
[Not stated]	N	N	Not stated	Plaza Chemical	Surface cleaner
[Not stated]	N	N	Not stated	Symbio Products	Surface cleaner
[Not stated]	N	N	Not stated	Blacktown Custom Packers Pty Ltd	Surface cleaner - general purpose ; Engine cleaner
[Not stated]	N	N	Not stated	JAL Chemicals Pty Ltd	Floor stripper ; Surface cleaner - general purpose
[Not stated]	N	N	Not stated	R & E Chemicals Pty Ltd	Surface cleaner
[Not stated]	N	N	Not stated	Home Carpet Shampoo Australia	Carpet cleaner
[Not stated]	N	N	"minor"	Colbar Aust	Rust converter
[Not stated]	N	N	Not stated	Calman Manufacturing Pty Ltd	Surface cleaner - general purpose ; Floor stripper
[Not stated]	N	N	94%	Fasson Pty Ltd	Cleaning of coating cylinders used in a silicone coating process

APPENDIX 2

QUESTIONNAIRE

Company name: .....

Contact person: .....tel.....

[Please tick appropriate box(es)]

Are you:

□ a reseller of 2-butoxyethanol

□ a formulator of cleaning products containing 2-butoxyethanol

□ a past formulator of cleaning products containing 2-butoxyethanol (before 5 April 1994)

□ an end-user of cleaning products containing 2-butoxyethanol

□ other (please specify).....

What is the product used for? *(if not specified on MSDS*) e.g. surface cleaner, floor stripper

.....

Who uses the product? e.g. household, office cleaners, mechanics

.....

How many workers are involved in the formulation process?

.....

How many hours/week (approx) are they potentially exposed to 2-butoxyethanol?

.....

What precautions are taken/recommended when using the product? (*if not on MSDS*)

.....

.....

Are you aware of any adverse health effects experienced by workers/customers after exposure to 2-butoxyethanol or products containing 2-butoxyethanol? If so, please describe.

.....

....

.....

Are you aware of any atmospheric monitoring that has been conducted during formulation and/or use of cleaning products containing 2-butoxyethanol?

.....

If so, please forward results.

APPENDIX 3

OCCUPATIONAL EXPOSURE CALCULATIONS

1. FORMULAE FOR EXPOSURE CALCULATIONS

For 2-butoxyethanol, the total body dose (D) is the sum of doses resulting from absorption of vapours (D_v) and dermal absorption of liquid (D_{dl}).

That is, $D = D_v + D_{dl}$ (equation 1)

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

$$D = (D_{iv} + D_{dv}) + D_{dl}$$ (equation 1a)

Exposure to vapours

The daily dose arising from the inhalation of vapours (D_{iv}) is as follows:

$$D_{iv} = \frac{C \times R \times E \times B}{BW} \text{ mg/kg/day}$$ (equation 2)

where C = concentration of substance in air (mg/m^3),

R = inhalation rate (m^3/h),

E = exposure duration (h/day),

B = bioavailability of vapours across the lungs (1 = 100%),

BW = average body weight of worker (kg).

In addition, 2-butoxyethanol vapours are also absorbed across the skin. From the results of recent studies in volunteers (Corley et al 1995) and PBPK modelling (Corley et al 1994), the dermal absorption of 2-butoxyethanol vapours (D_{dv}) comprises up to 20% of the total absorption of vapours (D_v). That is, for 2-butoxyethanol, D_{iv} is approximately 80% of D_v (see sections 9.2 and 9.6).

That is, $D_{iv} = 0.8\ D_v$, or $D_v = \frac{D_{iv}}{0.8}$. (equation 3)

Therefore, combining equations 2 and 3, the daily dose arising from vapour exposure (D_v), inhalational plus dermal, is as follows:

$$D_v = \frac{C \times R \times E \times B}{0.8 \times BW} \text{ mg/kg/day} \quad \text{(equation 4)}$$

For vapour exposure, the bioavailability (B) is the proportion of inhaled substance which is absorbed through the lungs, for example, some of the substance is exhaled. In inhalational (breathing zone) tests in volunteers, 57-78% of the inspired amount of 2-butoxyethanol was absorbed (see subsection 9.2.3). As these values are similar to the default value of 0.75 (75%) often used in international assessments, a value of 0.75 was used in this report.

For consistency with international assessments, a value of 1.3 m^3/h was used for the inhalation rate (R) for occupational exposure during light work activities (OECD 1993; European Commission 1994). Similarly, a value of 70 kg was used for body weight (BW).

The exposure duration (E) that workers may be potentially exposed to 2-butoxyethanol during a work shift, either during formulation or cleaning, was obtained from questionnaires sent to formulators (see section 8.4) or from assumptions regarding working times during end use (see section 8.5).

Exposure to liquid

The daily total dose arising from liquid exposure (D_{dl}) is as follows:

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

where: W = weight fraction of substance in product, for example, 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 fraction of exposure duration, for example, 0.2 for 20% of time),

BW = average body weight of worker (kg).

For skin absorption rate (S), two sets of human tissue data were available (see subsection 9.2.2). In one of the experiments, the results were reasonably consistent, with a mean of 0.20 mg/cm^2/h (range 0.14-0.35) obtained. Extremely variable results were obtained in the other tissue experiment, with the mean considerably higher at 1.19 mg/cm^2/h (range 0.57-1.91). The results of the former test agreed reasonably well with controlled studies in volunteers, where the mean rate was 0.14 mg/cm^2/h (range 0.05-0.68) (see section 9.2.3), so the value of 0.2 mg/cm^2/h was used for skin absorption rate (S) in this assessment.

For skin surface area (A), standard area estimates for the adult male include the following standard US EPA values (in cm^2):

arms	2280
upper arms	1430
forearms	1140
hands	840
head	1180

In this assessment, it was considered that dermal exposure would reasonably consist of no more than exposure to both hands (840 cm^2) or a hand and a forearm (1000 cm^2). For consistency, a value of 1000 cm^2 for was considered appropriate for feasible worst-case estimates.

For the case of dermal exposure to aerosols, for example, during spray use, exposed parts of the body may include the face, neck, hands and forearms. However, as exposure to aerosols would not be expected to occur simultaneously with exposure to liquid 2-butoxyethanol (as a solution), the skin surface area of 1000 cm^2 was considered appropriate for feasible worst-case estimates.

Liquid 2-butoxyethanol can be in contact with the skin for various fractions (F) of the exposure duration (E), so skin contact with liquid can be extensive, intermittent or incidental. For the purposes of this assessment, extensive dermal exposure is taken as continuous contact (F=1) with the skin. Taking into account assumptions made in the UK EASE (Estimation and Assessment of Substance Exposure) model* for dermal

exposure, intermittent exposure is taken as being skin contact for 20% of the time (F=0.2), and incidental exposure as skin contact for 1% of the time (F=0.01).

** The EASE model is the second version of the knowledge based system in development by the UK Health and Safety Executive (HSE), and was formerly called EES (Exposure Expert System). For a further description of EES, see: Marquart et al, Evaluation of Methods of Exposure Assessment for Premarket Notifications, TNO report V 94.229 TNO Nutrition and Food Research (Zeist), 1994.*

2. CALCULATIONS FOR VARIOUS SCENARIOS

The following estimates for exposure to vapours and liquid incorporate exposure to aerosols.

2.1 Manufacture (see section 8.3)

Exposure to vapours

For a maximum atmospheric concentration of 1.8 ppm (8.8 mg/m^3),

$$D_v = \frac{8.8\ mg/m^3 \times 1.3\ m^3/h \times 8h \times 0.75}{0.8 \times 70\ kg} = 1.2\ mg/kg/day.$$

Liquid (Dermal) exposure

For incidental skin contact (F=0.01) with a hand and a forearm (1000 cm^2) to 100% 2-butoxyethanol,

$$D_{dl} = \frac{1 \times 0.2\ mg/cm^2/h \times 1000\ cm^2 \times 8h \times 0.01}{70\ kg} = 0.2\ mg/kg/day.$$

Combined inhalational and dermal exposure

The combined inhalational and dermal uptakes would not be expected to exceed 1.4 mg/kg/day.

2.2 Formulation (see section 8.4)

Exposure to vapours

Substituting the constants in equation 4 above

$$D_v = \frac{C\ mg/m^3 \times 1.3\ m^3/h \times E\ h \times 0.75}{0.8 \times 70\ kg}\ mg/kg/day.$$

Liquid (Dermal) exposure

For intermittent skin contact (F = 0.2) with a hand and a forearm (1000 cm^2), and by substituting the constants in equation 5 above

$$D_{dl} = \frac{W \times 0.2\ mg/cm^2/h \times 1000\ cm^2 \times E\ h \times 0.2}{70\ kg}\ mg/kg/day.$$

Combined inhalational and dermal exposure

For each of the various scenarios, the combined inhalational and dermal uptakes would not be expected to exceed the values in the following table.

Table 1. Combined inhalational and dermal exposure during formulation

% 2-BE	W	C	E	Daily dose (mg/kg/day)		
				D_v	D_d	$D_v + D_{dl}$
10	0.1	9.8	3	0.5	0.2	0.7
10	0.1	9.8	8	1.4	0.5	1.9
30	0.3	49	3	2.6	0.5	3.1
30	0.3	49	8	6.8	1.4	8.2
60	0.6	49	3	2.6	1.0	3.6
60	0.6	49	8	6.8	2.7	9.5

Key: *W = weight fraction of 2-BE in product*
C = concentration of 2-BE in air (mg/m^3)
E = duration of exposure (h/day)
D_v = dose resulting from absorption of vapours
D_{dl} = dose resulting from dermal absorption of liquid

2.3 Cleaning (see section 8.5)

The combined inhalational and dermal uptakes for exposure during cleaning were calculated as for formulation, except that liquid (dermal) contact was assumed to be extensive, that is, continuous skin contact (F=1). The equations used for vapour absorption and dermal exposure to liquid respectively were therefore

$$D_v = \frac{C\ mg/m^3 \times 1.3\ m^3/h \times E\ h \times 0.75}{0.8 \times 70\ kg}\ mg/kg/day, \text{ and}$$

$$D_{dl} = \frac{W \times 0.2\ mg/cm^2/h \times 1000\ cm^2 \times E\ h \times 1}{70\ kg}\ mg/kg/day.$$

For each of the various scenarios, the daily dose would not be expected to exceed the values in the following table.

Table 2. Combined inhalational and dermal exposure during cleaning

% 2-BE	W	C	E	Daily dose (mg/kg/day)		
				D_v	D_{dl}	$D_v + D_{dl}$
0.1	0.001	9.8	5	0.9	0.01	0.9
0.1	0.001	9.8	8	1.4	0.02	1.4
1	0.01	9.8	5	0.9	0.1	1.0
1	0.01	9.8	8	1.4	0.2	1.6
10	0.1	19.6	5	1.7	1.4	3.1
10	0.1	19.6	8	2.7	2.3	5.0
30	0.3	49	5	4.3	4.3	8.6
30	0.3	49	8	6.8	6.9	13.7

Key: *W = weight fraction of 2-BE in product*
C = concentration of 2-BE in air (mg/m^3)
E = duration of exposure (h/day)
D_v = dose resulting from absorption of vapours
D_{dl} = dose resulting from dermal absorption of liquid

APPENDIX 4

OTHER INFORMATION SUBMITTED TO NICNAS DURING ASSESSMENT

During the assessment period, cleaners in NSW were invited to provide information to NICNAS regarding the use of cleaning products containing 2-butoxyethanol. The invitation was placed in the Winter 1994 edition of *Focus*, the newsletter of the Liquor, Hospitality and Miscellaneous Workers Union - Miscellaneous Workers Division. Also, a number of unsubstantiated case reports from persons previously exposed to cleaning products containing 2-butoxyethanol were submitted to Worksafe.

Survey of Cleaners in NSW

Information was provided by cleaners in the following locations. In all cases a surface cleaning solution of <10% 2-butoxyethanol or a dilution of the product was used.

Town/suburb	Workplace	Comments
Berkeley	school	Solution diluted 1:10 and used as spray;
workers (6)		
		have cough, nausea.
Blayney	school	Solution used to be used as spray; worker
		still has cough; no gloves worn.
Bonville	school	Cleaner experienced respiratory irritation.
Campbelltown	school	Spray use; worker had cough.
Cartwright	school	Solution used as spray; worker had persistent
cough;		
		rubber gloves worn.
Dunedoo		Solution diluted 1:10 and used as spray; worker
has		
		wheezing; gloves not worn.
Inverell	school	Spray use; worker had cough, eye, skin
problems;		
		rubber gloves worn.
Macksville		Solution applied by cloth; workers get eye
irritation and		
		nausea.

Moruya worked	school	Solution diluted 1:3 and used as spray; worker experienced headache, nausea, coughing; 28h/wk; mask and rubber gloves worn.
Narwee rubber	school	Spray use; worker experienced skin irritation; gloves worn.
Nowra headache.	club	Spray use; workers have cough, sore eyes,
Thornleigh fatigue,	office	Spray use; worker experienced headache, nausea; gloves worn.

Other Reports

Written submissions were received from a number of workers who had used cleaning solutions containing 2-butoxyethanol during their employment. These are summarised below.

Town/State	Workplace	Comments
Coffs Harbour NSW	contract cleaner	Floor stripping, solution diluted 1:1, worker reported symptoms including eye and respiratory irritation
Cranbourne Vic	school cleaner	General cleaning, including spray use, with diluted solution, and floor stripping with 10- 12% 2-BE solution; worker reported symptoms including eye irritation, dry cough, sleepiness, dizziness, confusion
Hampton Vic	office cleaner	Heavy duty cleaning, including use of 18.5% solution; poor ventilation; worker reported symptoms including headache, nausea, eye irritation, anaemia, sleepiness, dizziness, confusion

APPENDIX 5

ABSA STRUCTURED TRAINING PROGRAM FOR CLEANERS

This course has been designed by the Australian Building Services Association (ABSA) to cover the requirements of cleaning operatives (cleaners) and is available on an 'in-house' basis, for use by company trainers. It is a practical course covering basic cleaning skills and tasks, use of cleaning chemicals and equipment, and safety. The course can be modified to meet particular circumstances. The syllabus is as follows:

I	INDUCTION
II	SAFETY
III	BASIC SKILLS
	Dusting
	Dust Mopping
	Damp Mopping
	Wet Mopping
	Cleaning Status
	Toilet Cleaning
	Shower Cleaning
	Other Cleaning Tasks and Methods
	Safety
	CLEANING HARD FLOORS
	Buffing
	Spray Buffing
	Floor Scrubbing
	Stripping and Sealing
	Use of Chemicals and Equipment
	CARPET CLEANING AND MISCELLANEOUS
	Carpet Spotting and Stain Removal
	Spot Vacuuming (Back-Pack)
	Vacuum Cleaning

Carpet Shampooing

Internal Glass Cleaning

Venetian Blind Cleaning

Wall Washing

Refrigeration Cleaning

Cupboards

Other Cleaning Tasks as Required

Appendix 6

Sample Material Safety Data Sheet for **2-butoxyethanol**

Date of issue		Page 1	of Total 6

2-Butoxyethanol is classified as hazardous according to the National Occupational Health and Safety Commission's Approved Criteria for Classifying Hazardous Substances.

Company details

Company name

Address

State Postcode

Telephone number Emergency telephone number

Facsimile number Telex number

Identification

Product name
2-Butoxyethanol

Other names
Ethylene Glycol Monobutyl Ether, Butyl Ethoxol, EGBE

Manufacturer's product code

UN Number

Dangerous goods class and subsidiary risk
Combustible liquid

Hazchem code
2R

Poisons Schedule number
Schedule 6 (under Ethylene Glycol Monoalkyl Ethers)

Use

Physical description and properties

Appearance
Colourless liquid with unpleasant odour

Boiling point
171°C

Freezing point

Vapour pressure
1.17 hPa

Specific Gravity
0.90 g/mL

Flashpoint
62°C (closed cup)

Flammability limits
1.10 - 12.7%

Solubility in water
Miscible

Other properties

Vapour density: 4.91 g/L (20°C)

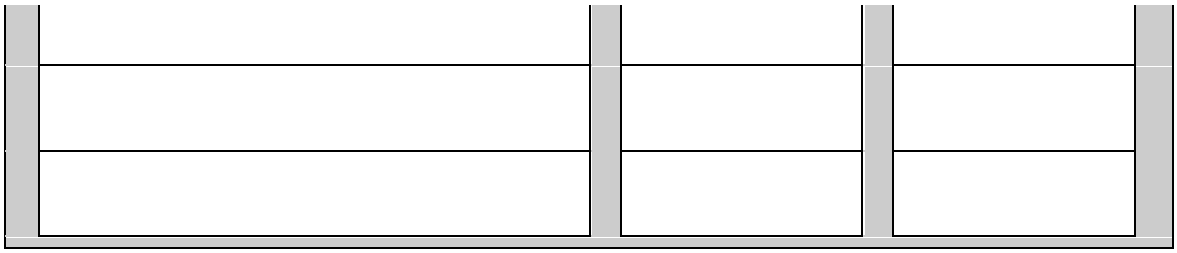
Density: 0.9 g/mL (20°C)

Autoignition Temperature: 230-245°C

Reactivity: Reacts with strong oxidising agents and strong caustics

Ingredients

Chemical entity	CAS Number	Proportion
2-Butoxyethanol	111-76-2	
Impurities		



Health hazard information

HEALTH EFFECTS

Acute:

Swallowed: May cause nausea, vomiting, irritation of the gastro-intestinal tract and loss of consciousness. Ingestion of very high doses may cause haemolysis of the red blood cells.

Eye: Severe irritant. Vapour also irritating.

Skin: Mild to moderate irritant in test animals. Slight irritant in humans but repeated or prolonged contact may cause contact dermatitis. Has degreasing action on skin. Readily absorbed through skin. Vapour also absorbed through skin.

Inhalation: Vapour irritating to respiratory system. May cause headache and nausea. Inhalation of high concentrations caused loss of co-ordination and breathing difficulties in animals.

Chronic:

No studies are available on the effects of long term exposure to 2-butoxyethanol in humans. Studies indicate that repeated exposure causes blood, liver and kidney disorders in animals.

FIRST AID

Swallowed: Rinse mouth with water. Give plenty of water to drink. Seek immediate medical attention.

Eye: Hold the eyes open and irrigate with lots of water for at least 15 minutes. Keep the eyelids open. Seek immediate medical attention.

Skin: Wash contaminated skin thoroughly with lots of water. Remove contaminated clothing and wash before re-use. Seek medical attention if irritation persists.

Inhalation: Remove person from exposure - avoid becoming a casualty. Remove contaminated clothing and loosen remaining clothing. Keep patient comfortable and warm. Make sure airways are clear and monitor breathing. Seek medical attention.

First aid facilities:

For further information, contact the Poisons Information Centre.

ADVICE TO DOCTOR

Treat symptomatically.

Precautions for use

2-Butoxyethanol is readily absorbed through the skin and absorption can occur in the absence of irritation. Precautions should be taken to minimise skin exposure to the chemical.

EXPOSURE STANDARDS

Australian Exposure Standard: 25 ppm (12/mg/m^3) TWA with 'skin' notation.

The 'skin' notation indicates that absorption through the skin may be a significant source of exposure.

ENGINEERING CONTROLS

Ensure that the process is enclosed or that ventilation is provided to maintain atmospheric concentrations below the exposure standard. Use local exhaust ventilation.

Engineering controls should be designed so that splashing and vapour and aerosol generation are avoided.

PERSONAL PROTECTION

Wear overalls, chemical goggles or safety spectacles with sideshields, and butyl or nitrile gloves. Where atmospheric concentrations may exceed the exposure standard, for example, during the cleanup of spills, wear an organic vapour respirator. Ensure that all personal protective equipment complies with the relevant Australian Standards. Wash contaminated clothing or equipment before re-use or storage. Ensure good personal hygiene.

FLAMMABILITY

Combustible liquid.

Safe handling information

STORAGE AND TRANSPORT
Correct Shipping Name: Combustible liquid

Identification Number: NA 1993

Packaging Group: III

Classified as a C1 (Combustible Liquid) for the purpose of storage and handling, in accordance with AS1940.

Store in a cool, well-ventilated area. Keep away from strong oxidising agents and strong caustics. Keep containers closed at all times and check regularly for leaks.

SPILLS
Increase ventilation. Shut off all possible ignition sources. Wear the appropriate personal protective equipment to prevent exposure. Contain the spill, clean up using an absorbent (soil, sand, vermiculite) and collect in labelled drums for disposal. Flush the contaminated area with water to drain.

DISPOSAL
Dispose of by incineration, recycling or removal by a licensed reclaimer. The relevant State Land Waste Management Authority should be consulted. Should not be disposed of to landfill.

FIRE/EXPLOSION HAZARD
Combustible liquid. On burning, will liberate toxic fumes of carbon monoxide and carbon dioxide. Cool containers with water-spray. To fight fires, use water-fog, dry chemical or carbon dioxide extinguishers. Firefighters should wear self-contained breathing apparatus if risk of exposure to vapours or combustion products.

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Environmental Impact

Readily biodegradable. Unlikely to accumulate in aquatic organisms.

Aquatic Toxicity

24h LC_{50} (goldfish): 1650 mg/L; 24h LC_{50} (brine shrimp): 1000 mg/L

4d LC_{50} (white shrimp): 130 mg/L; 4d LC_{50} (oyster): 90 mg/L

7d LC_{50} (guppy): 983 mg/L.

Other information

TOXICITY

Oral LD_{50}: male rat 560-3000 mg/kg, female rat 530-2800 mg/kg.

Dermal LD_{50}: rabbit 100-610 mg/kg, guinea-pig 210->2000 mg/kg.

Inhalational LC_{50}: rat 450-490 ppm/4h

Death in acute studies was generally caused by narcosis or respiratory failure, with kidney failure seen as a secondary cause.

The main toxic effect observed in acute and repeated-dose animal studies is haemolysis. The effect varies considerably between species, with rats and mice the most susceptible, rabbits less susceptible, and humans and guinea pigs least susceptible. In animals, the haemolytic effects are transient at low levels in repeated exposure studies.

In reproductive toxicity studies in animals, adverse effects are only observed at or above doses which are severely toxic to the adults. No evidence of teratogenicity has been observed.

In vitro genotoxicity studies indicate that 2-butoxyethanol is probably not genotoxic. No information is available on carcinogenicity.

Contact point

Contact name	Telephone number
Position title	
Address	
State Postcode Country	

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Glossary

abraded skin	Skin that has been scraped or roughened.
acidosis in excessive	A disturbance in the acid-base balance of the body which there is an accumulation of acids or an loss of bicarbonate in the blood and body tissues.
anaemia number or both.	A condition in which there is reduction in the of circulating red blood cells, or in haemoglobin,
antigen antibodies.	A substance which induces the formation of
atrophy tissue, organ	A wasting away, or reduction in size of a cell, or part.
BEI related to the agent its	Biological exposure index, a reference value evaluation of worker exposure to a substance or through measurement of the substance or agent or metabolite(s) in tissue, fluids or exhaled air.
bunded spills.	Embanked, for example, to prevent the spread of
cytotoxic	Cell destroying.
depot effect example, in	Temporary storage of absorbed material, for the skin.
dermatitis	Inflammation of the skin.
EC_{50} an effect unexposed	The concentration of a substance in water that has on 50% of exposed organisms, relative to controls.

embryotoxic	Toxic to the developing embryo (2 to 8 weeks).
epididymis	A small oblong body along the posterior border of the testis, consisting of a convoluted tube which provides for the storage, transit and maturation of spermatozoa.
erythema	Redness of the skin which may result from a variety of causes.
erythrocyte	A mature red blood cell or corpuscle.
eschar	A hard crust or scab on the skin.
foetotoxic	Toxic to the foetus.
gavage	Forced feeding through a tube passed into the stomach.
genotoxic	Toxic to cellular genetic material such as DNA.
haematocrit	The volume percentage of red blood cells in whole blood.
haematological	Pertaining to the blood.
haematotoxic	Poisonous to the blood and haematopoietic system
haemoglobin	The iron-containing pigment of the red blood cells.
haemoglobinuria	The presence of free haemoglobin in the urine.
haemolysis	The separation of haemoglobin from red blood cells and its diffusion into the plasma.
hepatic	Pertaining to the liver.
hydrolysis	Chemical decomposition in which a substance is split into simpler compounds by the addition of water.
hydrophilic	Having a strong tendency to bind or absorb water.
hydrophobic	Incapable of dissolving in water.
hypokalaemia	Abnormally low potassium concentration in the blood.

hypotension	Abnormally low blood pressure.
in vitro study for	A test conducted outside the body of the organism,
	example, with cell cultures.
in vivo study experimental	A test carried out within the living body of an animal.
intraperitoneal	Within the peritoneal cavity of the body.
LC_{50} death in It is	The concentration of a substance that will produce 50% of a population of test animals or organisms.
	used for estimating the acute lethality of chemicals
to	aquatic organisms or of airborne chemicals to
terrestrial	animals.
LD_{50} death in	The single dose of a substance that can produce
	50% of test animals.
leucocyte	White blood cell.
lymphocyte	A type of leucocyte.
manifold system outlets.	A system of pipes with a number of inlets and
metabolic acidosis in	A disturbance in the acid-base balance of the body
	which there is an accumulation of acids due to loss
of base	or retention of noncarbonic or fixed (non-volatile)
acids.	
mitogen transformation,	A substance that induces mitosis and cell
	especially lymphocyte transformation.
morphology organisms.	The science of the forms and structures of
narcosis system	Depression of function of the central nervous

	marked by stupor or unconsciousness.
necropsy of a	The examination of the organs of and body tissues
	dead animal to determine the cause of death or
	pathological condition.
necrosis healthy	Death of areas of tissue or bone surrounded by
	parts.
nephrosis changes in inflammation.	Kidney condition characterised by degenerative the renal tubules without the occurrence of
nystagmus eyeball.	A constant, involuntary, rapid movement of the
occlusive maximise the	Covered with a closely fitting dressing to
relation to	retention and absorption of the test substance (in dermal studies).
oedema	Swelling.
osmotic fragility when	The susceptibility of erythrocytes to haemolysis
	exposed to increasing hypotonic saline solutions.
ossification	The formation of bone or of a bony substance.
oxaluria (also known	An excess in excretion of oxalates in the urine as hyperoxaluria).
perineal anus and the	Pertaining to the area of the body between the scrotum or vulva.
photolysis	Chemical decomposition by the action of light.
Poisons Schedule *Drugs and*	The *Standard for the Uniform Scheduling of*
	Poisons, or SUSDP.
QSAR relates to a	Quantitative Structure Activity Relationship
	method used to predict the physical properties of a

	chemical and specific biological effects, using known information on structurally related chemicals.
renal	Pertaining to the kidney.
reticulocyte	A young red blood cell.
S9 fraction	An enzyme preparation used in *in vitro* genotoxicity testing for the purpose of determining whether the test substance requires metabolic activation to exert its effect.
sister chromatid exchange (SCE)	The reciprocal exchange of DNA between two sister chromatids of a duplicating chromosome.
sickle cell disease	Refers to sickle cell anaemia, a hereditary disease in which abnormal crescent shaped red blood cells, and an abnormal type of haemoglobin, haemoglobin S, are present.
spherocytosis	The presence of spherical red blood cells in the blood.
surfactants	Surface-active chemicals used in a wide variety of chemical products, especially cleaning agents.
teratogenic	Causing permanent structural or functional abnormalities in offspring during the period of embryonic development.