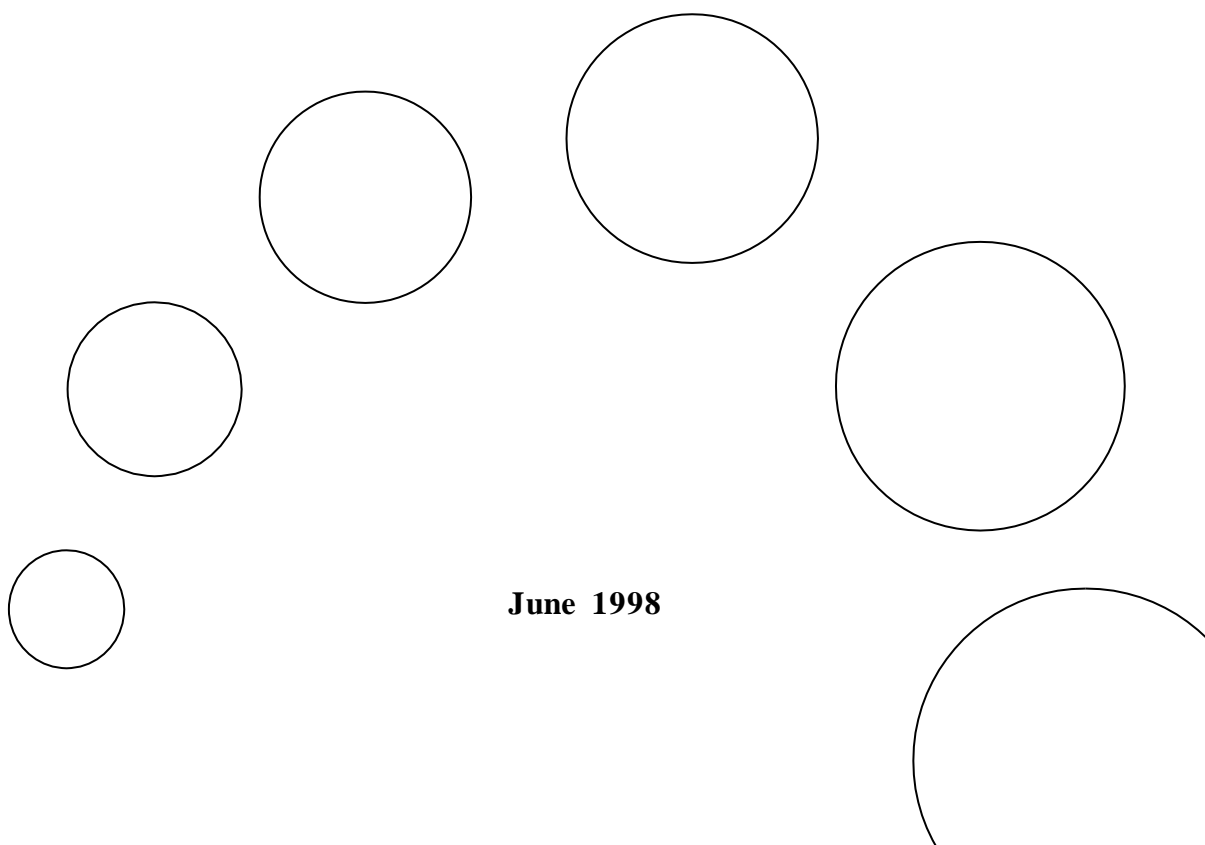**NICNAS**

National Industrial Chemicals Notification and Assessment Scheme

1,4-Dioxane
Priority Existing Chemical No. 7

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Full Public Report

June 1998

Preface

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

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

NICNAS is administered by the National Occupational Health and Safety Commission (NOHSC) and assessments are carried out in conjunction with Environment Australia (EA) and the Therapeutic Goods Administration (TGA), who carry out the environmental and public health assessments, respectively. NICNAS has two major programs: one focusing on the risks associated with new chemicals prior to importation or manufacture; and the other focussing on existing chemicals already in use in Australia.

As there are many thousands of existing industrial chemicals in use in Australia, NICNAS has an established mechanism for prioritising and declaring chemicals as Priority Existing Chemicals (PECs).

This Full Public PEC report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with the Act. Under Sections 60D and 60E of the Act, applicants were provided with a draft copy of the report for correction of errors and variation of content (for a period of 56 days). Concurrently, the report was also available to the public for variation of content (as notified in the March 1998 edition of the *Commonwealth Chemical Gazette*) for a period of 28 days. No requests for variation were received and a final report was prepared according to Section 60F of the Act. During all stages of preparation, the report has been subject to internal peer review by NICNAS, EA and TGA. This report was also peer reviewed by the Netherlands National Institute of Public Health and Environmental Protection (RIVM), as part of its collaborative work with Australia on 1,4-dioxane in the OECD 'Existing Chemicals Program'.

In accordance with Section 62 of the Act, publication of this report revokes the declaration of 1,4-dioxane as a PEC. However, under Section 64(2) of the Act, an introducer of 1,4-dioxane must inform the Director of any circumstances that may require a further assessment of risks to human health and the environment. For further details refer to Section 14 (Secondary Notification) in this report.

For the purposes of Section 78(1) of the Act, copies of Full Public Reports for New and Existing Chemical assessments may be inspected by the public at the Library, Worksafe Australia, 92-94 Parramatta Road, Camperdown, Sydney, NSW 2050 (between 10 am and 12 noon and 2 pm and 4 pm each weekday). Summary Reports are published in the *Commonwealth Chemical Gazette*, which is also available to the public at the above address.

Copies of this and other PEC reports can be purchased from NICNAS either by using the prescribed application form at Appendix 4 of this report, or directly from the following address.

92 Parramatta Road
CAMPERDOWN
NSW 2050
AUSTRALIA

Tel: +61 2 9577 9437
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Further information, available on request (Tel: +61 2 9577 9578) include:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on PEC and New Chemical assessment programs;
- application forms for New Chemical and PEC assessments;
- subscription details for the *Commonwealth Chemical Gazette*; and
- subscription details for the NICNAS *Handbook for Notifiers*.

PEC and New Chemical Summary Reports together with other information on NICNAS activities can be found on the NOHSC Web site [**http://www.worksafe.gov.au**].

Overview

Assessment findings

1,4-Dioxane (CAS No. 123-91-1) was declared a Priority Existing Chemical on 3rd May 1994 due to concerns over possible human carcinogenicity, its potential for widespread occupational and public exposure and high degree of partitioning to, and persistence in, the aquatic environment.

In Australia, 1,4-dioxane is used as a solvent in chemical synthesis, research and analysis (mainly laboratory applications) and in adhesive products used in celluloid film processing. During the period this assessment was underway, 1,4-dioxane was also used in optical lens manufacture as a surface coating agent. Until 1st January 1996, 1,4-dioxane was used in large quantities as a stabiliser in 1,1,1-trichloroethane. 1,4-Dioxane is also produced in trace amounts as an unwanted by-product in the manufacture of ethoxylated chemicals, in particular, surfactants.

Occupational and environmental exposure may occur from any of the above sources, as well as during formulation and use of ethoxylated chemicals. Exposure to the general public may occur from use of consumer products containing ethoxylated chemicals (e.g., detergents, cosmetics/toiletries, pharmaceuticals and food products) containing 1,4-dioxane as an impurity, in addition to its reported natural occurrence in certain foods.

1,4-Dioxane is absorbed by inhalation, dermal and oral routes. Metabolism in rats and humans appears to be similar, with the vast majority of the dose being rapidly excreted in urine as β-hydroxyethoxyacetic acid (HEAA) and small amounts of unchanged 1,4-dioxane being eliminated in urine and expired air. Evidence from animal studies indicates that metabolism may involve cytochrome P-450 and that saturation occurs at high doses, as indicated by an increase in unmetabolised 1,4-dioxane and a change in elimination kinetics. There is also some evidence to suggest that metabolic saturation is associated with toxicity, particularly hepatotoxicity. In animals, 1,4-dioxane is distributed to liver, kidney, spleen, lung, colon and skeletal muscle, with evidence of selective uptake by liver and kidney.

1,4-Dioxane exhibits low acute toxicity, but has been shown to cause irritation of eyes and respiratory tract in humans and animals. Short-term exposure to high levels of 1,4-dioxane is associated with severe kidney and liver damage in animals and humans. A number of human fatalities have been reported in the literature from occupational exposure (combined inhalation and skin contact) to high levels of 1,4-dioxane. The cause of death in all cases was reported as kidney failure (haemorrhagic nephritis). Liver necrosis and CNS nerve fibre damage were also reported at autopsy.

Chronic effects seen in animals include lesions (neoplastic and non-neoplastic) in kidney, liver, nose, testes, lung and spleen. The critical organ for adverse effects in chronic animal studies is the liver, where effects include hepatocyte degeneration, hyperplasia, adenoma, carcinoma and cholangioma (bile duct tumour). The chronic no observed adverse effect levels (NOAELs) in rats are 111 ppm (105 mg/kg/d) for inhalation and 10-40 mg/kg/d for oral exposure to 1,4-dioxane. A reliable NOAEL for chronic dermal effects has not been determined.

Effects from long term exposure to 1,4-dioxane in humans are not well characterised. Several epidemiological studies have been carried out in workers potentially exposed to 1,4-dioxane, with one study (comparative mortality study) indicating a significant increase in liver cancer, although potential exposure to other hepatotoxic chemicals, including alcohol, were confounding factors.

Based on the assessment of health effects, 1,4-dioxane should be classified in accordance with the NOHSC *Approved Criteria for Classifying Workplace Hazardous Substances* (NOHSC, 1994a), as 'Irritating to eyes and respiratory system' (risk phrase 36/37) and 'Carcinogen Category 3' (risk phrase R40), which is in accord with the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1994b). In accordance with the *Australian Code for the Transport of Dangerous Good by Road and Rail* (FORS, 1998), 1,4-dioxane meets the criteria for assignment to 'Class 3 (Flammable Liquid) - packaging group II'.

The **occupational risk assessment** concluded that, for known Australian work situations, potential atmospheric concentrations of 1,4-dioxane are unlikely to reach levels likely to cause acute effects, including eye or respiratory irritation. In addition, it is unlikely that workers in these occupations will be at risk from chronic adverse health effects related to 1,4-dioxane exposure, as margins of safety/exposure are generally high for inhalation and/or dermal exposure. In the absence of any monitoring data for workers involved in optical lens manufacture and the potential for inhalation exposure during the coating process, estimates for 1,4-dioxane exposure were obtained using the UK EASE model. Results from this modelling indicate a potential risk for exposed workers.

The **public health risk assessment** concluded that the main potential source of exposure to the general public is from exposure to consumer products containing 1,4-dioxane as an impurity. No analytical data were available on levels of 1,4-dioxane in consumer products in Australia, however levels were estimated from data on surfactant composition submitted by applicants and notifiers. A so-called 'worst case scenario' for daily intake (inhalation and dermal exposure) for 1,4-dioxane from consumer products (not including pharmaceuticals or food products) was calculated at around 7µg/kg based on an assumed level of 30 ppm 1,4-dioxane in end-use products. This represents a margin of safety of >1000 (with respect to the chronic animal (oral) NOAEL) and therefore 1,4-dioxane was not considered to pose a significant health risk to the general public.

The **environmental risk assessment** indicates that the majority of 1,4-dioxane used, and produced as by-product in Australia, will be released to sewer. 1,4-Dioxane released to soil is likely to leach to groundwater. Fugacity modelling (US EPA 1996a) predicts a partitioning of 91% to water and 9% to air. Rapid degradation (half-life < 7 hours) of 1,4-dioxane is expected in the atmosphere, whereas biodegradation and photooxidation half-lives in surface and ground waters were estimated at between 1 month and several years. 1,4-Dioxane was classified as practically non-toxic to aquatic organisms and on account of its high hydrophilicity and partition coefficient (log P_{ow}), the potential for bioaccumulation was considered negligible. Worst case scenarios for PEC/PNEC ratios for local and continental compartments suggest that 1,4-dioxane does not present a significant risk of adverse effects to the Australian aquatic environment. Similarly, 1,4-dioxane is considered unlikely to contribute to global warming or ozone depletion.

Recommendations

Recommendations for reducing potential occupational health and safety risks for 1,4-dioxane include: a revision of MSDS and labels in accordance with NOHSC requirements; specific workplace control measures for uses identified in Australia; and a review of the NOHSC exposure standard. In addition, an air monitoring survey is recommended to characterise 1,4-dioxane exposure to any workers potentially exposed during optical lens coating.

In the protection of public health, it is recommended that levels of 1,4-dioxane in consumer products be limited to 100 ppm. It was considered that the current poison schedule (SUSDP) classification, first aid instructions and safety directions for 1,4-dioxane are appropriate. With respect to the presence of 1,4-dioxane in pharmaceuticals and food, it is recommended that this report be forwarded to the Drug Safety Evaluation Branch of the Therapeutic Goods Administration (TGA) and the Australia and New Zealand Food Authority (ANZFA) for their information.

The usage and emissions of 1,4-dioxane are so low in Australia that risks for the environment were assessed as negligible and as such no specific recommendations are made.

Data gaps identified in this assessment report include: an animal skin irritation study carried out according to recognised guidelines and adequate data on fertility hazards. Further characterisation of the metabolic saturation level in humans and its relationship to cytotoxicity and other cellular perturbations would also permit further refinement of health risk estimates and the occupational atmospheric exposure standard. Despite efforts by industry to reduce the quantity of 1,4-dioxane impurities in ethoxylated chemicals, there is a paucity of data on levels in end-use products in the public domain in Australia.

CONTENTS

Abbreviations and Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ANZFA	Australia and New Zealand Food Authority
ADG	Australian Dangerous Goods
AUC	area under the curve (pharmacokinetic parameter)
ASTER	Assessment Tools for the Evaluation of Risk database
BCEE	bis(2-chloroethyl)ether
CAS	Chemical Abstracts Service
CHO	chinese hamster ovary
CNS	central nervous system
DEN	diethylnitrosamine
DMBA	7,12-dimethylbenz[a]anthracene
EASE	Estimation and Assessment of Substances Exposure
EC	European Commission
EHD	estimated human dose
EINECS	European Inventory of Existing Commercial Chemical Substances
EA	Environment Australia
EU	European Union
FID	flame ionisation detector
FTIR	Fourier-transform infrared spectrometry
GC	gas chromatography
GGT	gamma glutamyl transpeptidase or gamma-glutamyl transferase
GJIC	gap junction intercellular communication
HEAA	β-hydroxyethoxyacetic acid
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
IARC	International Agency for Research on Cancer
IUPAC	International Union for Pure and Applied Chemistry
i.p.	intraperitoneal
i.v.	intravenous
LD	lethal dose
LOAEL	lowest observed adverse effect level
MLD	minimum lethal dose

MOS	margin of safety
MS	mass spectrometry
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no observed adverse effect level
NOHSC	National Occupational Health and Safety Commission
PBPK	physiologically-based pharmacokinetic
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
RDS	replicative DNA synthesis
RTECS	Registry of Toxic Effects of Chemical Substances
S. typh	*Salmonella typhimurium*
SAR	structure activity relationship
SCBA	self contained breathing apparatus
SCE	sister chromatid exchange
SIDS	Screening Information Data Set
SLRL	sex-linked recessive lethal
SPIR	standardised proportionate incidence ratio
STEL	short term exposure limit
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TLC	thin layer chromatography
TPA	12-O-tetradecanoylphorbol-13-acetate
TWA	time weighted average
UDS	unscheduled DNA synthesis
UN	United Nations
US EPA	United States Environmental Protection Agency
USP	US Pharmacopoeia

1. Introduction

1.1   Declaration

The chemical 1,4-dioxane (CAS No. 123-91-1) was declared a Priority Existing Chemical (PEC) under the *Industrial Chemicals (Notification and Assessment) Act 1989* on 3 May 1994. The reasons for declaration were the potential for widespread occupational and public exposure to the chemical in Australia and its known adverse health effects, in particular, possible carcinogenic effects.

Because of its use as a solvent in a diversity of applications and its presence as an impurity in certain consumer products (e.g., cosmetic and detergent products), a need was recognised for further characterisation of exposure and associated health and environmental risks.

1.2   Background

Historically, large quantities of 1,4-dioxane have been used as a stabiliser in chlorinated solvents, particularly, 1,1,1-trichloroethane. However this use has declined substantially in countries that are phasing out the use of 1,1,1-trichloroethane under the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer, of which Australia is a signatory.

In Australia 1,4-dioxane is an important laboratory reagent used in research, development and analysis and has solvent applications in the film processing and optical lens[1] manufacturing industries. In addition to these deliberate uses of the chemical, 1,4-dioxane is present as a by-product in other chemicals, notably substances manufactured utilising ethoxylation reactions (e.g., surfactants). Surfactants and emulsifiers containing 1,4-dioxane are used in cosmetic, detergent and food products. The assessment of food contaminants comes under the auspices of the Australia and New Zealand Food Authority (ANZFA).

1,4-dioxane is also used in Australia as a solvent/reagent in the manufacture of pharmaceutical products, the assessment of which comes under the auspices of the Therapeutic Goods Administration (TGA).

1.3   Objectives

The objectives of this assessment were to:

- critically review the acute and chronic animal data, particularly data of relevance to carcinogenicity;
- characterise the potential hazards of 1,4-dioxane to human health and the environment;
- characterise the risk of adverse effects resulting from exposure to workers, the general public and the environment; and

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[1] Use of 1,4-dioxane as an ingredient in optical lens coatings has been discontinued by one company (notifier) since the commencement of this assessment report. It is not known whether other companies are using 1,4-dioxane-based formulations for this purpose in Australia.

- make appropriate recommendations to control exposures and/or reduce potential health and environmental risks.

1.4   Scope of the assessment

This report presents a summary and evaluation of information relevant to the assessment of the potential health and environmental hazards from 1,4-dioxane exposure.

Pertinent toxicological data were located through a comprehensive literature survey. Due to the availability of several overseas assessment reports, not all primary sources of data were evaluated, except in the areas of carcinogenicity, genotoxicity, human health, and Australian exposure information. However, relevant studies published since the cited reviews were assessed.

Unpublished toxicological studies were made available by applicants and OECD SIDS member countries (see Section 1.5 below). Information on use, product specifications and occupational/consumer exposure, made available by PEC applicants, in addition to information obtained from workplace site visits undertaken by NICNAS, was used as the basis for characterisation of health and environmental risks in Australia.

1.5   International collaboration

As part of its contribution to the OECD Existing Chemicals Program, Australia, in conjunction with the Netherlands, has sponsored 1,4-dioxane under the Screening Information Data Set (SIDS) program. The first draft of the SIDS Initial Assessment Report (SIAR) was discussed at the 7th SIDS Initial Assessment Meeting (SIAM7), which was hosted in Sydney by NICNAS on March 25-27, 1998.

Contributing NICNAS assessments to international chemical assessment programs not only helps towards the global assessment of existing chemicals but also improves access to overseas chemical assessments. This not only allows for the development of harmonised approaches to hazard and risk assessments, but also promotes sharing, rather than duplication, of assessment work.

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3. Chemical Identity

3.1 Chemical name (IUPAC)

1,4-Dioxane

3.2 Registry numbers

1,4-Dioxane is listed on the Australian Inventory of Chemical Substances (AICS).

CAS number	123-91-1
EINECS number	204-661-8
EC number	603-024-00-5
RTECS number	JG8225000

3.3 Other names

Diethylene dioxide

Diethylene-1,4-dioxide

1,4-Diethylene dioxide

Diethylene ether

Diethylene oxide

1,4-Dioxacyclohexane 1,4-

Dioxam

Dioxan

Dioxane

p-

Dioxane

para-Dioxane

Dioxyethylene ether

Glycol ethylene ether

Tetrahydro-*para*-dioxin

3.4 Trade names

1,4-Dioxan

NE 220

3.5 Molecular formula

$C_4H_8O_2$
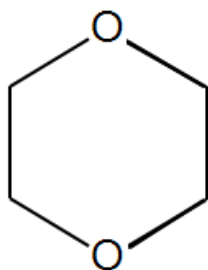
3.7 Molecular weight

88.12

3.8 Composition of commercial grade product

Composition of typical industrial product (Santodonato et al, 1985; GDCH, 1991):

1,4-Dioxane	99.8% (min)
2-Ethyl-1,3-dioxolane	0.1% max (1000 ppm)
2-Methyl-1,3-dioxolane	0.03% max (300 ppm)
Water	0.015% max (150 ppm)
Acidity (as acetic acid)	0.01% max (100 ppm)
Peroxides (as hydrogen peroxide)	50 mg/kg max (50 ppm)
Non-volatile matter	0.0025% (25 ppm)

Other impurities reported (HSDB, 1996; GDCH, 1991, Perone et al., 1976) for different grades/sources of product include:

- Bis (2-chloroethyl) ether (starting product)
- Hydroquinone (stabiliser)
- 2,6-Di-tert-butyl-*p*-cresol (stabiliser)
- Acetaldehyde
- Crotonaldehyde
- Paraldehyde
- Glycidol
- Ethylene diformate
- Methyl diformate
- Iron
- Lead

4. Physical and Chemical Properties

4.1 Physical state

1,4-Dioxane is a colourless liquid with a mild ethereal odour. The odour threshold has been reported to be between 6.5 mg/m^3 (Lundberg, 1992) and 9.8 mg/m^3 (NIOSH, 1977).

Conversion factors (at 25°C):

1 mg/m^3 = 0.28 ppm *and* 1 ppm = 3.60 mg/m^3

4.2 Physical properties

Table 1 - Physical properties

Property	Value	Reference
Boiling point	101.1°C (@ 760 mm Hg)	GDCH (1991)
Melting point	11.8°C	Sax (1988)
Density	1.034 kg/L (@ 20°C)	IUCLID (1995)
Specific gravity	1.036 (@ 20°C)	Santodonato et al. (1985)
Viscosity	1.31 centipoise (@ 20°C)	Santodonato et al. (1985)
Vapour density	3.0 (relative to air =1)	GDCH (1991)
Vapour pressure	3.9 kPa (@ 20°C)	NIOSH (1994)
	4.9 kPa (@ 25°C)	Lundberg (1992)
Evaporation rate	7.3 (relative to diethyl ether = 1)	GDCH (1991)
Latent heat of vaporisation	98.6 cal/g	Sax (1988)
Henry's law constant	2.8 x 10^{-6} atm/m^3/mol	US EPA (1996a)
Partition coefficient (Log Kow)	- 0.27 to - 0.49	Howard (1990) US EPA (1996a)
Adsorption coefficient (Log Koc)	1.07	US EPA (1996a)
Autoignition temperature	180°C (356°F)	Sax (1988)
Flash point	Closed cup: 12°C (54°F) Open cup: 23°C (73°F)	ECETOC (1983)
Explosive limits	Lower limit: 2% v/v Upper limit: 22% v/v	Sax (1988)

4.3   Reactivity and stability

4.3.1   Solubility

Infinitely soluble in water and most organic solvents.

4.3.2   Azeotropic mixtures

1,4-Dioxane forms azeotropes with water and a number of other organic compounds (EEC, 1988). Table 2 lists some binary azeotropes of 1,4-dioxane.

Table 2 - Examples of binary azeotropes of 1,4-dioxane

% 1,4-Dioxane (w/w)	Second component	% Second component (w/w)	Boiling point of mixture (°C)
82	Water	18	87.8
44	Heptane	56	91.8
45	n-Propyl alcohol	55	95.3

4.3.3   Hydrolysis

There are no readily hydrolysable groups.

4.3.4   Flammability

Highly flammable (NOHSC, 1994b).

Combustion products

Toxic gases and vapours may be released during combustion of 1,4-dioxane.

4.3.5   Reactivity

Polymerisation

Does not polymerise.

Explosivity

1,4-Dioxane is hygroscopic and reacts with water (in the presence of air) to form explosive peroxides (NOHSC, 1994b).

The following substances form explosive mixtures with 1,4-dioxane:
- hydrogen and hot Raney nickel
- silver perchlorate
- sulphur trioxide
- nitromethane
- boron trifluoride
- decaborane

5. Methods of detection and analysis

5.1 Identification

Infrared, Raman, ultraviolet, nuclear magnetic resonance (NMR) and mass spectrometry have been used for the identification of 1,4-dioxane (EEC, 1988).

5.2 Analysis in air

Sampling from air for 1,4-dioxane via charcoal tube is described in NIOSH method 1602 (NIOSH, 1994). An air flow rate of 0.01 to 0.2 L/min and sample size of 0.5 to 15L are recommended. A survey of the quality and reproducibility of sampling and analysis by this method was carried out by Larkin et al. (1977). For personal monitoring, diffusion charcoal badges have also been used (Baker, 1982).

The NIOSH method for analysis of 1,4-dioxane (NIOSH, 1994) uses gas chromatography (GC) with a flame ionisation detector (FID) after desorption from charcoal with CS_2. Using a 10L air sample, the method is applicable for concentrations of 1,4-dioxane in the range 5 to 190 ppm (20 to 700 mg/m^3). Alternative methods using GC/mass spectrometry (MS) (Cooper et al., 1971) or Fourier-transform infrared spectrometry (FTIR) have been used for identification and quantitative analysis (Baker, 1982; Ying & Levine, 1989).

5.3 Analysis in water and soil

Epstein et al. (1987) compared two methods for analysis of 1,4-dioxane in water. Analysis by charcoal tube enrichment GC/FID provided a lower limit of detection than a GC/MS purge and trap method incorporating a salting out stage, but the latter gave greater precision and a positive identification. Both methods provided a detection limit of around 2 ppb. The GC/MS purge and trap method was also found to be applicable to soil and sediment. GC/MS methods for analysis in water have also been reported by other authors (Kadokami et al., 1990; Priddle et al., 1992; Lesage et al., 1990). A further discussion of the analysis of 1,4-dioxane in water can be found in BUA Report 80 (GDCH, 1991).

5.4 Analysis in raw materials and consumer products

1.4-Dioxane has been analysed as a by-product in a variety of industrial raw materials and consumer products, including cosmetics. Preferred methods vary according to other ingredients present.

Headspace GC has been used for surfactants and shampoos (Dahlgran & Shingleton, 1987; US EPA, 1989a), with characterisation by MS where necessary (Rusenapp & Hild, 1987). A packed column GC method has also been used for shampoos, giving good recovery and reproducibility and linear results over the range 1 to 250 ppm 1,4-dioxane (Italia & Nunes, 1991). Use of GC/MS selected-ion monitoring (Hartung, 1989) and vacuum distillation/GC (Daniels et al., 1981) has also been reported.

Solid phase extraction with reverse phase high performance liquid chromatography (HPLC) has been used successfully on a wide range of cosmetics (Scalia & Menegatti, 1991). 1,4-Dioxane has also been assayed in varying types of cosmetic products using solid phase extraction followed by GC/MS selected-ion monitoring (Scalia, 1992). This method is claimed to have good sensitivity and to be both rapid and specific.

1,4-Dioxane has been analysed in ethylene oxide by extractive distillation/GC, and in various ethylene glycols by GC using on column injection (US EPA, 1989a). Methods reported in the Food Chemicals Codex (Committee on Food Chemicals Codex, 1996) and the US Pharmacopoeia (US Pharmacopoeia and National Formulary, 1995) use vacuum distillation with GC/FID.

5.5 Biological monitoring

Qualitative identification of 1,4-dioxane in expired air and body fluids was performed using IR (Erley & Stewart, 1963). A method for the simultaneous determination of 1,4-dioxane and its major metabolite, β-hydroxyethoxyacetic acid (HEAA), in plasma and urine by GC/MS selected ion monitoring has been described by Braun (1977). The detection limit for 1,4-dioxane in plasma and urine was 0.07 ppm, while for HEAA it was 0.5 ppm in plasma and 0.1 ppm in urine. Screening and quantification of volatile organic compounds (including 1,4-dioxane) in biological fluids has also been carried out by headspace GC with split flame ionisation electron capture (Streete et al., 1992).

A recent paper (Groves et al., 1997) describes work on an instrument for identification and quantification of organic vapours (including 1,4-dioxane) in exhaled air. The instrument employs an array of polymer-coated surface-acoustic-wave (SAW) sensors and a thermally desorbable adsorbent preconcentrator.

6. Manufacture, importation and use

6.1 Manufacture and importation

6.1.1 Manufacture of 1,4-dioxane

1,4-Dioxane manufacture does not occur in Australia, but is reported in Europe, USA and Japan. World-wide production figures were reported to be 10,000 - 20,000 tonnes/yr in 1991 and 8,000 - 10,000 tonnes/yr in 1994 (BASF, 1996). Reasons for the decline in consumption include the decreasing use of chlorinated hydrocarbons (containing 1,4-dioxane as stabiliser) and an increasing trend to recover the solvent in its use in the pharmaceutical industry (GDCH, 1991).

6.1.2 Importation of 1,4-dioxane

The major source of 1,4-dioxane in Australia has been importation of the pure material, and products and mixtures containing it as an ingredient.

Currently, only small quantities of 1,4-dioxane are being imported, mainly for laboratory and research uses (< 1000 kg per year).

Until recently, the largest volume of 1,4-dioxane (>20 tonnes/yr) was imported as a stabiliser in 1,1,1-trichloroethane, but this use has now been phased out as importation of 1,1,1-trichloroethane ceased (excluding certain 'small volume' products and essential uses) in December 1995 under the *Ozone Protection Act (1989)*.

6.1.3 Manufacture and importation of products containing 1,4-dioxane as an impurity

1,4-Dioxane is formed in trace quantities as an unintentional by-product (impurity) during the manufacture of other chemicals in Australia. A major source is the production of ethoxylated anionic and non-ionic surfactants, which is estimated to result in the formation of around 2 tonnes 1,4-dioxane per year.

1,4-Dioxane is also known to be present in trace levels as an impurity (residue or by-product) in certain imported chemicals, mainly ethoxylates, in both raw material and end-use products. Information on total quantities is not available, however, it is estimated that at least 500 kg per year might be introduced via this source.

6.2 Use and occurrence

6.2.1 Laboratory/research use

1,4-Dioxane has a wide range of applications as a laboratory reagent/solvent. The following are among the applications identified in Australia: solvent for chemical synthesis, solvent for organic, inorganic and polymer materials, cleaning solvent, extraction and analysis of plant material, chemical drying of soil samples and

analytical techniques such as chromatography, radiochemical analysis and titrimetry. An estimated 500 kg per year is currently used in such applications, although information made available to NICNAS indicate a likely increase in usage in the future.

6.2.2 Film processing

1,4-Dioxane is currently used as an ingredient (10-50%) in an imported specialist cement product used for gluing (splicing) celluloid film in the film processing industry. It has been estimated that up to 10 film laboratories carry out this type of work in Australia. One laboratory reported a usage of up to 12L of film cement per year.

6.2.3 Optical lens manufacture

Approximately 100L/yr of 1,4-dioxane has been used by at least one Australian lens manufacturer in a specialty anti-scratch coating used to treat plastic optical lenses. Its use for this purpose by one manufacturer (only notifier for this use) has reportedly ceased and substitute chemicals are currently being used in its place.

6.2.4 Pharmaceutical manufacture

1,4-Dioxane is used in the reaction medium during the manufacture of a pharmaceutical (active) material. Approximately 100 kg per year is being used for this purpose by one manufacturer.

6.2.5 Occurrence of 1,4-dioxane as an impurity

1,4-Dioxane can occur as an impurity in other materials, either as a residue or as a by-product. It may be present as a residue if 1,4-dioxane has been used in the reaction medium during manufacture (e.g., manufacture of flame retardant) or as a solvent during purification. It may also be formed as a reaction by-product, particularly in chemicals which are produced by ethoxylation. Not all sources of 1,4-dioxane as a by-product are known. Other possible sources, reported in the literature, have not been confirmed in Australia and include the manufacture of low molecular weight glycols, polyurethane and starches.

Ethoxylated chemicals

1,4-Dioxane can be formed as a by-product during the manufacture of alkoxylated (usually ethoxylated) chemicals, including anionic and non-ionic surfactants. A variety of such chemicals are imported or manufactured in Australia.

Alkyl ether sulphates (anionic surfactants)

1,4-Dioxane can be formed as a by-product in alkyl ether sulphates (AES), of which sodium lauryl ether sulphate is the most commonly used in Australia.

It is estimated that approximately half AES surfactant use in Australia is in domestic and industrial detergents. Another 25-30% is used in personal care products, such as hair and body shampoos, liquid hand washes and shower gels. The remainder is used in special industrial applications such as fire fighting foam, agricultural marker foam, as a plasterboard processing agent and drilling mud additives. Because AES are used in personal care as well as in other domestic products, the presence of 1,4-

dioxane as an impurity, has been a cause for concern. Over the last 15-20 years, levels of 1,4-dioxane in certain products have been reduced (GDCH, 1991) by controlling manufacturing conditions and by 'stripping' (see section 8.3.1). It is reported that in AES manufacture, the sulphation/sulphonation step is the major source of 1,4-dioxane (Milwidsky, 1988).

Quantities of AES used in Australia are estimated at approximately 10,000 tonnes per year, mostly as 28% or 70% aqueous solutions. From information available, this would contain up to 1 tonne 1,4-dioxane.

Australian formulators and end-users have access to grades of AES with varying amounts of 1,4-dioxane. Levels ranging from 10 ppm to 210 ppm have been reported on 100% active material, the lower levels usually reflecting that stripping has occurred. Both stripped and unstripped material may be used in personal care as well as household or industrial products. A shampoo, bath gel or liquid detergent using 15% active material may contain 1-30 ppm 1,4-dioxane, depending on the grade of AES used.

Other ethoxylated substances

Apart from AES surfactants, a variety of other manufactured and imported chemicals which are formed by ethoxylation have the potential to contain traces of 1,4-dioxane as a by-product. They include alkyl, alkylphenol, and fatty amine ethoxylates, polyethylene glycols and their esters, and sorbitan ester ethoxylates. Their uses cover food, cosmetic, agricultural/veterinary, therapeutic, household and varied industrial applications. For example, in cosmetics these materials are used as surfactants, emulsifiers, humectants, solvents, binders, anti-static agents and emollients (EEC, 1996).

Industry have reported that 1,4-dioxane levels in ethoxylated materials used in Australia vary from < 1 ppm to 3000 ppm but in general are lower than those reported for AES. Those for pharmaceutical, personal care and household use are generally reported to contain less than 10 ppm dioxane, although one polyethylene glycol ester was reported to contain 1000 ppm. An amine ethoxylate emulsifier used in agricultural chemical manufacture is apparently 'stripped' from 300 ppm to 10 ppm. Among the highest levels reported are 1000 ppm for an industrial fluorinated ethoxylate and 2000 ppm for alkyl ethoxylate/thionyl chloride used in industrial cleaners.

Total usage of this type of material in Australia is estimated at > 40,000 tonnes per year, accounting for up to 1 tonne of 1,4-dioxane.

Cellulosic polymers

One supplier of cellulosic and cationic cellulosic polymers used in hair and skin care products advised that typical products contained < 3 ppm 1,4-dioxane as a by-product.

Flame retardant

An importer (applicant) of a specialised caulking agent (for use in the construction industry) reported a level of 0.5% (max) 1,4-dioxane as a residue in a component organophosphorus flame retardant. Contamination results from the use of 1,4-dioxane as a solvent during manufacture and it is estimated that around 1 kg/yr 1,4-dioxane will be introduced into Australia via this product.

6.2.6 Other uses

Stabiliser

1,4-Dioxane has been used as a stabiliser for certain chlorinated solvents. This use, mainly as a stabiliser in 1,1,1-trichloroethane, accounted for a major part of 1,4-dioxane usage worldwide, including Australia, prior to the phase-out of 1,1,1-trichloroethane under the Montreal Protocol. In Australia in 1992, at least 30 tonnes of 1,4-dioxane was consumed in 1,1,1-trichloroethane, which was used mainly in degreasing applications.

Despite the phase-out of 1,1,1-trichloroethane under the *Ozone Protection Act (1989)*, some material may still be in use in Australia. Although most imports were banned from January 1996, there are some exempt uses. In addition, products containing 1,1,1-trichloroethane can still be imported, provided they meet certain specifications and existing stocks can still be consumed. However, the remaining uses for 1,1,1-trichloroethane are not expected to be high, and not all grades contain 1,4-dioxane.

Although 1,4-dioxane has been listed as a stabiliser used in trichloroethylene (IARC, 1995) and methylene chloride manufacture (Anderson, 1998), it has not been reported for this use in Australia.

Uses reported in the literature

Historically, solvent applications have constituted the major use for 1,4-dioxane. There are several uses reported for 1,4-dioxane in the literature, however, not all reported uses occur in Australia and some previous uses have been discontinued.

Uses reported in the literature, other than those identified above, include:

- solvent/extraction agent (e.g., for cellulose acetate, cellulose ethers, natural resins, mineral oils, vegetable oils and certain dyes and wood stains);
- solvent in cleaning agents (e.g., degreasing agents);
- reaction medium solvent/intermediate in organic chemical manufacture (e.g., pesticides, plastics);
- ingredient in surface coatings (e.g. pigment coating for magnetic tape, varnishes, lacquers and paints);
- ingredient in adhesives and anti-adhesive agents (e.g., in plastic products);
- wetting and dispersing agent (e.g., in textile/leather and pulp/paper industries);
- ingredient (stabiliser) for chlorinated solvents (e.g., methylene chloride);
- fluxing agent (soldering);
- ingredient in lubricants;
- ingredient in fumigant/deodorant;

- ingredient in cosmetics;

- catalyst/process regulators;

- membrane filter manufacture; and

- biological procedures (e.g., preparation of histological sections for microscopic examination).

Industry sources state that 1,4-dioxane is not currently used as an ingredient in the following applications/industries in Australia:

- textile, clothing and footwear industry;

- paints, varnishes and lacquers;

- electronics industry;

- manufacture of audio or computer magnetic tape; and

- rubber and tyre industries.

6.3   Summary

1,4-Dioxane manufacture does not occur in Australia. Large imports no longer occur due to the phase out of 1,1,1-trichloroethane, for which 1,4-dioxane was added as a stabiliser. Smaller imports still occur for laboratory use and niche industrial applications.

Another source of 1,4-dioxane in Australia is its occurrence as an impurity in certain manufactured and imported chemicals, primarily ethoxylated chemicals. Reported levels vary from <1 ppm to 3000 ppm. Some materials are 'stripped' after manufacture to reduce 1,4-dioxane levels.

7. Environmental Assessment

7.1   Environmental fate and exposure

The information available suggests that the majority of 1,4-dioxane will be released to sewer. Quantities used in laboratory and research use may be disposed of with other laboratory liquid waste, but quantities used by individual laboratories would be small, and release to sewer is the likely outcome.

7.1.1   Releases

The greatest occurrence of 1,4-dioxane in Australia will be as an impurity formed during the manufacture of alkyl ether sulphates (AES) and other ethoxylated substances. It is estimated that up to 2500 kg per annum of 1,4-dioxane may be produced as an impurity. Much of this can be expected to be removed through a 'stripping' process. Figures suggest that over 80% of the chemical present can be removed this way. Not all AES and other ethoxylated substances are subject to stripping, and based on available data, it will be assumed that 1200 kg of the 1,4-dioxane produced as an impurity will be released as stripper condensate.

As indicated by one applicant, typical levels of 1,4-dioxane in the stripper condensate are 300 ppm. This is discharged from the stripper through the normal plant effluent drainage system, where it is diluted by other waste streams, to the site effluent pond. The contents of the pond are discharged to sewer as trade waste. If the stripping process occurs for 200 days per year (for all applicants with this operation), then a total of 6 kg per day of 1,4-dioxane will be released to sewer through the manufacture of AES and other ethoxylated substances.

1,4-Dioxane remaining as a by-product in end use products (a large percentage of which may be used in domestic detergents and personal care products) will also be assumed to be released to sewer along with the surfactants, although this release will be in a far more diffuse way. 1,4-Dioxane may also be present as a surfactant impurity in cosmetics and as such may be discharged into the hydrosphere. Since there has been a sharp drop in the 1,4-dioxane content of cosmetics since 1986, emissions to the environment via this source should decrease.

Emissions of dioxane arising from its use as a stabiliser for 1,1,1-trichloroethane are expected to be very low due to the drop in consumption of 1,1,1-trichloroethane. Emissions to the hydrosphere and to wastewater requiring treatment cannot be quantified.

7.1.2   Aquatic fate

GDCH (1991) makes the claim that a major portion of 1,4-dioxane discharged into the environment gets into the atmosphere directly, partly from its use as a stabiliser for 1,1,1-trichloroethane (although this no longer occurs in Australia). It is further stated that the value for Henry's Law constant is such that, for 1,4-dioxane discharged into surface waters, mass transport from water to air via volatilisation would be expected.

This claim is in direct contrast to a number of other references. The level 1 MacKay fugacity model, as modelled by ASTER (US EPA, 1996a), indicates that at equilibrium, 91% of 1,4-dioxane will partition to water, with 9% partitioning to air. Additionally, Lyman et al. (1982) claim that with a Henry's constant in the range of 10^{-7} - 10^{-5} atm/m^3/mol, the substance volatilises only slowly, and the rate is controlled by slow molecular diffusion through air. Howard (1990) also states that the estimated Henry's constant suggests volatilisation will be slow.

Based upon estimated unacclimated aqueous aerobic biodegradation half-lives, Howard et al. (1991) provides half-lives for 1,4-dioxane in surface water with a range of 1 to 6 months, and ground water with a range of 2 to 12 months. The photooxidation half-life in water is higher with a range from 67 days to over 9 years. This half-life is based upon measured rates for reaction with hydroxyl radicals in water.

There are no hydrolysable groups on this compound and ethers have been classified as generally resistant to hydrolysis. Therefore, 1,4-dioxane would not be expected to hydrolyse significantly.

7.1.3 Atmospheric fate

The level 1 MacKay fugacity model, as modelled by ASTER, indicates that at equilibrium, 9% of 1,4-dioxane will partition to air (US EPA, 1996a).

There are 2 degradation pathways for organic substances in the atmosphere: direct photolysis with UV light and photooxidation through reaction with hydroxyl free radicals or ozone. Studies of direct photolysis of liquid dioxane at 185 nm show the principal products to be formaldehyde, ethylene and glycol monovinyl ether. Since the wavelength of light in the troposphere is greater than 290 nm, photolysis does not occur in the lower atmosphere (GDCH, 1991).

Any 1,4-dioxane which enters the atmosphere is expected to degrade fairly quickly. After 3.4 hours, 50% of dioxane had degraded when in the presence of nitrogen monoxide and subjected to environmental UV radiation (light wavelength greater than 290 nm). A half-life of 6.69 hours was estimated for the reaction of 1,4-dioxane with atmospheric hydroxyl radicals. The expected products of this reaction are aldehydes and ketones (Howard, 1990).

7.1.4 Terrestrial fate

ASTER gives an estimated log soil adsorption coefficient (Koc) of 1.07 (US EPA, 1996a). Compounds with a Koc of this magnitude are considered mobile in soil and this, along with its infinite water solubility, indicates that 1,4-dioxane, when released to soil, could leach to groundwater. 1,4-Dioxane is not expected to bioconcentrate in fish or biodegrade in soil or water (Howard, 1990).

Overseas (Delaware, USA), 1,4-dioxane was found at concentrations ranging from 0.1 to 2.5 ppb in 37% of groundwater samples taken near a landfill site in 1977. Additionally, leachate from the vicinity of two landfills for low-level radioactive waste in Kentucky and New York States contained 1,4-dioxane, although no information is provided about concentrations at the time of sampling. 1,4-Dioxane was detected (below 1 ppm) between 1983 and 1986 in ground water near a landfill at North Bay, Southern Ontario, Canada (GDCH, 1991). In 1982, the highest level of 1,4-dioxane in the groundwater beneath a landfill in Gloucester, Canada, was 500 ppb.

Investigations show that 1,4-dioxane is mobile in soil and can be washed out into groundwater (GDCH, 1991).

7.1.5 Biodegradation and bioaccumulation

1,4-Dioxane has been found to be resistant to biodegradation and has been classified as relatively undegradable and is therefore not expected to biodegrade rapidly in the environment (Howard, 1990; Howard et al., 1991).

GDCH (1991) reviewed several biodegradation tests performed on 1,4-dioxane and concluded that 1,4-dioxane does not undergo biodegradation and is eliminated in part physically from systems simply by stripping.

Results of the biochemical oxygen demand test for this chemical indicate that negligible oxygen is consumed over a 20-day test period. It has also been noted that degradation of the compound was not observed in cultures of sewage microorganisms exposed for 1 year to wastewater treatment plant effluent adjusted to contain 1,4-dioxane at concentrations ranging from 100 to 900 ppm (Klecka & Gonsior, 1986).

In the 1986 MITI (Japan) list, 1,4-dioxane is classified as being a compound that accumulates either not at all or only slightly (GDCH, 1991). On account of its high hydrophilicity and low log P_{ow} (-0.27 to -0.49), the potential for bioaccumulation must be estimated as being extremely slight.

7.1.6 Summary

Due to the very high water solubility, low partition coefficient and vapour pressure of this product, a high level of partitioning to the water compartment would be expected. When released to water, volatilisation of 1,4-dioxane should be very slow, and hydrolysis is not expected. Because of the low estimated soil sorption partition coefficient, any 1,4-dioxane released to soil would be expected to be mobile and potentially leach to groundwater.

1,4-Dioxane is not expected to bioconcentrate in fish but is expected to biodegrade slowly in soil or water. However, 1,4-dioxane entering the atmosphere is expected to degrade fairly quickly due to photooxidation, with half-lives measured as low as 3.4 hours.

7.2 Environmental effects

Toxicity of 1,4-dioxane to aquatic species obtained from a number of sources is summarised in Table 3.

Table 3 - Summary of effects on aquatic organisms

Organism	Test duration	Result (mg/L)	Source
Micro-organisms			
Bacteria (*Pseudomonas putida*)	16 h (cl)	2,700* (nc)	GDCH (1991); Dow (1995)
Cyanobacteria (*Microcystis aeruginosa*)	8 d (cl)	575* (nc)	GDCH (1991)
Protozoa (*Entosiphon sulcatum*)	72 h (cl)	5,340*	GDCH (1991)
Green alga (*Scenedesmus quadricauda*)	8 d (cl)	EC_{50} = 5,600 (nc)	GDCH (1991); Dow (1995)
Invertebrates			
Water flea (*Daphnia magna*)	24 h (op)	EC_{50} = 4,700	GDCH (1991); Dow (1995)
Water flea (*Daphnia magna*)	48 h (s)	EC_{50} = 5,500	US EPA (1996a)
(*Gammarus pseudolimnaeus*)	48 h (f)	EC_{50} = 2,274	Dow (1995)
(*Ceriodaphnia dubia*)	24 h; 48 h	EC_{50} = 299; 163	GDCH (1991); Dow (1995)
(*Ceriodaphnia dubia*)	7 d (chronic)	LOEC = 1250 (nc)	Dow (1995)
(Ceriodaphnia dubia)	7 d (chronic)	NOEC = 625	Dow (1995)
Fish			
Golden orfe (*Leuciscus idus melanotus*)	48 h (s)	LC_{50} = 8,450	GDCH (1991); Dow (1995)
Fathead minnow (*Pimephales promelas*)	32 d (chronic)	NOEC = 145 (m)	GDCH (1991); Dow (1995)
Fathead minnow (*Pimephales promelas*)	96 h (f)	LC_{50} = 9,850	US EPA (1996a)
Sand smelt (*Menidia beryllina*)	96 h (s)	LC_{50} = 6,700 (nc)	GDCH (1991)
Bluegill sunfish (*Lepomis macrochirus*)	96 h (s)	LC_{50} > 10,000 (nc)	GDCH (1991)
Channel catfish (*Ictalurus punctatus*)	96 h (f)	LC_{50} = 6,155	US EPA (1996a)
Rainbow trout (*Oncorhynchus mykiss*)	96 h (f)	LC_{50} = 7,961	US EPA (1996a)

* Values were expressed in the literature as toxic threshold concentrations.
cl = closed system   nc = nominal conc.   op = open system
f = flow through   m = measured conc.   s = static

7.2.1 Summary

Experimental results available in the literature and further toxicity calculations obtained from the ASTER database provided data on both acute and chronic effects of 1,4-dioxane on aquatic species. From the results obtained, 1,4-dioxane can be classified as practically non-toxic to aquatic micro-organisms, plants, invertebrates and fish.

7.3   Environmental risks

Products where 1,4-dioxane exists as an impurity will count for the largest exposure of this chemical to the environment. These products are largely in the public domain, and account for up to 2500 kg of 1,4-dioxane per annum. A further 750 kg per annum may be expected to be released from its use *per se*. As a worst case, it will be assumed that all release of 1,4-dioxane will be to sewer.

A worst case predicted environmental concentration (PEC) can be derived using the following assumptions:

- All 1,4-dioxane used in Australia is released to the environment;

- 100% of release will be via a sewage treatment plant (STP);

- For smaller uses (laboratory/research; film processing and as a solvent in pharmaceutical manufacture) release occurs over 50 days per annum;

- Release to sewer as a result of stripping operations during manufacture of ethoxylated substances will occur on 200 days per annum;

- Release through end use of ethoxylated substances occurs on 300 days of the year;

- 50% of all release during end use, and 100% of release of condensate from stripping operations will be assumed to occur in the Sydney metropolitan area, for which the PEC_{local} is calculated, and is sent through a single STP with an output of 250 ML per day;

These assumptions provide a maximum daily output to a single STP of 15.6 kg per day. With a daily output flow rate of 250 ML, a concentration in the STP of 61.15 µg/L. Assuming a dilution factor of 10:1 in receiving waters, PEC can be expected to be 6.11 µg/L.

This is several orders of magnitude lower than the lowest observed environmental effects concentration (NOEC = 145 mg/L) in a 32 day (chronic) study on Fathead minnow (*Pimephales promelas*). A PEC/PNEC ratio of several orders of magnitude would therefore be predicted, suggesting that 1,4-dioxane does not present a significant risk to the aquatic environment.

The MacKay Level 1 fugacity model predicts that at equilibrium, 9% (292 kg per annum) will partition to the atmosphere. 1,4-Dioxane is unlikely to provide any contribution to global warming or ozone depletion due to this small percentage of release likely to partition to the atmosphere and its relatively short half-life in the atmosphere.

8. Occupational Exposure

Occupational exposure in Australia may result from direct use of 1,4-dioxane or manufacture, formulation and use of products containing it as an ingredient or impurity.

8.1   Methodology for assessing exposure

In the assessment of occupational exposure to chemicals, it is generally necessary to evaluate intake from all potential routes of exposure (i.e., ingestion, inhalation and dermal exposure).

In the case of 1,4-dioxane, ingestion is unlikely from current uses in Australian occupational scenarios. Occupational exposures to 1,4-dioxane in workers overseas has been reported by both inhalation and skin absorption. However, an evaluation of available data (information on use profiles obtained from users and suppliers and from site visits) indicates that for Australian occupational exposure scenarios, inhalation is likely to be the major source of exposure.

This assumption was validated by comparing the theoretical potential daily intake of 1,4-dioxane from inhalation and skin absorption scenarios. In the following calculations, exposure parameters (F and C) were derived from the EASE (Estimation and Assessment of Substances Exposure) model, developed by the UK Health and Safety Executive.

Assuming incidental exposure to 1,4-dioxane, the dermal uptake (D_{sk}) can be calculated using the following formula:

$$D_{sk} = \frac{W \times S \times A \times E \times F}{BW} \quad mg/kg/day$$

where:

W = weight fraction of 1,4-dioxane (i.e., 1 = 100%)

S = skin absorption rate (i.e., 0.3 mg/cm^2/hr) – Appendix 1

A = skin surface area exposed (i.e., hands only = 840 cm^2)

E = exposure duration (i.e., 8 hr/day)

F = skin contact time (i.e., 1% = 0.01)

BW = average body weight of worker (70 kg)

thus:

$$D_{sk} = \frac{1 \times 0.3 \times 840 \times 8 \times 0.01}{70} \quad mg/kg/day$$

$$D_{sk} = 0.29 \text{ mg/kg/day}$$

Such a level of exposure is likely to be a considerable overestimate for potential dermal exposure to liquid 1,4-dioxane in Australian occupational scenarios as the calculation assumes exposure to total surface area of both hands during an 8 hr working day.

Assuming an exposure of between 10-50 ppm (calculated using EASE model), the inhaled dose of 1,4-dioxane can be calculated using the following formula:

$$D_{inh} = \frac{C \times R \times E \times B}{BW} \quad mg/kg/day$$

where:

C = concentration of 1,4-dioxane in air (mg/m^3)

R = human respiration rate (m^3/hr)

E = exposure duration (hr/day)

B = bioavailability of 1,4-dioxane vapour across lung (1 = 100%)

BW = average body weight of worker (70 kg)

thus:

$$D_{inh} = \frac{35\text{-}180 \times 1.3 \times 8 \times 1}{70} \quad mg/kg/day$$

$$D_{inh} = 5.3 \text{ - } 26.7 \ mg/kg/day$$

As with dermal exposure, this is likely to be a considerable overestimate for exposure to 1,4-dioxane in Australian occupational scenarios.

The above data indicate that dermal exposure may account for up to 5% of total daily dose, but most likely would not exceed 1%.

In light of this, together with other factors, such as the high acute dermal LD_{50} (Derosa et al., 1996), the low level of chronic dermal toxicity (Perone et al., 1976) in animal bioassays and the high rate of evaporation of 1,4-dioxane from the skin surface (Bronaugh, 1982), it was not considered necessary to account for potential dermal exposure in evaluating occupational exposures to 1,4-dioxane in Australia.

Limited air monitoring data are available for occupational exposure to 1,4-dioxane in Australia and as such, data from similar uses overseas, has been included in the following use profiles, where available.

8.2 Exposure during use of 1,4-dioxane and 1,4-dioxane-containing products

Although a wide range of uses have been reported in the literature, it is believed that apart from its applications as a laboratory reagent, only niche uses now occur in Australia. The following applications (Sections 8.2.1-8.2.4) have been identified as the major sources of exposure to 1,4-dioxane.

8.2.1 Research/development (and analytical applications)

A number of applications have been reported for 1,4-dioxane as a solvent and reagent for the purposes of research, development and analysis (see Section 6).

No data were available on levels likely to be encountered by laboratory workers or the number of workers likely to be exposed in Australia. Two papers on the monitoring of airborne levels of 1,4-dioxane in chemical laboratories overseas were found in the literature, where a number of different applications were monitored, including solvent extraction and TLC, although no details were provided on quantities of 1,4-dioxane used. The highest time-weighted average (TWA) level obtained from personal monitoring was 1.8 ppm (Hertlein, 1980; Rimatori et al., 1994).

It can be assumed that exposures to 1,4-dioxane during specific applications are likely to be similar in different laboratories, as most are equipped with fume cupboards/hoods and dilution ventilation. Higher peak exposures may occur during procedures where large quantities of 1,4-dioxane are used e.g., use of 1,4-dioxane as a cleaning solvent for laser dye equipment (it is reported that up to 4 litres of 1,4-dioxane may be used in the process and around 50 L per year is used for this purpose by one research establishment) or applications where 1,4-dioxane is recycled and re-used. However, TWA exposures would still be expected to be small, as the majority of workers will only be exposed intermittently to 1,4-dioxane due to the infrequency of such applications and filling and emptying of the solvent reservoir is reportedly carried out in a fume cupboard.

Despite a potential for acute dermal exposure from spillage of 1,4-dioxane, the contribution from dermal exposure to total body burden of 1,4-dioxane is expected to be minimal in laboratory applications.

8.2.2 Film (celluloid) processing

Workers involved in splicing or repairing celluloid movie film in the film processing industry or during archiving may be exposed to 1,4-dioxane used as an ingredient (10-50%) in specialist cements/adhesives.

In one workplace where new film is processed, the splicing operation is a manual, open process which involves the cutting of film in a specialised tool followed by the application of adhesive/cement (containing 1,4-dioxane) with a small brush to the edges to be glued. The cut film is then joined by closing the tool, which is preheated to 35°C to facilitate drying of the cement. No personal protective equipment was used by workers at the site studied. Approximately 12 litres of cement were used annually at the site visited.

No Australian air monitoring data were available for assessment. Exposure to a variety of chemicals was investigated in two film laboratories in the USA (Okawa & Coye, 1982). The method used for film splicing was similar to that carried out in Australia and 1,4-dioxane was an ingredient of the adhesive/cement. In this study TWA worker breathing zone samples were below 1 ppm. It was noted that skin contact also occurred during this process, but as stated in Section 8.1, this is likely to be insignificant with respect to exposure via inhalation.

Up to 10 laboratories are carrying out this type of work in Australia, with around 3 workers potentially exposed (up to 8 hr/day) at each site. An unknown additional number of workers could be estimated to be exposed in workplaces specialising in

celluloid film repair. In celluloid film processing and repair laboratories, acute and chronic exposure to 1,4-dioxane is expected to be very low.

Although not considered representative of the method of application under discussion, higher levels of 1,4-dioxane (range 7 - 14 ppm) were measured in workroom air from a US company using a polyester/solvent based adhesive containing 1,4-dioxane (percentage not stated), in the manufacture of plastic tubing (Salisbury & Arnold, 1987). The description of the process suggests that exposure would be greater than in the film processing workplace described above, however, it is of interest to note that levels did not exceed the exposure standard (see Section 11.4.2), despite the extensive use of glue and the reported inadequacy of local exhaust ventilation.

8.2.3   Optical lens manufacture

Workers involved in optical lens manufacture are potentially exposed to 1,4-dioxane, which has been used in Australia[2] at a concentration of between 30 - 60% in an anti-scratch coating.

The coating process observed at one factory can be summarised as follows:

- preparation of the coating solution by mixing component ingredients (in a fume cupboard);
- the manual transfer of coating solution to baths (1-2 litres) housed in specialised (airtight) cabinets situated in a separate work room (together with ovens);
- the manual transfer of lenses (stacked in baskets) to cabinets and immersion into coating solution baths;
- the manual transfer of lens baskets to ovens for drying/curing; and
- the manual removal of 'cured' lenses from ovens.

At the site visited, coating solutions were made up twice a week (in a fume cupboard) and then transferred (manually) to the cabinets for coating. There is a potential for dermal exposure during transfer of solutions and during loading and unloading of the lens baskets following coating. Although gloves were not worn by workers at this site, dermal exposure is likely to be minimal in the normal course of events, and is unlikely to contribute significantly to total body burden of 1,4-dioxane (see Section 8.1). No air monitoring data were available for this process (in Australia or overseas).

The greatest potential for inhalation to 1,4-dioxane is expected to be during activities in the coating/oven room. Ventilation in this workroom consisted of a single hooded extractor fan fitted to the side of each coating cabinet, in addition to normal air conditioning. Solvent fumes from the ovens were considered the most likely source of 1,4-dioxane emissions.

In light of the lack of monitoring data, the UK EASE model was used to estimate exposure from inhalation. An exposure (TWA) range of 10-50 ppm 1,4-dioxane was predicted for exposures resulting from a non-dispersive use pattern, where local exhaust ventilation is present. The EASE calculation is based on the use of 1,4-dioxane *per se* and is therefore likely to be an overestimate for airborne levels of 1,4-dioxane resulting from use of the coating product assessed.

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[2] The only notifier for this use in Australia has ceased using 1,4-dioxane for this purpose since the commencement of this PEC report.

One manufacturer estimated that up to 20 workers per week (4 workers per day) may be exposed to 1,4-dioxane in the above process and the maximum time that any worker might be exposed was estimated to be between 10 and 20 hours/week. At least 2 other manufacturers are known to be involved in lens coating in Australia.

8.2.4 Exposure associated with use of 1,1,1-trichloroethane

Because of the large quantities of 1,1,1-trichloroethane previously used in Australia, past occupational exposure to 1,4-dioxane (used as a stabiliser) may have been significant, particularly in metal degreasing operations. As importation and manufacture of 1,1,1-trichloroethane has now ceased, only limited exposure now occurs from this source whilst remaining supplies of 1,1,1-trichloroethane are used up. Certain products containing 1,1,1-trichloroethane can still be imported, provided they meet certain quantity restrictions, however, due to its phase out globally, it is inevitable that alternative solvent(s) will be used in the future (Shaw, 1996).

8.3 Exposure to 1,4-dioxane as an impurity

Occupational exposure to 1,4-dioxane may also result from manufacture, formulation and use of certain chemical products (mainly ethoxylated chemicals), where it occurs as an impurity. In general, such exposures are likely to be low.

8.3.1 Manufacture of ethoxylated chemicals

Workers involved in the manufacture of ethoxylated chemicals in Australia may be exposed to 1,4-dioxane from its occurrence as a by-product, and in particular, during the 'stripping' process which is carried out to remove 1,4-dioxane from certain ethoxylated chemicals (mainly surfactants and emulsifiers). The principal ethoxylated chemicals manufactured in Australia are alkyl and alkyl phenol ether sulphates, polyethylene glycols, and ethoxylates of alcohols, alkylphenols, sorbitan esters, amides and amines. The highest levels produced during manufacture (before any stripping occurs) were reported (by PEC applicants) in a specialist industrial ethoxylate/thionyl chloride surfactant (2000 ppm 1,4-dioxane w/w), ethoxylated amines (typically 300 ppm) and alkyl ether sulphates (typically 100-200 ppm).

Manufacture of ethoxylated chemicals is generally a closed process involving automated feedstock addition to a reactor and automatic feed of reactor product(s) to ancillary 1,4-dioxane stripping (if present) plant. Product(s) are transferred to blenders which are covered, except for feed ports (which one manufacturer reported may be left open) and stripper condensate transferred to the site effluent pond. At one site, possible sources of 1,4-dioxane emissions in this process were identified as the sulphonation plant, blender feed ports, stripper vacuum exhaust and the site effluent pond.

Limited air monitoring data were available for assessment. Personal monitoring carried out at one Australian surfactant manufacturing plant indicated that levels of 1,4-dioxane were below 1 ppm in the drumming-off area (ICI, 1995). Another surfactant manufacturer estimated (based on equilibrium vapour concentrations) that levels of 1,4-dioxane in product handling are unlikely to exceed 9 ppm and in well-ventilated areas would be less than 1 ppm. Levels of 1,4-dioxane measured in stripper vacuum exhaust and air above the effluent pond were below the level of detection.

The principal source of 1,4-dioxane emissions from the plant is the stripper condensate which one manufacturer reported may contain up to 350 ppm 1,4-dioxane, resulting in an effluent concentration of < 10 ppm. Another manufacturer estimated that around 0.5 tonne of 1,4-dioxane is released in stripper effluent annually.

Although the total number of sites is unknown, approximately 120 employees at 4 known sites in Australia are potentially exposed to 1,4-dioxane through various stages of the manufacture of ethoxylated chemicals. At one plant, it was estimated that laboratory staff and workers 'drumming off' the final product would be the most likely to come in contact with product containing 1,4-dioxane.

Finished product is stored in bulk tanks or in drums (200 - 1000L capacity) and packed in bags ranging from 20 to 650 kg capacity. Some products, particularly US Pharmacopoeia (USP) grade materials, are packed under nitrogen to reduce oxidation during storage.

8.3.2 Formulators and end users

No information was provided on potential occupational exposure to 1,4-dioxane during the formulation of products containing ethoxylated chemicals or other chemicals containing 1,4-dioxane as an impurity. Product formulations containing 1,4-dioxane (as impurity) include cosmetics, household and industrial detergents, pharmaceuticals, fire-fighting and agricultural marker foams and other agricultural products. In view of the relatively small amounts of 1,4-dioxane contained in the ethoxylated ingredients in such products, resultant exposure is likely to be low (< 1 ppm), particularly where specifications exist for low amounts of 1,4-dioxane impurity levels in final products.

Occupational exposure to 1,4-dioxane may also occur during end use of such products. The following examples are illustrative only, and do not cover all uses or industry sectors where workers may use products containing 1,4-dioxane as an impurity.

Workers involved in the leather and textile industries may be potentially exposed to 1,4-dioxane due to its presence as a by-product in ethoxylated surfactants (fatty amine and alcohol polyglycol ethers) used as scouring and levelling agents in leather processing and dyeing. One manufacturer reported imports of approximately 35 tonnes of ethoxylated surfactants for this use, containing levels of 1,4-dioxane by-product at less than 100 ppm w/w for fatty amine polyglycol ethers and less than 10 ppm w/w for alcohol polyglycol ethers. No information was provided on the use profile or the numbers of workers potentially exposed.

The literature reports on a number of materials containing 1,4-dioxane (as impurity) being used in the construction industry. Details of one such product provided for assessment is as follows:

1,4-Dioxane is present as a residue in a phosphate alcohol flame retardant at a concentration (typical) of around 2000 ppm w/w. This product is being imported as an ingredient (5%) in a fire resistant caulking agent (i.e., around 100 ppm 1,4-dioxane w/w present in the caulk). Approximately 2000 workers may be exposed to this product. Exposure to 1,4-dioxane may occur during application and curing and when grouted surfaces undergo sanding. Less than 100 kg of this material will be imported annually.

8.4   Summary

In summary, exposure to 1,4-dioxane may occur from inhalation and skin contact, however exposures from inhalation are more relevant to current Australian workplace scenarios. In general, exposures during use of 1,4-dioxane are likely to be low, however no monitoring data was available for Australian applications. In particular, modeling of 1,4-dioxane exposures to workers involved in optical lens coating indicates a requirement for monitoring (see Section 13.6).

Similarly, exposure to 1,4-dioxane (by-product) during manufacture of ethoxylated chemicals is likely to be low and monitoring data provided from one surfactant manufacturer (applicant) supports this conclusion. Levels of 1,4-dioxane present (as an impurity) in end-use ethoxylated products appear unlikely to exceed 100 ppm (0.01% w/w). Such a level of 1,4-dioxane impurity, together with the fact that use profiles would generally preclude workers (formulators and end-users) from chronic exposure to such products, again indicates a low potential for exposure to 1,4-dioxane.

9. Hazard Identification and Assessment

9.1 Toxicokinetics and metabolism

9.1.1 Humans

Absorption

An inhalation study has been carried out in human volunteers exposed to 50 ppm (180 mg/m^3) 1,4-dioxane for 6 hr. In this study absorption of 1,4-dioxane was estimated at around 80% of dose. The maximum uptake (10.9 mg/kg) was around 50% of that measured in rats following similar exposure (see Section 9.1.2) (Young et al., 1977). Because of its rapid biotransformation to β-hydroxyethoxyacetic acid (HEAA), the body burden of 1,4-dioxane was estimated to be no more than 1.2 mg/kg at steady state.

No data were available for dermal uptake for 1,4-dioxane in humans (*in vivo*), although skin absorption was considered a potential route of exposure in case reports of human fatalities from short term exposures (see Section 9.5.1).

Significant differences exist for dermal penetration (in diffusion cell studies on human skin) of 1,4-dioxane under occluded and non-occluded conditions. Up to 3.2% of applied 1,4-dioxane (dissolved in lotion) was absorbed under occlusion for 3.5 hr, whereas only 0.3% absorption occurred under non-occluded conditions (Bronaugh 1982). Differences in the amount of absorption were accounted for by the high volatility of 1,4-dioxane (see Section 9.1.2). A permeability constant (Kp) of 2.7 x 10^{-4} cm/hr was determined for the occluded test system (Bronaugh, 1982) which is similar to that calculated for undiluted 1,4-dioxane using the formula (see Appendix 1) of Potts and Guy (1992). The absorption rate for 1,4-dioxane (under occlusion) was calculated (see Appendix 1) to be approximately 0.3 mg/cm^2/hr which compares with other solvents reported as being readily absorbed in *in vitro* skin (human) tests (refer to Table 8 in NICNAS 1996).

From the solubility characteristics alone, Grandjean (1990) predicted that 'considerable uptake' by the skin could be expected for 1,4-dioxane, but that oxidation and evaporation from the skin surface would limit the total amount absorbed. Almost 90% (as a percentage of applied dose) evaporation of 1,4-dioxane in a lotion was demonstrated within 15 minutes of application (to a non-absorbent test material), with the remainder evaporating over the next 24 hr (Bronaugh, 1982).

Metabolism and elimination

The major metabolite of 1,4-dioxane in humans is HEAA. Four volunteers were exposed to 50 ppm 1,4-dioxane for 6 hr (Young et al., 1977). A steady state plasma level of 10 μg/ml 1,4-dioxane was reached after 3 hr inhalation exposure, with a steady state plasma concentration of 8μg/ml HEAA reached 1 hr after cessation of exposure (i.e., after 7 hr). The

plasma half-lives for 1,4-dioxane and HEAA were around 1 and 2.5 hr respectively. HEAA accounted for around 99% of recovered 1,4-dioxane in urine. Clearance of 1,4-dioxane from kidneys was around 400 times slower than HEAA (Derosa et al., 1996). The authors concluded that the pharmacokinetics of 1,4-dioxane in humans can be described by a one compartment (open system) model with zero order uptake and first order elimination and that repeated exposure to 50 ppm 1,4-dioxane would not lead to accumulation in plasma.

In workers exposed to a time-weighted average concentration of 1.6 ppm (5.8 mg/m^3) 1,4-dioxane for 7.5 hr (Young et al., 1976), the average concentrations of 1,4-dioxane and HEAA in samples of urine collected at the end of each workday were 3.5 and 414 μmol per litre respectively.

The high ratio of HEAA to 1,4-dioxane in the above studies suggests that at low-exposures 1,4-dioxane is rapidly metabolised to HEAA, with no evidence of non-linear pharmacokinetics, that is, no evidence of saturation of biotransformation of 1,4-dioxane to HEAA (Dietz et al., 1982). Metabolic rate constants developed for 1,4-dioxane in humans in a PBPK model were K_m = 3.0 mg/L and V_{max} = 6.35 mg/kg/hr (Reitz et al., 1990).

1,4-Dioxane may inhibit the oxidative metabolism of other substances as it has been shown to inhibit human CYP2A6 activity in liver microsomes *in vitro* (Draper et al., 1997).

9.1.2 Animals

Absorption

Studies on the absorption of 1,4-dioxane have been carried out in Sprague-Dawley rats (inhalation and oral) and in rhesus monkeys (dermal).

Administration of single gavage doses of 10, 100 or 1000 mg/kg of ^{14}C-1,4-dioxane or repeat doses (17 days) of 10 or 1000 mg/kg/day to rats showed that greater than 95% 1,4-dioxane was absorbed from the gastrointestinal tract (Derosa et al., 1996).

Following inhalation (head only) of 1,4-dioxane (50 ppm for 6 hr), approximately 7 μg of 1,4-dioxane and 21 mg of HEAA were excreted in rat urine after 48 hr. As the theoretical dose of 1,4-dioxane absorbed is around 16 mg (assuming a minute volume of 0.25 L/min and 100% absorption), this study indicates complete absorption of 1,4-dioxane (Derosa et al., 1996).

Between 2 and 3.5% of the applied dose (4μg/cm^2 1,4-dioxane, in methanol or skin lotion) was absorbed from unoccluded skin (15cm^2) in non-human primates exposed over a 24 hr period (Marzulli et al., 1981). The extent of evaporation from the application site during the course of the experiment was not determined, but the fact that between 30 - 50% of the absorbed dose was absorbed within the first 4 hr indicates it is likely to be high.

Distribution

Single intraperitoneal doses (1-7 mg/kg) of radiolabeled 1,4-dioxane in Sprague-Dawley rats showed that the chemical is distributed to blood, liver, kidney, spleen, lung, colon and skeletal muscle, with levels decreasing in each tissue during a 16 hr observation period (Derosa et al., 1996). Mikheev et al., (1990) concluded that selective uptake of 1,4-dioxane takes place in liver and kidney, due to the fact that T_{max} (maximum accumulation time) values for these organs were less than that for blood.

Covalent binding was found to be significantly higher in the liver, spleen and colon than in other tissues. In the liver, the highest covalent binding was in the nuclear fraction followed by mitochondrial and microsomal fractions. Binding to macromolecules was non-specific and not associated with DNA (Derosa et al., 1996). This finding was consistent with investigations into hepatic DNA alkylation in rats (Sprague-Dawley) carried out by Stott et al. (1981).

Pretreatment of rats with inducers of microsomal mixed-function oxidases such as phenobarbital and methylcholanthrene had no significant effect on the covalent binding of 1,4-dioxane in the liver (Woo et al., 1977).

Physiologically based pharmacokinetic (PBPK) modelling of rat data by Reitz et al., (1990) indicated that liver concentrations of 1,4-dioxane were approximately 2.5 times greater from ingestion than from inhalation of similar doses (i.e., 0.1% in water or 111 ppm in air) of 1,4-dioxane.

Metabolism

Increased and decreased acute toxicity following administration of inducers and inhibitors of cytochrome P-450 indicate a role for microsomal mixed function oxidases in 1,4-dioxane metabolism (Derosa et al., 1996; GDCH, 1991).

Braun and Young (1977) identified HEAA as the major urinary metabolite of 1,4-dioxane in rats. Other minor metabolites reported by these authors were diglycolic acid, oxalic acid and possibly diethylene glycol.

It is unclear whether 1,4-dioxane is metabolised directly to HEAA or whether 1,4-dioxane-2-one is the principle metabolite which undergoes hydrolysis to HEAA. The identification of HEAA vs 1,4-dioxane-2-one may depend on the methods of analysis (Derosa et al., 1996). NIOSH proposed the following pathway for 1,4-dioxane biotransformation: initial formation of an oxonium ion; nucleophylic attack by water to open ring, with the formation of the corresponding alcohol; rapid reduction of the alcohol to β-hydroxyethoxy acetaldehyde; and rapid oxidation of the aldehyde to HEAA (Derosa et al., 1996).

Young et al. (1978) demonstrated that the pharmacokinetics of 1,4-dioxane in rats differ markedly depending on the dose. A single oral dose of 10 mg/kg is rapidly metabolised and excreted in urine as HEAA. However, the metabolism of 1,4-dioxane to HEAA appears to be saturated at high doses as a larger fraction of 1,4-dioxane is retained in the body and eliminated in the breath. Repeated daily administration of 1000 mg/kg results in a marked decrease in the body burden of 1,4-dioxane after a few days, indicating that induction of enzymes involved in the metabolism to HEAA occurs. Similar body burdens of 1,4-dioxane were observed following repeated exposure to 10 mg/kg/day and 1000 mg/kg/day following this induction period.

Young et al. (1978) suggested that the metabolism of 1,4-dioxane in rats is saturated at plasma levels above 100 μg/ml.

Pharmacokinetic parameters determined for 1,4-dioxane in rats (3-1000 mg/kg by i.v) were K_m = 20.93 mg/L and V_{max} = 13.3 mg/kg/hr (Young et al., 1978).

Doses of 1,4-dioxane in excess of that required for metabolic saturation have been associated with toxicity (including carcinogenicity) in rats (Dietz et al., 1982; Kociba et al., 1975). 1,4-Dioxan-2-one and β-hydroxyethoxy acetaldehyde, diglycolic and oxalic acids have been proposed as possible metabolites associated with toxic/carcinogenic effects resulting from 1,4-dioxane exposure. However, there is no evidence that these or other metabolites are increased during metabolic saturation. There is evidence to suggest that metabolic induction occurs during repeated dosing (above metabolic saturation levels) with a concomitant reduction in 1,4-dioxane body burden over time (Young et al., 1978).

Elimination and excretion

Following inhalation exposure of rats for 6 hr to 50 ppm 1,4-dioxane, the metabolite HEAA accounted for around 99% of urinary metabolites (Young et al., 1978). In this study 75% of 1,4-dioxane and 36% of total HEAA was eliminated during the exposure period. The concentration of 1,4-dioxane in plasma decreased in a first order manner from 7.3 μg/ml at the end of exposure to non-detectable levels at 11 hr (i.e., 5 hr post-treatment).

Oral dosing (single) of rats to 10, 100 and 1000 mg/kg of labelled 1,4-dioxane resulted in approximately 99%, 85% and 75% of dose in urine and approximately 0.5%, 5% and 25% of dose as expired 1,4-dioxane, respectively. Metabolites in faeces were 1-2% irrespective of dose. The excretion of 1,4-dioxane *per se* was measured in rats administered i.v. doses of labelled 1,4-dioxane. Total 1,4-dioxane in urine was 4% and 11% of dose at 10 mg/kg and 1000 mg/kg respectively (Young et al., 1978).

The same authors measured plasma levels of 1,4-dioxane following single i.v administration of 3, 10, 30, 100, 300 and 1000 mg/kg 1,4-dioxane. Doses up to 10 mg/kg were eliminated from plasma by linear kinetics, whereas above 30 mg/kg plasma clearance was markedly non-linear and could be described by Michaelis Menten kinetics. Plasma half-lives increased from 1.1 hr to 14.2 hr after injection of 10 mg/kg and 1000 mg/kg respectively. The area under the curve (AUC) for plasma concentrations of 1,4-dioxane also increased disproportionately with dose, indicating that elimination of 1,4-dioxane from blood is a saturable process (Dietz et al., 1982). Neither pulmonary or renal clearance rates were significantly different, at low (10mg/kg) or high (1000 mg/kg) 1,4-dioxane doses, to account for the dose-dependent decrease in plasma clearance rates, which was interpreted by the study authors as evidence for saturation of 1,4-dioxane biotransformation rather than elimination (Young et al., 1978).

9.2 Effects on experimental animals

9.2.1 Acute toxicity

Lethality

A number of acute lethality studies have been conducted with 1,4-dioxane using different routes of administration and are summarised in Table 4.

Table 4 - Summary of acute lethality studies

Route	Species	Results	Reference
Oral			
	Rat	LD_{50} = 5400-7300 mg/kg	Derosa et al. (1996)
	Rat	LD_{50} = 5170 mg/kg	BASF (1973))
	Mouse	LD_{50} = 5700 mg/kg	ECETOC (1983)
	Mouse (m)	MLD_4 = 4500 mg/kg	Mirkova (1994)
	Mouse (f)	MLD_4 > 5000 mg/kg	Mirkova (1994)
	Guinea pig	LD_{50} = 1270-3900 mg/kg	GDCH (1991)
	Rabbit	LD_{50} = 2000 mg/kg	Derosa et al. (1996)
	Cat	LD_{50} = 2000 mg/kg	Patty (1994)
Dermal			
	Rabbit	LD_{50} = 7600 mg/kg	Derosa et al. (1996)
	Rat	Lethal dose > 8000 mg/kg	Derosa et al. (1996)
Inhalation			
	Rat	LC_{50} (2hr) = 12,780 ppm (46 g/m^3)	ECETOC (1983)
	Rat (f)	LC_{50} (4hr) = 14,250 ppm	Derosa et al. (1996)
	Mouse	LC_{50} (2hr) = 18,000 ppm (65 g/m^3)	ECETOC (1983)
	Cat	Lethal dose (7hr) = 10,900 ppm (44 g/m^3)	EEC (1988)
Intravenous			
	Rabbit	LD_{50} = 1500 mg/kg	EEC (1988)
Intraperitoneal			
	Rat	LD_{50} = 5300 mg/kg	Appel (1988)
	Mouse	LD_{50} = 8.97 mM/kg (790 mg/kg)	Karel et al. (1947)
	Mouse	LD_{50} = 4100 mg/kg	Morita (1994)
	Mouse	LD_{50} = 5790 mg/kg	BASF (1973)
	Rat (f)	LD_{50} = 3976 - 5910 mg/kg	Lundberg et al. (1986)

MLD_4 = 4-day minimum lethal dose
m = male
f = female

Systemic effects

Acute toxic effects reported in animals are mainly CNS depression, kidney and liver damage.

Overt CNS effects (including convulsions) have been reported in rabbits administered (i.v.) 5ml (2060 mg/kg) of 1,4-dioxane in solution (Anon, 1989). Subtle effects on CNS function, as assessed by perturbations of certain neurotransmitters in male rats (Sprague-Dawley) have been reported following an oral dose of 1050 mg/kg 1,4-dioxane (Kanada et al., 1994). A study of the effects of 1,4-dioxane on electrically evoked seizure discharge, considered to be a sensitive indicator of neurotropic effects, revealed that a 30% depression in response following inhalation of 1860 ppm (4hr) in rats and 2400 ppm (2 hr) in mice (Frantik et al., 1994).

Acute renal effects are generally reported as glomerular and tubular damage and have been characterised clinically by slight proteinuria and histologically by tubular cell vacuolation and necrosis (Anon, 1989; GDCH, 1991). A study by Fairley et al., (1934) reported degeneration

of the renal cortex and medulla (plus haemorrhaging) in rabbits up to one month following intravenous administration of 400 - 2000 mg/kg 1,4-dioxane.

Acute hepatic effects include increased serum enzymes (glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), ornithine carbamyl transferase (OCT) and sorbitol dehydrogenase) at an estimated 600 mg/kg (Drew et al., 1978; Lundberg et al., 1986); increased cytochrome P-450 activity and vacuolar degeneration (>2500 mg/kg, oral) (Kitchin & Brown, 1990). No overt symptoms or histopathological lesions were seen in rat liver following administration of 1000 mg/kg 1,4-dioxane by gavage or 8,300 mg/kg applied dermally (Derosa et al., 1996).

Other organs affected following acute exposures include spleen, thymus, lungs (pulmonary congestion and atelectasis) and brain (oedema) and blood dyscrasias (leucocytosis and anisocytosis) (Cortese, 1941; Karel et al., 1947; GDCH, 1991).

Immunological effects for 1,4-dioxane have been evaluated in mice both *in vivo* and *in vitro*. Although induction of B-cell responses and inhibition of T-cell responses were seen at 25 g/L *in vitro*, little immunosuppression was seen *in vivo* even at near lethal doses (Thurman et al., 1978). The meaning of such observations in terms of possible effects on immune function is unclear.

9.2.2 Irritation

Skin

Slight dermal erythema and severe scale formation were reported (BASF, 1973) in rabbits up to 8 days after dermal application of 1,4-dioxane (dose not reported). Mild irritation was also observed in rabbit skin following an application of 515 mg 1,4-dioxane in an open Draize Test (EEC, 1988). However, skin irritation was not seen in rats exposed (unoccluded) to 8,300 mg/kg 1,4-dioxane (Clark et al., 1984).

Evidence of skin irritation was not seen in guinea pigs, rabbits or mice following repeated (studies ranging from 50-100 days) dermal exposure to 1,4-dioxane (above 50 mg) applied two or three times per day (Hartung, 1989; Perone et al. 1976).

Eye

1,4-Dioxane has been reported to have a miotic effect in rabbits at concentrations (not provided in study abstract) below that causing alterations in the conjunctiva or cornea, with pupils returning to normal 10 to 15 minutes after administration (Golubev, 1969). Liquid 1,4-dioxane has been reported to cause eye irritation in rabbits. Muir (1985) reported damage to rabbit cornea induced by 1,4-dioxane which correlated with *in vitro* studies on bovine cornea opacity (Igarashi and Northover, 1987). In guinea pigs, both liquid 1,4-dioxane (10 μl) and exposure to 2000 ppm 1,4-dioxane vapour produced eye irritation (EEC, 1988).

Lung

Irritation of the nose and lung has been reported following inhalation of 1,4-dioxane (>2000 ppm) in guinea pigs, mice and cats (Wirth & Klimmer, 1936; ACGIH, 1991).

9.2.3 Sensitisation

1,4-Dioxane was negative in a well conducted guinea pig maximisation test (BASF, 1993).

9.2.4 Sub-acute and sub-chronic toxicity

Several sub-acute and sub-chronic studies have been conducted with 1,4-dioxane, the majority of which were carried out between 1930 and 1960. As such, some concern arises over the adequacy of testing protocols and according to ECETOC (1983) many of these studies lack details. Table 5 is not a comprehensive account of all such studies undertaken for 1,4-dioxane, but comprises the most commonly reported studies in the literature for the different species tested. It should be noted that the original (primary) reference sources were not necessarily sighted.

In summary, sub-acute and sub-chronic studies for 1,4-dioxane have been carried out in rats, mice, guinea pigs, rabbits, dogs and cats. Effects reported include narcosis, behavioural changes, haematological effects, cardiac effects and histopathological lesions of the kidneys, liver and brain. In general, the doses used in these studies are very high and as such provide little useful information on critical effects (i.e., most sensitive effects) and no observed adverse effect levels (NOAELs).

Table 5 - Summary of sub-acute and sub-chronic studies

Test animal	Exposure (Route/Dose & Duration)	Reported findings/comments	Study ref.
Dog, rat & rabbit	**Inhalation** **50 - 100 ppm** in rats & rabbits **50 ppm** in dogs (up to 136 days, 5 day per week)	No adverse effects based on growth, organ weights, mortality, haematology, clinical chemistry and pathology.	EEC (1988)
Cat, rabbit & guinea pig	**Inhalation** **2700 ppm** (up to 34 days)	Fatalities (majority of animals) Emaciation, narcosis, renal & hepatic toxicity.	ACGIH (1997)
Cat	**Inhalation** **1400- 100,000 ppm** (duration not reported)	Haematological effects at low dose. Cardiac effects above 10,000 ppm. Cardiac arrest occurred within 5 min of exposure to high dose.	Wirth & Klimmer (1936)
Rat	**Inhalation** **1500, 3000 and 6000 ppm** (4hr/day, 5 day per week up to 2 weeks)	Behavioural effects (inhibition of avoidance response) at 3000 ppm and above. Effects were most pronounced after 2 days. NOAEL = 1500 ppm. Animals began to recover during study with complete recovery in some cases.	Grasso et al. (1984)
Rabbit	**Inhalation** **800 ppm** (up to 30 days)	Fatalities. Severe kidney damage.	ACGIH (1991)
Guinea pig	**Inhalation** **50 ppm** (up to 82 days, 5 day per week)	No adverse effects based on growth, organ weights, mortality, haematology, clinical chemistry and pathology.	EEC (1988)
Rabbit & guinea pig	**Dermal application** (80% aqueous 1,4-dioxane solution) **10 drops** in rabbits **5 drops** in guinea pigs (11 times per week for up to 100 days)	CNS effects - incoordination & narcosis. Renal & liver effects - histopathology included hepatocellular degeneration and lesions of the renal medulla, tubules and glomeruli. Non-occlusive repeated application.	ACGIH (1997) GDCH (1991) Appel (1988)
Dog	**Oral** Total dose of **3000 mg/kg** (over 9 days)	Fatalities. Severe kidney and liver damage.	ACGIH (1991)

Table 5 - Summary of sub-acute and sub-chronic studies (cont.)

Test animal	Exposure (Route/Dose & Duration)	Reported findings/comments	Study ref.
Rat	**Drinking water** **10-1000 mg/kg/day bw** (up to 11 weeks)	No effects at low dose. Minimal hepatic effects (increased liver/bw ratio and minimal centrilobular swelling) at high dose.	Stott et al. (1981)
Rat	**Drinking water** (1%) approx. **1000 mg/kg/day** (up to 2 weeks)	No lesions (histological) in the nasal cavity.	Goldsworthy et al. (1991)
Rat	**Drinking water** (5%) approx. 4150 **mg/kg/day** (up to 10 days)	35/50 animals died. No kidney lesions (histological) seen up to 3 days exposure, after which time observations included swelling of epithelial cells (proximal area of nephron); vesicular degeneration and necrosis of tubular epithelium.	David (1964)
Rat/mouse	**Drinking water** **50,000 mg/l** (4-5%) (up to 67 days) Dose estimates: rats: 7,200 mg/kg/day mice: 9,800 mg/kg/day	Some deaths in both species. Renal & liver effects. Histopathology included vascular congestion and cellular degeneration of the renal cortex and hepatocellular degeneration.	Derosa et al. (1996) Appel (1988)
Mouse	**Gavage or i.p. injection** **1000 mg/kg bw** (3 times a week for 8 weeks)	No macroscopic changes were seen in the liver (or other unspecified organs).	Stoner et al. (1986)
Rabbit	**Drinking water** **500- 1000 mg/kg bw** (3 times per week)	Increase in blood urea (214%). Kidney damage (with capsular oxidate & cortical necrosis).	Appel (1988)

9.2.5 Chronic toxicity/carcinogenicity

Several chronic (>1 year duration) studies have been carried out in rats, mice and guinea pigs and are detailed in Table 6. In general, the non-neoplastic lesions observed and organs affected (liver/kidney) are consistent with observations from acute and sub-chronic studies. Studies are summarised according to the route of exposure and results are divided into non-neoplastic and neoplastic effects.

Oral studies

Several oral drinking water studies have been carried out in rats, mice and guinea pigs (see Table 6). All percentage doses referred to in this section refer to the percentage of 1,4-dioxane w/w in drinking water. Intake estimations for oral studies were provided by study authors, except for studies by Yamazaki et al. (1994), where estimates for rat and mouse intakes were calculated from intake data provided by Kociba et al. (1974) and NCI (1978), respectively.

a) Non-neoplastic effects

In rats, gross effects (decreased body weight) were observed at 0.5% with increased relative and absolute liver weights at 1% 1,4-dioxane. Hepatic and renal histopathological effects were seen at 0.1% (Kociba et al., 1974). The NOAEL$_{(oral)}$ for non-neoplastic effects was 0.01 - 0.02% 1,4-dioxane (equivalent to 10-40 mg/kg/day) derived from Kociba et al. (1974) and Yamazaki et al. (1994) and based on the increased incidence (dose related) of spongiosis hepatis seen in males at and above 0.02% (statistically significant at 0.1%).

In mice, gross effects (decreased body weight) were observed at 0.2% (Yamazaki et al., 1994), with pulmonary, hepatic and nasal effects at and above 0.5% (equivalent to 400-700 mg/kg/day) 1,4-dioxane (NCI, 1978). A NOAEL$_{(oral)}$ was not identified in this study.

In guinea pigs, pulmonary effects were reported at 0.5 to 2.0% (equivalent to >2000 mg/kg/day, calculated from total intake data) 1,4-dioxane (Hoch-Ligeti & Argus 1970). A NOAEL$_{(oral)}$ was not identified in this study.

b) Carcinogenic effects

Liver tumours

1,4-Dioxane (in drinking water) produced liver tumours in rats, mice and guinea pigs.

Hepatocellular adenomas and carcinomas were significantly increased in rats at 0.1% and 0.5% 1,4-dioxane, respectively (Yamazaki et al., 1994). Cholangiomas were also reported in a single rat study at 1% (Kociba et al., 1974). A NOAEL$_{(oral)}$ for all liver tumours in rats was determined between 0.01 and 0.02% 1,4-dioxane (equivalent to 10-40 mg/kg/day) in studies by Kociba et al. (1974) and Yamazaki et al. (1994), based on the increased incidence (dose-related) of adenomas in male animals at and above 0.02% (statistically significant at 0.5%).

Hepatocellular adenomas and carcinomas were also significantly increased in mice at the lowest dose level, 0.05% (equivalent to 40-70 mg/kg/day) 1,4-dioxane. However, a clear dose-response relationship for adenomas was not evident in mice (Yamazaki et al., 1994). A NOAEL$_{(oral)}$ was not identified in this mouse study.

An increase in benign tumours (hepatomas) was noted in guinea pigs at a dose of 0.5 to 2.0% (equivalent to >2000 mg/kg/day) 1,4-dioxane (Hoch-Ligeti & Argus, 1970). A NOAEL(oral) for guinea pigs was not identified in this study.

Nasal tumours

1,4-Dioxane (in drinking water) produced nasal tumours in rats and mice. A number of different tumour types were reported, including adenocarcinomas, epidermoid and squamous cell carcinomas.

Statistically significant increases in nasal carcinomas were seen in rats at 0.5% 1,4-dioxane (NCI, 1978; Yamazaki et al., 1994). The NOAEL(oral) for nasal tumours in rats was 0.1% (equivalent to 90-150 mg/kg/day) (Kociba et al., 1974; Yamazaki et al., 1994).

Biologically significant increases in adenocarcinomas were noted in mice at 0.5% 1,4-dioxane (NCI, 1978). The NOAEL(oral) for nasal tumours in mice (Yamazaki et al., 1994) was 0.2% (equivalent to 160-280 mg/kg/day).

Other tumours

Other tumours reported in drinking water studies with 1,4-dioxane included mammary adenomas and mesotheliomas of the testes and peritoneum seen in rats and renal pelvis carcinoma, myeloid leukaemia, kidney adenoma and gallbladder carcinomas seen in guinea pigs at and above 0.5% 1,4-dioxane (Argus et al.,1965; Hoch-Ligeti & Argus, 1970; NCI, 1978; Yamazaki et al., 1994).

Inhalation studies

A single chronic rat inhalation (whole body) study with 1,4-dioxane was available for assessment (Torkelson et al., 1974). Details and results of this study are summarised in Table 6.

a) Non-neoplastic effects

No treatment-related effects were reported following chronic inhalation. Gross microscopy was carried out on over 20 organs/tissues including liver, kidney, nose, testes, lung and spleen. The NOAEL(inh) determined from this study was 0.4 mg/L (111 ppm). The internal dose equivalent as calculated by the study author was 105 mg/kg/d.

b) Carcinogenic effects

In addition to the study by Torkelson et al. (1974), the results (no study details provided) of a rat carcinogenicity study on 1,1,1-trichloroethane containing approximately 4% 1,4-dioxane were provided for assessment (Dow, 1990). Exposure to 1,4-dioxane was estimated as 103 ppm (0.4 mg/L), assuming that its airborne concentration was directly proportional to its concentration in 1,1,1-trichloroethane. Neither inhalation study reported an increase in tumours.

Dermal studies

Two chronic dermal toxicity studies have been conducted in mice (King et al., 1973; Perone et al., 1976). Details and results of these studies are summarised in Table 6.

a) Non-neoplastic effects

Only one study (King et al., 1973) reported non-neoplastic lesions, however, these were only reported following DMBA pre-treatment (i.e., a promotion study). Insufficient data were available in this study to estimate the applied doses of 1,4-dioxane. In another study by Perone et al. (1976), no gross or compound-related histological lesions were seen in animals treated with approximately 50 mg 1,4-dioxane (100%) applied 3 days per week (estimated applied dose of 1500 mg/kg/d, assuming a mean animal body weight of 20g and averaging 3 day dose over 5 day week). It was not stated in either study whether doses were applied under occlusion. Neither study was considered suitable for the derivation of a NOAEL$_{(derm)}$.

b) Carcinogenic effects

In both the King et al. (1973) and Perone et al. (1976) studies, increases in tumours (lymph node, skin, hepatic and pulmonary neoplasms) were reported to be within normal limits.

Table 6 - Summary of chronic toxicity/carcinogenicity studies

Test animal	Exposure (route/dose & duration)	Gross observations	Clinical & pathological effects (non-neoplastic)	Tumour incidence in target organs (by test group)					Comments	Study ref.
ORAL										
Rat (Wistar) 26 (m) per test group 6 (m) controls	*Drinking water* **1.0%** Ad libitum (7 day/ wk for **63 wk**).		Severe kidney damage including effects on tubular & glomerular epithelium (including proliferation). Enlarged hyperchromic nuclei in the liver.	6/26 test animals developed liver tumours, of which one also had a renal pelvis carcinoma (transitional cell) & another had myeloid leukaemia.					1/6 control animals developed lymphosarcoma. Study inadequate according to recognised protocols.	Argus et al. (1965)
Rat (Charles River CD) 30 (m) per group	*Drinking water* **0.75%** [a] **1.0%** [b] **1.4%** [c] **1.8%** [d] Ad libitum (7 day/ wk for **13** months).		Precancerous lesions reported in the anterior nasal cavity. No other pathology reported.	*Liver:* Hep carc (m) *Nose:* Adenocarc (m) Epid carc (m) Sqam carc (m) Epith pap (m)	[a] 0 1 0 0 1	[b] 0 0 1 1 0	[c] 2 1 0 0 0	[d] 2 0 1 0 0	1 control animal developed a nasal fibroma. Latency for nasal tumours was >330 days.	Hoch-Ligeti et al. (1970)
Rat (Charles River CD) 30 (m) per group	*Drinking water* **0.75%** [a] **1.0%** [b] **1.4%** [c] **1.8%** [d] Ad libitum (7 day/ wk for **13 months**).		Marked kidney damage reported in all test grps.	*Liver:* Hepatoma (m) nodules (m)	[a] 0 4	[b] 0 9	[c] 3 13	[d] 12 11	Malignancy was established for some liver tumours.	Argus et al. (1973)
Rat (Sherman) 60 per sex per group.	*Drinking water* **0** [a] **0.01%** [b] **0.1%** [c] **1.0%** [d] Ad libitum (7 day/ wk for **2 yr**).	Relative liver weight increased* in [d]. Body weight decreased* in [d] from week 1.	Hep deg^n & necrosis in [c & d]. Renal tubular epithelial deg^n in [c] & [d]. No haematological effects.	*Liver:* Hep carc Cholang *Nose:* Sqam carc	[a] 1 0 0	[b] 0 0 0	[c] 1 0 0	[d] 10** 2 3***	Rats in grps [c] & [d] showed evidence of hep and tubular reg^n.	Kociba et al. (1974)

Table 6 - Summary of chronic toxicity/carcinogenicity studies (cont.)

Test animal	Exposure (route/dose & duration)	Gross observations	Clinical & pathological effects (non-neoplastic)	Tumour incidence in target organs (by test group)					Comments	Study ref.
Rat (Osborne-Mendel) 35 per sex per group.	*Drinking water* **0** [a] **0.5 %** [b] **1.0 %** [c] Ad libitum (7 day/ wk for **110 wk).**	Body weight in [b & c] decreased in males in 2nd year of study & slightly reduced in [c] females	Fatty metamorphosis & hyperplasia of liver in [b] & [c]. Haemosiderosis & atrophy of spleen in [c] males.	**Liver:** Hep aden (m) Hep aden (f) **Nose:** Carc (m) Carc (f) **Testes:** Meso (m)	[a] 0 0 0 0 0	[b] 0 10 12 10 3	[c] 0 11 16 8 5		Lower survival rates in test groups. Nasal carcinomas (inc. sqam epithelial carc; adenocarc; and rhabdomyoma) appeared after 1 year treatment. Nasal tumours stat. sig. in [b & c].	NCI (1978)
Rat (F344/DuCrj) 50 per sex per group.	*Drinking water* **0** [a] **0.02**% [b] **0.1**% [c] **0.5**% [d] Ad libitum (7 day/ wk for **2 yr).**	Body weight decreased in both sexes in [d]	Liver hyperplasia (dose related) in both sexes [c]*&[d]**. Spongiosis hepatis (dose related) in [b],[c]*,[d]** males and [d] **females. Nasal squamous cell metaplasia & proliferation of nasal gland in both sexes [d]**.	**Liver:** Hep carc (m) Hep carc (f) Hep aden (m) Hep aden (f) **Nose:** Sqam carc (m) Sqam carc (f) Other (m&f)_	[a] 0 0 0 1 0 0 0	[b] 0 0 2 0 0 0 0	[c] 0 0 4 5 0 0 0	[d] 14** 10** 24** 38** 3** 7** 5	Decreased survival in [d] related to incidence of nasal tumours. Increased incidence (52%) of peritoneal mesothelioma (m)** & (20%) mammary adenoma (f)* in [d].	Yamazaki et al. (1994)
Mouse (Crj:BDF1) 50 per sex per group.	*Drinking water* **0** [a] **0.05**% [b] **0.2**% [c] **0.8**% [d] Ad libitum (7 day/ wk for **2 yr).**	Body weight decreased in both sexes in [c&d]	Nasal and lung epithelial atrophy & nuclear enlargement in [d]** both sexes. Hepatic fatty change in [d]** males. Kidney proximal tubule nuclear enlargement in [d]** males.	**Liver:** Hep carc (m) Hep carc (f) Hep aden (m) Hep aden (f) **Nose:** Adenocarc(f) Esthesio (m)	[a] 15 0 7 4 0 0	[b] 20 6 16 30 0 0	[c] 23 30** 22* 20** 0 0	[d] 36** 45** 8 2 1**** 1****	Decreased survival in [c]&[d] related to incidence of liver tumours (f).	Yamazaki et al. (1994)

Table 6 - Summary of chronic toxicity/carcinogenicity studies (cont.)

Test animal	Exposure (route/dose & duration)	Gross observations	Clinical & pathological effects (non-neoplastic)	Tumour incidence in target organs (by test group)				Comments	Study ref.
Mouse (B6C3F1) 50 per sex per group.	*Drinking water* **0** [a] **0.5**% [b] **1.0**% [c] Ad libitum (7 day/ wk for **90 weeks**).	Body weight: increased in [c] males & [b] females; decreased in [c] females	Lung inflammation in all test groups. Inflammation of nasal turbinate in females. Hepatic hyperplasia in [b] only & necrosis in [b] & [c]		[a]	[b]	[c]	Decreased survival in [c]. Tumours appeared after 81 weeks in females & 58 weeks in males.	NCl (1978)
				Liver:					
				Hep aden (m)	0	1	4		
				Hep aden (f)	0	9	6		
				Hep carc (m)	2	18	24		
				Hep carc (f)	0	12	29		
				Nose:					
				Adenocarc (m)	0	0	1		
				Adenocarc (f)	0	1	0		
Guinea pig 22 (m) in test group. 10 (m) control	*Drinking water* **0** [a] **0.5 - 2.0**% [b] Ad libitum (7 day/ wk for **23 months**).		9/22 test animals developed bronchial adenomatous epithelial hyperplasia (control = 1/10) & infiltration of mononuclear cells (control = 4/10)		[a]	[b]			Hoch-Ligeti & Argus (1970)
				Liver:					
				Hepatoma (m)	0	3			
				Kidney:					
				Adenoma (m)	0	1			
				Gallbladder:					
				Carcinoma (m)	0	2			
INHALATION									
Rat (Wistar) 288 per sex) in test group 192 per sex in control	*Inhalation* **0.4 mg/L (111 ppm)** 7 hr/day, 5 day/wk for **2 years**		No clinical effects	Incidence of tumours similar in test & control grps. No hepatic or nasal tumours observed. Slight increase in mammary gland adenomas & reticulum cell sarcomas in both sexes.				Whole body study & therefore body burden (105 mg/kg/d) may be an underestimate	Torkelson et al. (1974)
DERMAL									
Mouse (C3H/HeJ Agouti) 30 animals (m) per test group	*Dermal* **0.05ml (50 mg)** (100% 1,4-dioxane) 3 applications per wk for 78 wk	Early deaths (see Comments) were reportedly caused by respiratory failure due to infection.	No clinical effects	Hepatic (5) & pulmonary (1) neoplasms observed in treated animals were reported to be within normal limits. The 'control group' was treated with ethanol.				4 grades of 1,4-dioxane were tested. Not known whether test substance applied under occlusion. Only 40 of 120 test animals survived to end of study.	Perone et al. (1976)

Table 6 - Summary of chronic toxicity/carcinogenicity studies (cont.)

Test animal	Exposure (route/dose & duration)	Gross observations	Clinical & pathological effects (non-neoplastic)	Tumour incidence in target organs (by test group)	Comments	Study ref.
Mouse (Swiss Webster) 30 animals per sex in test group	*Dermal* **0.2 ml** *(of solution of test substance in acetone vehicle).* No information on dose provided. 3 applications per wk for **60 wk**		*Carcinogenicity study:* No pre-neoplastic lesions reported. *Promotion study:* Mild liver lesions (include megalocytosis, occasional centrilobular necrosis & fibrosis); skin lesions include hypertrophy & hyperplasia.	*Carcinogenicity study:* Subcut tumour = 1/22 males Skin carcinoma = 1/25 females *Promotion study:* After 20 weeks in promotion study, approximately 80% of males had skin tumours. At end of study tumours included: skin (inc. a squam carcinoma of nasal septum), lung, kidney & liver seen in 15 /30 animals.	Pre-treatment with 50 µg DMBA (as initiator) in promotion study. Experimental details limited - not known whether 1,4-dioxane applied under occlusion. Control data not reported.	King et al. (1973)

including 2 esthesioneuroepitheliomas and 1 rhabdomyosarcoma.

[a], [b] etc = test group designations	aden = adenoma	grps = groups	
m = male	adenocarc = adenocarcinoma	hep = hepatocellular	
f = female	carc = carcinoma	meso = mesothelioma	
* $p \leq 0.05$	cholang = cholangioma	meta = metaplasia	
** $p \leq 0.01$	deg^n = degeneration	prolif = proliferation	
*** $p > 0.05$	DMBA = dimethylbenzanthracene	reg^n = regeneration	
**** $p = 0.50$	epid = epidermoid	sqam = squamous cell	
	epith pap = epithelial papilloma	subcut = subcutaneous	
	esthesio = esthesioneuroepithelioma		

Other carcinogenicity screening studies

Shimkin's lung adenoma test

1,4-Dioxane was administered both by gavage (1000 mg/kg, 3 times a week for 8 weeks) and i.p injection (200, 500,1000 mg/kg, 3 times a week for 8 weeks) to male and female A/J mice to test for the induction of lung tumours (Stoner et al., 1986). A significant increase (38%) in lung tumours (compared with controls) was seen only in males dosed at 500 mg/kg by i.p. injection. The authors concluded that this finding was the result of a low incidence of tumours in control animals. Since many known carcinogens have demonstrated false negative effects in this assay, a negative result is not considered meaningful in the absence of other bioassays (Ito et al., 1992).

Tumour initiation and promotion studies

A number of studies have been performed to test the initiation/promotion potential of 1,4-dioxane.

In female Sencar mice administered 1000 mg/kg 1,4-dioxane (oral, dermal or sub-cutaneous) as an initiator, followed by treatment with the promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), 3 times a week for 20 weeks, no significant increases in the formation of papillomas were observed (Bull et al., 1986).

1,4-Dioxane (881 mg/kg) administered by i.p. injection to male Sprague Dawley rats (1 day after partial hepatectomy), followed by administration of 500 ppm sodium phenobarbitone (in drinking water) for 49 days, showed a lack of initiation activity as demonstrated by measurement of gamma-glutamyl transferase (GGT) positive foci in the liver (GDCH, 1991).

In a study by King et al. (1973), 1,4-dioxane was a potent promoter of tumours following dermal application (see Table 6) to Swiss-Webster mice, following administration of the initiator 7,12-dimethylbenz[a]anthracene (DMBA). Tumours of skin, nose, lung, kidney and liver were reported. Apparently these findings could not be reproduced in a repeat study (GDCH, 1991).

Tumour promoting activity was also demonstrated in Sprague Dawley rats where there was a statistically significant increase in gamma-glutamyl-transpeptidase (GGT) positive foci in the liver following i.p administration (1 day after partial hepatectomy) of the initiator diethylnitrosamine (DEN), with subsequent oral dosing of 1,4-dioxane at 1000 mg/kg/day for 7 weeks. No increase in GGT positive foci was noted in animals not initiated with DEN (Lundberg et al., 1987).

Significant dose-related increases in hepatic ornithine decarboxylase (ODC) activity in the liver of Sprague Dawley rats were observed following a single dose of 840, 2550 and 4200 mg/kg 1,4-dioxane, suggestive of strong promoter activity (Kitchin & Brown, 1990). In addition, cytochrome P-450 was also induced at these doses.

Other studies supporting the role of 1,4-dioxane as a tumour promoting agent, include its ability to inhibit gap junction intercellular communication (GJIC) *in vitro* (Chen et al., 1984), a property shared by a number of non-genotoxic carcinogens and promoters (Swierenga & Yamasaki, 1992). In addition, 1,4-dioxane has been shown to induce cell proliferation (in nasal turbinates and hepatocytes) *in vivo* at cytotoxic doses (Goldsworthy et al., 1991). Regenerative cell proliferation has been linked to 'preferential' growth of pre-cancerous cells (Butterworth et al., 1992).

9.2.6 Reproductive and developmental toxicity

No effects on fertility were reported in OCR Swiss mice given 1,1,1-trichloroethane containing 3% 1,4-dioxane stabiliser during a 2-generation drinking water study (Derosa et al., 1996). Doses of 1,4-dioxane were estimated as 3, 10 and 30 mg/kg/day. The validity of this study has been questioned due to the nature of the test material and the fact that the upper dose level was not shown to be approaching maternally toxic doses (EEC, 1988). Testicular tumours were seen in rats in a chronic feeding study carried out by NCI (NCI, 1978), however, other chronic studies failed to corroborate this finding (see Table 4). Effects (reversible) on certain hormones, including gonadotropin-releasing hormone (LHRH) and prolactin, involved in regulation of reproductive function, have been reported in rats (Stepanov et al., 1995). Chen et al. (1984) reported that 1,4-dioxane inhibits GJIC (*in vitro*), a mechanism which has been associated with reproductive dysfunction in adult germ tissue. 1,4-Dioxane did not induce chromosomal aberrations *in vitro* (in CHO cells) or *in vivo* (male mouse germ cells), indicating a low potential for reduced fertility or inherited genetic effects (Galloway et al., 1987; Appel 1988).

The potential for 1,4-dioxane to induce developmental effects in the offspring of Sprague Dawley rats given 0, 0.25, 0.5 and 1.0 ml/kg/day (0, 258, 517 and 1033 mg/kg/day) by gavage, on days 6-15 gestation, has been reported (Giavini et al., 1985). Slight maternal toxicity, as evidenced by reduced weight gain, was observed at the highest dose. There were no differences between control and treated groups in implantation numbers, live foetuses, post-implantation loss or major malformations. Slight embryotoxicity, manifested by reduced foetal weight and reduced sternebral ossifications, occurred only at the highest dose level. In another study, no treatment-related developmental effects were seen in the offspring of Sprague Dawley rats or Swiss Webster mice exposed (7 hr/day) by inhalation to 1,1,1-trichloroethane containing 3.5% 1,4-dioxane on days 6-15 gestation (Schwetz et al., 1975). The exposure concentration for 1,4-dioxane was estimated to be 32 ppm (0.12 mg/L) (GDCH, 1991).

9.3 Genotoxicity and other related bioassays

In this section, studies relevant to the assessment of adverse effects on the genome are evaluated. Such studies include standard tests carried out to determine mutagenic and clastogenic potential and tests designed to help characterise the mechanism of 1,4-dioxane induced carcinogenicity.

9.3.1 Studies on 1,4-dioxane

1,4-Dioxane has been investigated in several *in vitro* and *in vivo* assays for a number of genetic endpoints. Studies are summarised in Table 7A (*in vitro*) and Table 7B (*in vivo*). Results of these studies are discussed below.

Gene mutations

Assays (7 *in vitro* and 1 *in vivo*) for gene mutations were all negative. Standard assays included 4 Ames tests (using at least 8 test strains of *S. typhimurium*) conducted with and without metabolic activation, and an *in vivo* sex-linked recessive lethal (SLRL) test in *Drosophila melanogaster*.

DNA effects

In assessing DNA effects (7 *in vitro* and 12 *in vivo* studies), 3 *in vitro* and 4 *in vivo* assays had positive end-points, with a further *in vivo* study for replicative DNA synthesis (RDS) considered equivocal. Of the 7 positive studies, the following comments are made: with regard to the 2 positive assays for DNA damage, positive results were either 'weak' or seen only at high test doses (Sina et al., 1983; Kitchin & Brown, 1990). Similarly, the *in vitro* sister chromatid exchange (SCE) assay was only 'weakly positive' at high test doses (Galloway et al., 1987). *In vivo* unscheduled DNA synthesis (UDS) (Stott et al., 1981) and RDS (Goldsworthy et al., 1991; Miyagawa et al., 1997) assays were only positive following prolonged exposure or single exposure at high doses (1000 - 2000 mg/kg bw).

Chromosomal aberrations

Both *in vitro* chromosomal aberration (somatic and germ cells) assays were negative. There was only one positive *in vivo* micronucleus test (Mirkova, 1994) of 4 studies carried out in 5 different strains of mice. Also, a similar test with a similar dosing regime carried out in the same strain (C57BL6) was negative (Tinwell & Ashby, 1994). 1,4-Dioxane has also been reported to give negative results (*in vivo*) in the mouse dominant lethal test (Appel, 1988). Conflicting results were seen in lymphocytes of workers exposed to 1,4-dioxane (Thiess et al., 1976; Thiess et al., 1981).

Other relevant bioassays

Of the tests not included in the above end-points (4 *in vitro* and 1 *in vivo* tests), 3 assays (cell transformation and GJIC *in vitro* and RNA polymerase transcription inhibition *in vivo*) were reported as positive (Sheu et al., 1988; Chen et al., 1984, Kurl et al., 1981).

Table 7A - Summary of *in vitro* genotoxicity studies

Type of test	Test system	Dose of 1,4-dioxane	Result	Comments	Reference
GENE MUTATION ASSAYS					
Ames test *(reverse mutation)*	*S. typh.* (strains TA1535; TA1537; TA98; TA100)	100; 333; 1000; 3333; 10,000 µg/plate	**Negative** (+ & - MA)	Results were consistent between 2 testing laboratories.	Haworth et al. (1983)
Ames test *(reverse mutation)*	*S. typh.* (strains TA1535; TA100)	10 -103 mg/vessel	**Negative** (+ & - MA)	1,4-Dioxane added to open glass Petri dishes.	Nestmann et al. (1984)
Ames test *(reverse mutation)*	*S. typh.* (strains TA1535; TA1537; TA1538; TA98 ; TA100)	0 - 103 mg/plate	**Negative** (+ & - MA)	Cytotoxicity at 62.0 mg/plate without metabolic activation.	Stott et al. (1981)
Ames test *(reverse mutation)*	*S. typh.* (8 strains, inc. TA98; TA100; TA102)		**Negative** (+ & - MA)		Khudoley et al. (1987)
Point mutation	*S. cerevisiae* (strain D61.M)	1.48% - 4.31%	**Negative**	Severe effects on cell morphology at 3%	Zimmermann et al. (1985)
Mutatox test *(reverse mutation)*	*Photobacterium phophoreum* (strain M169)	Not stated	**Negative** (- MA)	Experimental results not published in paper.	Kwan et al. (1990)
Mammalian cell gene mutation (*forward*) assay	Mouse (L5178Y) lymphoma cells	312 - 5000 ug/ml	**Negative** (+ & - MA)	Duplicate trials were conducted. No toxic responses were observed.	McGregor et al. (1991)
ASSAYS FOR DNA EFFECTS					
DNA damage (alkaline elution)	Rat hepatocytes	0.03 mM - 30.0 mM	**Positive**	Maximum response seen at 3 mM accompanied by > 30% cytotoxicity.	Sina et al. (1983)
DNA repair	Rat primary hepatocytes	0.001-1.0mM	**Negative**	Metabolic induction involved pretreatment of animals with 1-2% dioxane (in drinking water) for 1 week.	Goldsworthy et al. (1991)
Differential DNA repair	*E. coli* (strain K12 - uvrB/recA)	1150 mM/L	**Negative** (+ &- MA)	Assay measures differential lethality in DNA repair deficient & proficient bacteria.	Hellmer & Bolcsfoldi (1992)
UDS	Rat primary hepatocytes	10^{-8} to 1 M (88 mg/ml)	**Negative** (+ &- MA)		Stott et al. (1981) US EPA (1989b)
Mitotic recombination	*S. cerevisiae* (strain D61.M)	1.48% - 4.31%	**Negative**	Severe effects on cell morphology at 3%.	Zimmermann et al. (1985)

Table 7A - Summary of *in vitro* genotoxicity studies (cont.)

Type of test	Test system	Dose of 1,4-dioxane	Result	Comments	Reference
ASSAYS FOR DNA EFFECTS (cont.)					
SCE	CHO cells	1050-10,500 µg/ml	**Weakly positive** (- MA)	Positive at highest test dose.	Galloway et al. (1987)
DNA synthesis - inhibition	HeLa S3	DI_{50} = 400 mM/L	**Positive**	Many non-genotoxic carcinogens give positive results in this test.	Heil & Reifferscheid (1992)
ASSAYS FOR CHROMOSOMAL ABERRATIONS					
aberration	(wheat)	solution	(- MA)		(1986)
Chromosome aberration	CHO cells	1050-10,500 µg/ml	**Negative** (+ & - MA)	Details of analyses not reported.	Galloway et al. (1987)
OTHER					
Induction of aneuploidy	*S. cerevisiae* (strain D61.M)	1.48% - 4.31%	**Negative**	Severe effects on cell morphology at 3%.	Zimmermann et al. (1985)
Cell transformation assay	Mouse BALB/3T3 cells	0.25 - 4.0 mg/ml Treatment periods of 48 hr and 13 days	**Positive** (-MA)	1,4-Dioxane induced type III foci (indicative of transformation) at 0.5 & 2.0 mg/ml.	Sheu et al. (1988)
Cell transformation assay	SA7/SHE test system	62-1000 µg/ml	**Negative**	1,4-Dioxane did not increase frequency of virus-transformed foci.	Heidelberger et al. (1983)
GJIC	Chinese Hamster V79 cells	5 – 80 µl/5ml	**Positive**	1,4-Dioxane increased recovery of 6-thioguanine (HGPRT) cells above 10µl/5ml.	Chen et al. (1984)

+MA = *with* metabolic activation
-MA = *without* metabolic activation

CHO = Chinese hamster ovary
C. capillaris = *Crepis capillaris*

DI_{50} = Conc. of agent which inhibits DNA synthesis by 50%

E. coli = *Escherichia coli*
GJIC = Gap-junction intercellular communication
S. cerevisiae = *Saccharomyces cerevisiae*

S. typh. = *Salmonella typhimurium*
SA = Simian adenovirus
SCE = sister chromatid exchange
SHE = Syrian hamster embryo cells
UDS = Unscheduled DNA synthesis

Table 7B - Summary of *in vivo* genotoxicity studies

Type of test	Test system	Dose/route	Result	Comments	Reference
GENE MUTATION ASSAYS					
Sex-linked recessive lethal	*Drosophila melanogaster*	35,000 ppm (feeding) & 50,000 ppm (injection); (3 days exposure)	**Negative**	Criteria for positive test > 0.2% lethals.	Yoon et al. (1985)
ASSAYS FOR DNA EFFECTS					
	(male)	4 hr before sacrifice			
	(Hepatic DNA)				US EPA (1989b)
DNA damage (alkaline elution)	Rat (female) (Hepatocytes)	0, 168, 840, 2550 or 4200 mg/kg (gavage) 21 hr & 4 hr before sacrifice	**Weakly positive**	Hepatic DNA damage (43-50%) at 2 highest dose levels. DNA damage seen without cytotoxicity.	Kitchin & Brown (1990)
DNA damage	Rat (male) (Kidney cells)	Dose stated as approx. half LD$_{50}$	**Negative**		Sai et al. (1989)
UDS	Rat (male) (Hepatocytes)	1000 mg/kg (2-12 hr prior to sacrifice) or up to 2% dioxane in the drinking water for 1 week	**Negative**		Goldsworthy et al. (1991)
UDS	Rat (Hepatocytes)	10, 100, 1000 mg/kg (gavage) 7 days prior to sacrifice	**Negative**		Stott et al. (1981)
UDS	Rat (Hepatocytes)	10 & 1000 mg/kg/day (in drinking water) for 11 weeks	**Negative** at 10 mg/kg **Positive** at 1000 mg/kg		Stott et al. (1981)
UDS	Rat (male) (Nasal epithelium)	1% in drinking water for 8 days plus 10-1000 mg/kg (gavage) 12hr prior to sacrifice	**Negative**	Nasal epithelial cells derived from the nasoturbinate or the maxilloturbinate.	Goldsworthy et al. (1991)
RDS	Rat (male) (Nasal epithelium)	1% in drinking water for 2 weeks	**Negative**	Nasal epithelial cells derived from the nasoturbinate or the maxilloturbinate.	Goldsworthy et al. (1991)

Table 7B - Summary of *in vivo* genotoxicity studies (cont.)

Type of test	Test system	Dose/route	Result	Comments	Reference
ASSAYS FOR DNA EFFECTS (cont.)					
RDS	Rat (male)	Single dose of 1000 mg/kg (gavage) or 1% in drinking water for 2 weeks	**Negative** (single dose)		Goldsworthy et al. (1991)
	(Hepatocytes)		**Positive** (repeat dose)	2-fold increase in hepatic LI (drinking water grp).	
RDS	Rat (male)	1000 & 2000 mg/kg (single oral dose) 24, 39 & 48 hr	**Equivocal**	An equivocal effect (1.1% hepatocytes) on RDS incidence was seen after 24 hr without a decrease in cell viability. 1,4-Dioxane caused decreased cell viability at 39 & 48 hr in both test groups without an increase in RDS.	Uno et al. (1994)
RDS	Rat (male)	2000 mg/kg (single oral dose). 24, 39 & 48 hr	**Positive**	A positive effect (4.0% hepatocytes) on RDS incidence was seen after 24 hr. No histopathological changes induced.	Miyagawa et al. (1997)
RDS	Mouse (CBA/J) (male)	injection of 0.5 ml of 0.1% - 20% 1,4-dioxane solution (daily for 7 days).	**Negative**	Incorporation rates where recorded for isolated lymphocytes. No histopathological changes induced.	Thurman et al.. (1978)
ASSAYS FOR CHROMOSOMAL ABERRATIONS					
Micronucleus (bone marrow)	Mouse (CBA & C57BL6 strains) (male)	1800 & 3600 mg/kg (single oral dose)	**Negative**	3 independent assays undertaken. P/N ratio: 0.6 to 1.0	Tinwell & Ashby (1994)
Micronucleus (bone marrow)	Mouse (C57BL6 & BALB/c strains) (male/female)	450 - 5000 mg/kg (oral gavage) in C57BL6 5000 mg/kg in BALB/c mice 24 & 48 hr before sacrifice	**Positive** in C57BL6 strain **Negative** in BALB/c strain	Dose-related increase in MPE in C57BL6 strain from 900 mg/kg (males) & females at 5000 mg/kg (only dose tested).	Mirkova (1994)
Micronucleus (bone marrow)	Mouse (B6C3F1 strain)	500 - 4000 mg/kg (i.p) 24 & 48 hr before sacrifice	**Negative**		McFee et al. (1994)
Micronucleus (peripheral erythrocytes)	Mouse (CD-1 strain) (male)	500 - 3200 mg/kg (i.p) animals were injected twice (24 hr apart)	**Negative**	Blood samples analysed 24, 48 & 72 hr following second injection.	Morita (1994)

Table 7B - Summary of *in vivo* genotoxicity studies (cont.)

Type of test	Test system	Dose/route	Result	Comments	Reference
ASSAYS FOR CHROMOSOMAL ABERRATIONS (cont.)					
Dominant lethal test (germ cells)	Mouse (male)	2.5 ml per kg (i.p) (approx 2500 mg/kg) one injection	**Negative**	Original study carried out by BASF in 1977 not sighted.	Appel (1988)
Clastogenicity (lymphocytes)	Human (male)	Up to 48 mg/m^3 (13 ppm) 1,4-dioxane (TWA)	**Negative**	Workers (24) exposed (average duration of 25 years) during manufacture and handling of 1,4-dioxane.	Thiess et al. (1976)
		No data on 1,4-dioxane exposure	**Positive**	Workers (11) exposed (>20 yr) to alkylene oxides (including ethylene oxide, propylene oxide and 1,4-dioxane).	Thiess et al. (1981)
OTHER					
RNA-polymerase transcription inhibition (hepatic nuclei)	Rat (male)	10 mg & 100 mg (single intravenous injection) 24 hr before sacrifice	**Positive**	Decreased levels of RNA polymerases A and B peaked at 4 hr post injection.	Kurl et al. (1981)

LI = labelling index
MPE = Micronucleated polychromatic erythrocytes
N = normochromatic erythrocytes
P = polychromatic erythrocytes
RDS = replicative DNA synthesis
UDS = unscheduled DNA synthesis

9.3.2 Studies on 1,4-dioxane metabolites

The 1,4-dioxane metabolite, 1,4-dioxan-2-one, did not cause point mutations in the Ames test (*S.typhimurium* strains TA 98; 100; 102; 1535; 1537; 1538), CHO (HGPRT assay) cells (0.1 - 4.65 mg/ml) or guinea pig V79 cells (GDCH, 1991). Negative results were also demonstrated in the rat (male F-344) primary hepatocyte DNA repair assay (0.001-1.0 mM) (Goldsworthy et al., 1991). A positive result was seen in a mouse cell (BALB/3T3) transformation assay (above 0.25 mg/ml), but only without metabolic activation (GDCH, 1991).

A structure activity relationship (SAR) evaluation of the 1,4-dioxane metabolite, ß-hydroxyethanoxyacetic acid (HEAA) using TOPKAT computer (rat/mouse) models predicted HEAA to be non-mutagenic in the Ames test (Derosa et al., 1996).

9.4 Summary of animal data for 1,4-dioxane

Table 8 summarises results of the most relevant toxicological studies, including critical effects and NOAELs/LOAELs (where determined).

Genotoxicity studies are not included in Table 8 as they are summarised in Tables 7A and 7B.

Table 8 - Summary of animal data for 1,4-dioxane

Study type	Route of administration	Species	Result
Acute toxicity			
Lethality	Oral	Rat	LD_{50} = 5170-7300 mg/kg
		Mouse	LD_{50} = 5700 mg/kg
		Guinea pig	LD_{50} = 1270-3900 mg/kg
		Rabbit	LD_{50} = 2000 mg/kg
		Cat	LD_{50} = 2000 mg/kg
	Dermal	Rabbit	LD_{50} = 7600 mg/kg
		Rat	LD_{50} > 8000 mg/kg
	Inhalation	Rat	LC_{50} (2hr) = 12,780 ppm (46 g/m^3)
		Mouse	LC_{50} (2hr) = 18,000 ppm (65 g/m^3)
	Intravenous	Rabbit	LD_{50} = 1500 mg/kg
	Intraperitoneal	Rat	LD_{50} = 5300 mg/kg
		Mouse	LD_{50} = 4100 - 5790 mg/kg
CNS effects	Oral	Rat	Perturbations of neurotransmitters at lowest test dose (1050 mg/kg)
Liver effects	Oral	Rat	Mild histological effects (at and above 2550 mg/kg)
Irritation	Skin	Rabbit	Mild irritant
		Guinea pig	Non irritant
		Rat	Non irritant
		Mouse	Non irritant
	Eye	Rabbit	Irritant
		Guinea pig	Irritant
	Respiratory system	Guinea pig	Irritant (>2000 ppm)
		Mouse	Irritant
		Cat	Irritant
Sensitisation	Skin	Guinea pig	Non sensitising

Table 8 - Summary of animal data for 1,4-dioxane (cont.)

Study type	Route of administration	Species	Result
Sub-acute & sub-chronic effects			
Behaviour study *(2 weeks)*	Inhalation	Rat	Inhibition of avoidance response. - NOEL = 1500 ppm
9 days	Oral	Dog	Severe kidney and liver damage & some fatalities. LOAEL = approx 350 mg/kg/d
8 weeks	Oral (gavage)	Mouse	NOAEL= 3000 mg/kg bw per week
11 weeks	Oral (dw)	Rat	Mild hepatic effects. - LOAEL= 1000 mg/kg/day - NOAEL= 10 mg/kg/day
30 days	Inhalation	Rabbit	Severe kidney damage. - LOAEL= 800 ppm
27 weeks	Inhalation	Dog	NOAEL= 50 ppm
Chronic effects			
78 weeks	Dermal	Mouse	No treatment related effects. No effects seen following 150 mg/wk (1500 mg/kg/d)*
2-year	Inhalation	Rat	No treatment related effects. - NOAEL= 0.4 mg/L or 111 ppm (105 mg/kg/d).
23-month	Oral (dw)	Guinea pigs	Tumours (liver & gallbladder) and lung effects. - LOAEL = 5-2.0% (>2000 mg/kg/day)
2-year	Oral (dw)	Rat	Liver tumours: - NOAEL = 0.01 - 0.02% (10-40 mg/kg/day) - LOAEL = 0.1% (90-150 mg/kg/day) Nasal tumours: - NOAEL = 0.1% (90-150 mg/kg/day) - LOAEL = 0.5% (250-350 mg/kg/day.
2-year	Oral (dw)	Mouse	Liver tumours: - LOAEL = 0.05% (40-70 mg/kg/day). Nasal tumours: - NOAEL = 0.2% (160-280 mg/kg/day); - LOAEL = 0.5% (400-700 mg/kg/day).
Reproductive effects			
Development	Oral (gavage)	Rat	Effects only at maternally toxic doses. - NOAEL = 517 mg/kg/day
Fertility	Oral (dw)	Rat	Effects on sex homones (LHRH and prolactin) (critical doses not ascertained)

dw = drinking water study   study not considered of sufficient quality to derive a NOAEL

9.5   Human health effects

9.5.1   Fatalities

A total of six fatalities from exposure to 1,4-dioxane have been reported in the literature.

Barber (1934) reported 5 fatalities amongst a group of workers exposed to 1,4-dioxane vapours during textile (artificial silk) manufacture. All deaths occurred within a two week period, between 4 and 8 weeks after an alteration in the process, which led to an increase in potential exposure (inhalation) to 1,4-dioxane (dermal contact may have contributed to body burden). No estimates of 1,4-dioxane exposure levels or duration of exposure were reported in this study (although Johnstone (1959) reported an exposure period of up to 16 months for this study) apart from the fact that one death occurred following only 5 days exposure. Clinical signs of toxicity included severe epigastric pain, convulsions and coma. Histology revealed centrilobular liver necrosis and symmetrical necrosis (outer cortex) of the kidney. Haemorrhagic nephritis was reported as the ultimate cause of death. The author concluded that the deaths resulted from 'intensive acute exposure' to 1,4-dioxane, rather than cumulative exposure, based on the fact that 3/5 cases worked extended shifts (up to 12 hrs) prior to the onset of illness. A further 4 workers were reported as similarly exposed in the above process, of which 2 exhibited symptoms of liver toxicity.

Another occupational fatality following exposure to 1,4-dioxane was reported by Johnstone (1959). Following 1 week (presumably 5 days) exposure to an estimated average concentration of 470 ppm (range 208-650 ppm) 1,4-dioxane in air (dermal absorption was also possible), a worker using 1,4-dioxane as a solvent to remove glue, died 6 days after being admitted to hospital with severe epigastric pain. Postmortem examination revealed hepatic (centrilobular necrosis) and renal (necrosis of cortex) lesions as well as demyelination and loss of nerve fibre in the CNS. The author concluded that alcohol consumption may have increased the susceptibility of the worker to 1,4-dioxane intoxication, but made no conclusions as to the nature of the exposure (i.e., acute or cumulative) associated with the elicited effects.

Sullivan (1994) reported the fatality of a worker exposed to a concrete sealant containing 1,1,1-trichloroethane (80%) and 1,4-dioxane (2.5%). The autopsy report listed the cause of death as trichloroethane intoxication. The sealant product has since been recalled by the manufacturer.

9.5.2   Irritation and sensitisation

Skin

No controlled studies have been conducted to evaluate the sensitisation potential of 1,4-dioxane in humans. Several weeks of dermal exposure to 1,4-dioxane resulted in inflammatory skin changes in a female laboratory technician. This study reported that renewed exposure, some 4 weeks later, led to a relapse with clinical symptoms of eczema. However, it was concluded from negative results on 2 other volunteers that this reaction was idiosyncratic and may have been related to a previously sustained chemical burn (GDCH, 1991). A single positive patch test response to 1,4-dioxane was reported in a worker presenting with dermatitis apparently caused by skin contact with 1,4-dioxane used as a degreasing solvent (Adams, 1983).

Eye and respiratory irritation

In a study of four male volunteers exposed to 50 ppm (180 mg/m³) for 6 hr, the only effect reported was eye irritation (Young et al., 1977).

In a series of studies, volunteers exposed to 200-300 ppm 1,4-dioxane for 15 min, 1600 ppm for 10 min and 5500 for 1 min, complained of eye, nose and throat irritation whereas no such effects were reported in volunteers exposed to 1000 ppm for 5 min or 2000 ppm for 3 min (Derosa et al., 1996).

In subjects exposed to concentrations ranging from 0.7 to 2800 ppm for unspecified durations, slight mucous membrane irritation was reported at 280 ppm (1000 mg/m³), becoming more severe at 1400 and 2800 ppm (Derosa et al., 1996).

9.5.3 Chronic effects

In a matched-pair study of 151 workers exposed from 1 to 6 years to high atmospheric concentrations (1.4 mg/L) of 1,1,1-trichloroethane blended with 4% 1,4-dioxane (exposure levels not reported) stabiliser, no adverse effects on the liver or heart were reported (GDCH, 1991).

In an unpublished study reported to NIOSH, 4 cancer deaths (1 each from colonic cancer, pulmonary carcinoma, lymphosarcoma and glioblastoma) were reported from a cohort of 80 'dioxane workers'. Observed deaths were not considered significantly different from expected cancer deaths (Santodonato et al., 1985).

In a retrospective mortality study of 165 workers exposed to 1,4-dioxane during manufacture and processing, the observed cancer deaths (3) were not significantly different from the expected number (1.7). Exposure periods for tumour onset were between 1 and 4 yr. The workers concerned had apparently been exposed to less than 25 ppm 1,4-dioxane. Cancer deaths were reported as carcinoma of stomach, alveolar cell and mediastinal tumour. A death from chronic hepatitis/cirrhosis was also reported. Results were inconclusive according to study authors for reasons such as the small cohort size and relatively short exposure duration (Buffler et al., 1978).

In a study of 74 workers, no increased incidence in cancer was observed. The workers were exposed to 1,4-dioxane during manufacture and handling, for an average duration of 25 yr, with an estimated exposure to 0.02 to 48 mg/m³ (0.006 - 13 ppm). The authors concluded that increased serum transaminase levels seen in 6 of 24 workers currently exposed may have been related to alcohol consumption. In addition, chromosomal aberrations were not increased in lymphocytes of exposed subjects (Thiess et al., 1976). In a further study, a significant increase in mean lymphocyte chromosomal aberration frequency was found in 11 workers exposed (>20 yr) to alkylene oxides (including 1,4-dioxane). Exposures to known mutagens such as ethylene oxide and propylene oxide confound any conclusions with regard to causation (Thiess et al., 1981).

In a comparative mortality study (Hansen, 1993) of over 19,000 cases in the Danish cancer register, a standardised proportionate incidence ratio (SPIR) of 1.64 was determined for liver cancer in male workers employed in companies between 1970 - 1984 using 1,4-dioxane. The authors concluded that this increase (64%) was significant ($p = 0.04$) and that confounding factors, particularly alcohol consumption, could not account for this.

However, when a latency period (minimum 10 years) is incorporated in the analysis, the SPIR is reduced to 1.15. Statistically, the confidence intervals (1.03 - 2.48) indicate the possibility of a real effect however, uncontrolled factors, such as the potential for exposure to other carcinogenic chemicals, particularly 1,1,1-trichloroethane, and the lack of quantitative exposure data for 1,4-dioxane confound any conclusions regarding a causal association with liver cancer in this study. An increase in liver cancer of 50% was identified in one workplace where only 1,4-dioxane was used. Again, alcohol consumption alone could not account for this increase.

The same authors (Hansen et al., 1993) carried out a workplace exposure survey (1983-91) and reported that the majority of 1,4-dioxane levels measured were less than 10 mg/m^3 (3 ppm). However, these data were insufficient to speculate on workplace exposure levels in the comparative mortality study (Hansen, 1993).

9.5.4 Reproductive and developmental effects

Studies on 'reproductive outcome' were conducted in pregnant women (314 workers) exposed to chemicals (including 1,4-dioxane) in the electronics industry (Ailamazian, 1990). Effects included an increased incidence of miscarriages, premature births, maternal toxicosis, foetal ossifications and decreased birth weights. Gonadotoxic effects, associated with 1,4-dioxane exposure, also in the electronics industry, were reported by Mikheev et al. (1979). Insufficient data were available in these studies to draw any conclusions with respect to 1,4-dioxane exposure and the effects observed. A PBPK model, developed for lactating women, indicated that exposure to 25 ppm 1,4-dioxane in air may give rise to a significant lactational transfer (Fisher et al 1997).

9.6 Hazard evaluation and classification

In this section, pertinent data on physicochemical and health hazards are evaluated in order to classify the hazards of 1,4-dioxane to humans. In extrapolating results from experimental studies (animal and *in vitro* bioassays), consideration has been given to important issues, such as quality of data, weight of evidence, mechanism of action, pharmacokinetic/dose-response relationship and relevance to humans.

Workplace substances are classified as 'hazardous' to health if they meet the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1994a), and 'dangerous' in terms of physicochemical hazards, if they satisfy the criteria of the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) (FORS, 1998).

The classification recommended for 1,4-dioxane is incorporated in the following assessment of health and physicochemical hazards.

9.6.1 Physicochemical hazards

1,4-Dioxane is a volatile liquid (vapour pressure 4.9 kPa @ 25°C) with a flash point (closed cup) of 12°C and boiling point of 101°C. In addition, 1,4-dioxane can form explosive peroxides (on standing in contact with air) and reacts vigorously with oxidising agents and certain incompatible materials.

Classification status

1,4-Dioxane meets the ADG Code (FORS, 1998) criteria for assignment to *Class 3 (Flammable liquid) - Packaging Group II*. It is also noted in the ADG Code that 1,4-dioxane has a potential to form explosive peroxides in the presence of air.

The European Commission (EC, 1993a) has classified 1,4-dioxane as *highly flammable* and *may form explosive peroxides* (R11 and R19 respectively).

9.6.2 Kinetics, metabolism and mechanistic considerations

1,4-Dioxane vapour is rapidly absorbed from lungs in humans (~80%) and animals (~100%). Around 3% of an applied dermal dose was absorbed from unoccluded skin in monkeys (over 24 hrs), however, evidence indicates that higher levels are likely to be absorbed if evaporation is prevented (Bronaugh, 1982).

In animals, 1,4-dioxane is widely distributed to the various organs, including target organs (liver and kidney), where selective accumulation has been reported. Covalent binding was only demonstrated in liver, spleen and colon.

Administration of inhibitors and inducers of cytochrome P-450 results in an increase and decrease in the LD_{50} for 1,4-dioxane respectively, indicating a role for the microsomal mixed function oxidase system in metabolism and potentiation of acute toxicity. 1,4-Dioxane is rapidly metabolised in both humans and animals to HEAA, which is excreted in urine with a small amount of unchanged 1,4-dioxane. In humans, clearance of HEAA (from kidneys) is much faster (approx. 400 fold) for HEAA than for 1,4-dioxane. Metabolism and plasma half-lives for 1,4-dioxane are similar in animals and humans.

A metabolic threshold for biotransformation of 1,4-dioxane has been demonstrated in rats, above which a larger proportion (increasing with dose) of unchanged 1,4-dioxane is eliminated (in urine and expired air). Although the dose of 1,4-dioxane at which metabolic saturation occurs has not been fully elucidated in either animals or humans, it has been estimated that saturation occurs at a plasma level (steady state) of 100 µg/ml 1,4-dioxane in rats. No evidence of metabolic saturation was seen in humans exposed to 50 ppm 1,4-dioxane for 8 hours, which lead to plasma levels (steady state) of 10µg/ml 1,4-dioxane and 8µg/ml HEAA.

Toxicological data indicate that the metabolic saturation dose may be associated with chronic tissue damage, which in turn may be a precursor of neoplastic effects. Although increased retention of unmetabolised 1,4-dioxane has been proposed as a primary cause of liver/kidney damage, a number of metabolites, including 1,4-dioxan-2-one, β-hydroxyethoxy acetaldehyde, diethylene glycol and oxalic acids, have also been implicated in the toxic/carcinogenic effects of 1,4-dioxane. However, available data are inconclusive as (i) there is no evidence that any of the above metabolites are increased during metabolic saturation and (ii) evidence indicates that induction of metabolic enzymes occurs during repeated dosing (above metabolic saturation levels) with a concomitant reduction in 1,4-dioxane body burden (Young et al., 1978).

Route of administration would also appear to have a bearing on toxicity and carcinogenicity (Kociba et al., 1975), which may be due to differences in distribution to target organs (Reitz et al., 1990). Thus, extrapolations between ingested and inhaled doses (i.e., in the derivation of LOAEL/NOAELs) are considered inappropriate, unless differences in toxicokinetics are well understood.

9.6.3 Health hazards

Acute effects

In animals, 1,4-dioxane has a low acute toxicity by all routes of exposure. The oral LD_{50} for rats was >5,000 mg/kg bw and the inhalation LC_{50} was >12,500 ppm (>45 mg/L/2 hr). No data were available for dermal LD_{50} in rats, although a level of 8,300 mg/kg bw reportedly produced no evidence of toxicity in Wistar rats (Derosa et al., 1996). The dermal LD_{50} in rabbits was >7000 mg/kg bw.

The main acute effects in animals are CNS depression, kidney and liver damage. Limited data exist on irreversible effects after single exposure. In rats, clinical effects have been reported above 300 mg/kg 1,4-dioxane with subtle effects on CNS function >1000 mg/kg. Acute histopathological (hepatic) effects have been reported >2500 mg/kg, however, the reversibility of these lesions was not investigated.

Classification status

1,4-dioxane does *not* meet the Approved Criteria (NOHSC, 1994a) for *acute lethal effects* by oral, dermal or inhalation exposure.

Inadequate data were available to classify 1,4-dioxane for *non-lethal (irreversible) effects after single exposure*.

Irritant effects

Skin irritation

Isolated cases of 1,4-dioxane-induced skin irritation have been seen in workers. Two tests (skin) carried out in rabbits indicate that 1,4-dioxane (one study of around 50 mg application) is a mild skin irritant, however, one test was carried out on unoccluded skin and the other (summary only) did not provide any study details. Insufficient details were available to assess the reported lack of irritation, from repeated dermal application of 1,4-dioxane, in rabbits, guinea pigs and mice. In particular, these studies did not report whether doses were applied under occlusion.

Classification status

Inadequate data were available to classify 1,4-dioxane for *skin irritation*.

Eye irritation

Eye irritation has been reported in humans exposed to 50 ppm (180 mg/m^3) 1,4-dioxane for 6 hr. Acute eye irritation (transient corneal damage) has been reported in animals (rabbits and guinea pigs) from liquid and vapour 1,4-dioxane.

Classification status

1,4-Dioxane meets the Approved Criteria (NOHSC, 1994a) for *eye irritation* (R36).

Respiratory irritation

1,4-Dioxane causes slight irritation of nose and throat in humans above 280 ppm (1000 mg/m^3) with more severe irritation occurring above 1400 ppm (5000 mg/m^3). Respiratory irritation (nose and lung) has been reported in guinea pigs (above 2000 ppm (7000 mg/m^3) 1,4-dioxane), mice and cats.

Classification status

1,4-Dioxane meets the Approved Criteria (NOHSC, 1994a) for *irritation to the respiratory system* (R37).

Sensitisation

A few cases of eczema and dermatitis (including a positive patch test response to 1,4-dioxane) have been reported in humans following repeated exposure to 1,4-dioxane. However, these cases would appear to be circumstantial or idiosyncratic in nature. 1,4-dioxane was not a sensitiser in a well conducted guinea pig maximisation test (BASF, 1993).

Classification status

1,4-Dioxane does *not* meet the Approved Criteria (NOHSC, 1994a) for *sensitising effects* (*skin*).

Effects (non-carcinogenic) following repeated exposure

Effects seen in humans from repeated short-term exposure to 1,4-dioxane include CNS, kidney and liver damage, convulsions, coma and death. Exposures associated with these adverse effects are unquantified, but are estimated to be high. Fatalities have been reported following 6 days to 2 months exposure to 1,4-dioxane which, in one case, was estimated to be 470 ppm (1700 mg/m^3) in air (Johnstone (1959). Exposure via skin absorption was also likely in these cases.

Similar effects (CNS, kidney and liver damage) have been seen in sub-chronic and chronic animal studies. None of the sub-acute or sub-chronic studies were considered of sufficient quality to derive LOAELs. A LOAEL of 0.1% (90 - 150 mg/kg/d) 1,4-dioxane was determined for chronic oral exposure in rats (most sensitive species). LOAELs were not determined in either chronic inhalation or dermal studies, although no effects were seen in rats or mice exposed to 111 ppm and 1500 mg/kg per day respectively.

Classification status

Based on the data available, 1,4-dioxane does *not* meet the Approved Criteria (NOHSC, 1994a) for classification under *severe effects after repeated/ prolonged exposure.*

Reproductive effects

Fertility

Limited evidence exists in humans regarding gonadotoxic effects from occupational exposure to 1,4-dioxane. Testicular tumours were seen in rats in a carcinogenicity study carried out by NCI, however, other chronic studies failed to corroborate this finding. No effects on fertility (2-generation study) were reported in mice administered 1,1,1 - trichloroethane containing 1,4-dioxane (up to 30 mg/kg/day). However, doses used in this study were an order of magnitude lower than those required to elicit toxic effects in chronic mouse studies. Limited evidence exists in rats that 1,4-dioxane has effects on certain sex hormones.

Classification status

Inadequate data were available to classify 1,4-dioxane for *effects on male or female fertility* (EC, 1993b).

Development

An increased incidence of effects on 'reproductive outcome', including miscarriages, premature births and decreased birth weights, were reported in women exposed to chemicals (including 1,4-dioxane) in the electronics industry. Concurrent exposures to other chemicals preclude any conclusions with respect to 1,4-dioxane causation.

No effects on implantation numbers, live foetuses, post-implantation loss or major malformations were seen following administration (oral) of up to 1.0 ml/kg/day (1033 mg/kg/day) 1,4-dioxane to pregnant rats. This dose caused slight maternal toxicity as evidenced by reduced weight gain.

Classification status

1,4-Dioxane does *not* meet the European Commission criteria for *developmental toxicity* (EC, 1993b).

Genotoxicity

Studies on the chromosomal aberration frequency in lymphocytes from 1,4-dioxane-exposed humans have provided conflicting results, although it would appear that positive results have only been seen in workers with a history of exposure to other known mutagens, such as ethylene oxide and propylene oxide.

No alkylation of hepatocellular DNA was seen in rats at 1,4-dioxane doses associated with carcinogenicity. This is supported by evidence from structure-activity (SAR) modelling using the Computer Automated Structure Evaluation (CASE), which indicates a lack of intrinsic electrophilicity for 1,4-dioxane and metabolites (Rosenkranz & Klopman, 1992).

Negative results were seen in all gene mutation assays (including Ames *Salmonella* assays and *Drosophila* SLRL); both *in vitro* 'germ cell' cytogenetic assays; all assays (*in vitro* and *in vivo*) for UDS; 4 out of 5 assays for micronuclei induction (bone marrow and peripheral erythrocytes) and in a mouse dominant lethal test. This battery of tests would be expected to identify most genotoxic chemicals.

Of the positive results, a feature of assays for DNA effects (*in vitro* and *in vivo*) was that they were mainly seen at cytotoxic concentrations. The only positive chromosome aberration (*in vitro* and *in vivo*) assay (apart from study on human lymphocytes, already mentioned above) was a mouse micronucleus test (bone marrow) which, when repeated (using the same strain of animals), gave a negative result, in agreement with similar tests in 4 other mouse strains.

1,4-Dioxane produced positive results in cell proliferation (RDS), cell transformation, DNA synthesis-inhibition (Heil & Reifferscheid, 1992) and gap-junction intercellular communication (GJIC) assays (Chen et al., 1984), all of which have been used to screen for non-genotoxic carcinogens and in particular tumour promoting agents (Swierenga & Yamasaki, 1992; Ramel, 1992).

1,4-Dioxane has also been shown to inhibit transcription regulation (RNA-polymerase activity) *in vivo* (Kurl et al, 1981), an effect that has been linked with non-mutagenic carcinogenesis (Tennant, 1993).

The metabolite 1,4-dioxan-2-one also gave negative results in the Ames and HGPRT tests in addition to UDS *in vitro*. This is despite the fact that a number of lactones with a similar structure to this metabolite have been demonstrated as carcinogenic (Pitot & Dragan, 1996).

Overall, the weight of evidence from *in vitro* and *in vivo* tests indicates that 1,4-dioxane is unlikely to be a mutagen. Although the mechanism for carcinogenicity for 1,4-dioxane has not been established, the apparent lack of genotoxic effects of 1,4-dioxane metabolites, together with the fact that 1,4-dioxane exhibits tumour promoter properties support a non-genotoxic mechanism of carcinogenicity.

Classification status

1,4-Dioxane does *not* meet the Approved Criteria (NOHSC, 1994a) for *mutagenic effects.*

Carcinogenicity

Available cancer mortality studies of workers exposed to 1,4-dioxane indicate that observed cancer rates are not significantly higher than the number expected, although the populations studied were considered of insufficient size to detect a 'weak' carcinogenic effect (Goodman & Wilson, 1991). A significant increase in deaths from liver cancer in workers with a history of exposure to 1,4-dioxane was seen in a comparative mortality study (using Danish cancer registry data), however, confounding factors (such as co-exposures to other chemical substances, lack of data on alcohol consumption and lack of exposure data) preclude any firm conclusions with respect to a causal association with 1,4-dioxane exposure.

1,4-Dioxane has been shown to cause malignant tumours (multiple sites) in more than one animal species. Tumour sites associated with 1,4-dioxane exposure in animal studies were: liver (rat, mouse and guinea pig), nose (rat and mouse) and gall bladder (guinea pig). Liver tumours were the only tumours seen in all species tested and were elicited at lower doses than nasal tumours in rats and mice (only one dose was tested for guinea pigs). In addition, an increase in liver tumours was reported in one epidemiological study on workers exposed to 1,4-dioxane.

Mechanistic considerations

It is considered likely that 1,4-dioxane tumourigenicity is elicited via a non-genotoxic mechanism, as the weight of evidence indicates that neither 1,4-dioxane nor its major metabolite, 1,4-dioxan-2-one are genotoxic. There is evidence to suggest that the mechanism of 1,4-dioxane elicited carcinogenicity may be associated with one or more of the following: promotion of endogenous carcinogen(s), cytochrome P-450 induction (the majority of promoters of hepatocarcinogenesis are P-450 inducers), tissue damage (cytotoxicity), increased cell proliferation, DNA replicative synthesis (RDS) and saturation pharmacokinetics. A widely postulated mechanism of action is tissue damage followed by increased cell proliferation and RDS.

There is little evidence to elucidate whether 1,4-dioxane *per se* or a metabolite (e.g., diethylene glycol, 1,4-dioxan-2-ol or HEAA) is associated with carcinogenicity.

Treatment of mice with 1,4-dioxane for 3 days increased lipid peroxidation (Mungikar & Pawar, 1978), a potential mechanism of cell damage and precursor of carcinogenicity. However, the same authors suggested that 1,4-dioxane metabolites

acted as antioxidants as indicated by a significant reduction in the 'diene conjugation band' in the ultraviolet spectrum of liver microsomal lipids (Pawar & Mungikar, 1976).

Effects on certain sex hormones have been reported in rats (Stepanov et al., 1995). In addition, 1,4-dioxane has been demonstrated to possess protein denaturing activity *in vivo* (Argus et al., 1965). Irrespective of whether such effects are related, perturbations in hormonal regulation have also been linked to carcinogenicity in humans and animals.

The possibility of 1,4-dioxane inducing liver tumours via proliferation of hepatic peroxisomes (a mechanism of tumour formation thought *not* to be relevant to humans) has been investigated. Oral treatment of rats with 1.0% 1,4-dioxane (in the drinking water) for 5 days or 2000 mg/kg/day (gavage) for 11 days, did not elicit an induction of palmitoyl CoA oxidase activity, despite increases in absolute and relative liver weights (Goldsworthy et al., 1991; US EPA, 1989b). Results indicate that 1,4-dioxane does not elicit tumourigenicity via peroxisome proliferation.

The possibility of carcinogenicity elicited by impurities in 1,4-dioxane is also considered unlikely. Argus et al. (1973) analysed 1,4-dioxane used in a chronic bioassay for the presence of hydroperoxides (known to be carcinogenic). None were detected (detection limit 15 μM) either in original 1,4-dioxane or following mixing with tap water used in drinking water study.

A number of other impurities (see Section 3.8) have been reported in different grades of 1,4-dioxane, including the recognised human carcinogen, bis (2-chloroethyl) ether (BCEE). BCEE is reported as a starting product in one method of 1,4-dioxane manufacture, however, it was not reported as a potential impurity by notifiers.

Summary

Overall, indications are that the primary mechanism(s) of tumourigenicity for 1,4-dioxane in animals is non-genotoxic. A number of possible epigenetic mechanisms (including tumour promotion, endocrine-modifying, immunosuppressant, cytotoxic, mitogenic/cell proliferation etc.,) have been proposed. However, data from mechanistic studies are largely inconsistent and it is possible that a novel mechanism may be involved (Derosa et al., 1996).

The most important considerations with respect to classification are that:

- Insufficient data (from animal or human studies) exist to discount the relevance to humans of tumours, particularly liver tumours, seen in animal studies;

- Evidence from genotoxicity studies (*in vitro* and *in vivo*) indicate that 1,4-dioxane is a non-genotoxic carcinogen;

- Pharmacokinetic data indicate similarities between rat and human metabolism of 1,4-dioxane; and

- Evidence from animal studies indicates the existence of a threshold dose for toxicity and carcinogenicity at doses where 1,4-dioxane metabolism becomes saturated.

Classification status

In accordance with the Approved Criteria (NOHSC, 1994a), 1,4-dioxane should be classified as a *Category 3 carcinogen* (R40).

International carcinogen classifications for 1,4-dioxane

1,4-Dioxane has been classified by the European Commission (EC, 1993a) as a category 3 carcinogen (Risk phrase R40) and by IARC (IARC, 1987) as a Group '2B' carcinogen ('possible human carcinogen').

The US EPA has classified 1,4-dioxane as a 'B2' carcinogen ('probable human carcinogen') (Derosa et al., 1996) and ACGIH (ACGIH, 1997) as 'A3' ('animal carcinogen').

Germany (DFG, 1996) has classified 1,4-dioxane as a group IIIB carcinogen ('suspected of possessing significant carcinogenic potential'). Denmark (Jensen & Niemela, 1997) and Norway (Jorgensen, 1995) have classified 1,4-dioxane as a carcinogen category 'K3' with risk phrase R215 ('risk of cancer cannot be excluded with prolonged exposure') and Sweden (KEMI, 1997) with risk phrase R340 ('some risk of cancer cannot be excluded after frequently repeated exposure').

10. Occupational Health Risk Characterisation

In this section, the results of the hazard and occupational exposure assessments have been integrated to characterise the risk of adverse effects in workers potentially exposed to 1,4-dioxane. The assessment of risks to workers has been carried out for specific occupational groups (potentially exposed to 1,4-dioxane) identified in Australia.

Results from the risk characterisation process provide the basis for health risk management strategies (i.e., methods to reduce exposure and/or increase worker awareness of potential hazards and safe handling of 1,4-dioxane).

10.1 Methodology

The risk to human health from exposure to 1,4-dioxane has been characterised using methodology commonly adopted in international assessments (EC, 1994; OECD 1994).

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

1. Identification of the critical effect(s).

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

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

$$MOS = NOAEL / EHD$$

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

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

The 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 potential adverse effects decreases. In deciding whether the MOS is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process, such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability.

10.2 Critical health effects and exposures

10.2.1 Acute effects

The critical effects from acute exposure to 1,4-dioxane to humans are eye and respiratory irritation and liver and kidney damage following high exposures. Eye irritation has been reported at atmospheric levels as low as 50 ppm, but appears to be more prevalent above 200 ppm.

Six fatalities were reported from exposure (5 days to several months) to 1,4-dioxane. All deaths resulted from liver and/or kidney failure, and were preceded by severe epigastric pain, convulsions and coma. It is not known whether deaths resulted from acute exposure to 1,4-dioxane or cumulative exposure. Exposure data for one worker were estimated between 208-650 ppm (750-2340 mg/m^3) in air for 1 week. The author noted that dermal exposure was also possible (Johnstone, 1959).

10.2.2 Chronic effects

Effects from long-term repeated (chronic) exposures are not well characterised in human populations. 1,4-Dioxane elicits tumours in animals in multiple species and at multiple sites and hence most human (epidemiological) studies have focused on carcinogenic effects. Limited evidence from a single epidemiological study indicate that liver tumours may be associated with occupational exposure to 1,4-dioxane.

Insufficient human data exist to correlate chronic exposures to 1,4-dioxane with adverse effects. However a number of chronic studies have been carried out in a variety of animal species (by different routes of exposure).

Oral exposure

Only chronic *oral* studies have been carried out in more than one species. In rats, mice and guinea pigs the critical non-neoplastic and neoplastic endpoints are hepatic effects.

The available data indicate a similar sensitivity with regard to hepatic tumours in rats and mice. A NOAEL$_{(oral)}$ for hepatic effects has only been identified in rats (10 - 40 mg/kg/day).

Inhalation

No treatment-related effects were seen in a chronic (2-year) rat inhalation study at a single exposure level. The chronic NOAEL$_{(inhal)}$ was 0.4 mg/L (111ppm). The study author estimated this exposure to be equivalent to an internal dose of 105 mg/kg/day.

Dermal exposure

No treatment-related effects were seen in chronic dermal studies in mice, the only species tested. However, neither available study (Perone et al., 1976; King et al., 1973) was considered of sufficient quality for the purpose of deriving a chronic NOAEL$_{(derm)}$.

Conclusions

The available data indicate that, on grounds of similarities between metabolic profiles and sensitivity to 1,4-dioxane, the rat is the most suitable species for estimating risks from repeated dose (inhalation) exposure to humans. Although the mouse may be an

appropriate model for assessing dermal risks from contact with 1,4-dioxane in humans, a definitive NOAEL (dermal) could not be determined from available studies. However, the available data indicate that the applied dose is likely to be high.

10.3 Occupational health and safety risks

Occupational health risks may result from acute and/or chronic exposure to 1,4-dioxane via inhalation and dermal exposure. Other occupational safety risks may arise from physicochemical hazards.

10.3.1 Risk from physicochemical hazards

1,4-Dioxane is a highly flammable liquid with an explosive/flammability limit of 2% in air at standard temperature and pressure. The high vapour pressure and rate of evaporation indicate high volatility for 1,4-dioxane. These properties, in addition to its vapour density (about 3 times more dense than air), account for its potential to travel considerable distances to an ignition source with a consequent risk of 'flash back'. In addition, 1,4-dioxane can form explosive peroxides (on standing) under certain conditions and reacts vigorously with oxidising agents and certain incompatible materials.

Risks of fire and/or explosion from 1,4-dioxane are highest from its use as a solvent (i.e., when used undiluted), particularly under conditions of low humidity, and in this respect 1,4-dioxane may present a fire/explosion risk to laboratory workers. Such risks from the use of products containing 1,4-dioxane as an ingredient are largely dependent on the physicochemical properties of other ingredients present and should be determined for the mixture. A flammability risk also exists for products used in optical lens coating and film processing.

10.3.2 Acute health risks

Despite the high volatility of 1,4-dioxane (4.9 kPa), it is considered unlikely that, for uses identified in Australia, vapour levels would reach those required to elicit acute systemic effects (from inhalation) or respiratory irritation, although eye irritation may occur where inadequate ventilation exists.

There is limited evidence from animal studies (with alcohol dehydrogenase (ADH) inhibitors) to suggest that alcohol intake may increase the acute toxicity of 1,4-dioxane in humans (GDCH, 1991).

10.3.3 Chronic health risks

It is generally considered appropriate that risk characterisation of non-genotoxic carcinogens (i.e., those that are carcinogenic via an epigenetic mechanism) should be treated differently to genotoxic carcinogens, in that the former group of chemicals (which includes 1,4-dioxane) may be treated as requiring a threshold dose to elicit effects (ECETOC, 1996). Therefore an MOS approach is generally recommended for non-genotoxic carcinogens. Risk assessments for genotoxic carcinogens have traditionally been carried out using low-dose extrapolation models (e.g., Linear Multistage (LMS) model), often referred to as quantitative risk assessment or mathematical modelling techniques.

Despite the fact that exposures are not well characterised for occupational scenarios with potential exposure to 1,4-dioxane either in Australia or overseas, information on

known use profiles and data obtained from the UK EASE model (see Section 8) have enabled estimates of risk to be made. Because dermal exposure is unlikely to contribute significantly to body burden (see Section 8.1) only exposure via inhalation has been assessed in the following occupational scenarios. Margins of safety (MOS) were calculated using the NOAEL$_{(inhal)}$ of 111 ppm reported in the study by Torkelson et al. (1974).

Research/development and analytical applications

With regard to research/development and analytical applications, exposure to 1,4-dioxane is likely to be intermittent. In addition, potential 1,4-dioxane exposure is likely to be minimised in the majority of applications, due to the availability of fume cupboards and the small amounts used at any one time. A single published overseas study reported levels of airborne 1,4-dioxane in laboratories, to be less than 2 ppm TWA (8 hr). However, the source(s) of 1,4-dioxane was not reported in this study, and it is not known how representative this study is of other laboratory applications of 1,4-dioxane. In view of the lack of exposure data, it was not considered appropriate to carry out MOS calculations, however, it is concluded that, due to the pattern of use (intermittent) and engineering controls (fume cupboards) the risk of adverse chronic health effects is likely to be low.

Manufacture, formulation and use of ethoxylated chemicals

With regard to manufacture of ethoxylated chemicals, exposure to 1,4-dioxane is likely to be low due to a number of factors, which include the generally small amounts of 1,4-dioxane formed as an impurity and the containment of the process within plant reactors. Information provided for surfactant manufacture indicates that levels of 1,4-dioxane in plant rooms are unlikely to exceed 1 ppm. Therefore it is estimated that for most manufacturing scenarios an MOS >100 is likely and hence risks of adverse chronic health effects are likely to be low.

In view of the relatively small amounts of 1,4-dioxane in ethoxylated chemical end products, adverse health risks to formulators (e.g., cosmetics and detergent industries) and end users (e.g., leather processing) are also considered to be low.

Film (celluloid) processing

Despite being a continuous 'open' process, exposure to 1,4-dioxane during film cementing is likely to be low, due mainly to the very small amounts of cement (containing 10-50% 1,4-dioxane) applied during each splicing procedure. Monitoring data from two film splicing laboratories in the USA indicate that breathing zone levels of 1,4-dioxane were below 1 ppm. This process was thought to be representative of Australian film laboratories and hence, an MOS of >100 is estimated, which indicates that risks of adverse chronic health effects from exposure to 1,4-dioxane are likely to be low.

Optical lens manufacture

No monitoring data for 1,4-dioxane levels were available for optical lens manufacture either in Australia or overseas. Although potential exposure to 1,4-dioxane during the coating process is intermittent, it is possible that some workers may be exposed for up to 20 hours per week, although rotation of staff, which was practiced at one site visited, would reduce individual exposures. In addition, the potential for exposure is

considered to be high as several litres of coating solution are used at any one time and, at one site visited, the exhaust ventilation used was of questionable adequacy, particularly with respect to clearing fumes emitted from ovens used in the drying process.

Estimated airborne levels of 1,4-dioxane obtained from the UK EASE model were between 10 and 50 ppm (see Section 8.2.3). Such exposure levels provide an MOS of between 2 and 11 for potential effects from inhalation (dermal absorption of 1,4-dioxane vapours is likely to be minimal). Thus, if this exposure range is representative of actual TWA (8 hr) exposures, the MOS would indicate some cause for concern with respect to chronic effects. In addition, exposures at the upper level estimated by UK EASE may be associated with a risk of eye irritation.

10.3.4 Uncertainties in the calculation of margins of safety (MOS)

A consideration of uncertainties in the risk characterisation process is necessary when discussing the acceptability and implications of estimated MOS. Examples of uncertainties inherent in the assessment of risk for 1,4-dioxane are as follows:

Inadequate data

- lack of exposure monitoring data;

- lack of representative worker exposure profiles (i.e., degree of worker exposure may vary from factory to factory); and

- inadequate data on human health effects following chronic exposure.

Assumptions in the assessment process

- that occupational dermal absorption (of vapours and liquid) is minimal;

- that absorption and bioavailability of 1,4-dioxane via inhalation is similar in humans and rats;

- that chronic hepatic effects seen in animals are relevant for humans; and

- that dose-response relationships are likely to be similar (on a ppm in air basis) in rats and humans.

Experimental data

- the $NOAEL_{(inhal)}$ for 1,4-dioxane was derived from a single dose study and as such may be a considerable underestimate (i.e., actual MOS may be higher);

- evidence indicates that human uptake by inhalation (on mg/kg basis) may be up to 50% lower than in animals (i.e., actual MOS may be higher);

- evidence indicates that metabolic saturation (thought to be associated with adverse effects in animals) does not occur in humans exposed to 50 ppm 1,4-dioxane (i.e., the MOS approach to risk assessment may not be appropriate at low level exposures).

11. Management of Occupational Risks

In this section, measures currently employed in the management of human health risks from occupational exposure to 1,4-dioxane are discussed. The information reviewed includes national and international standards, together with relevant guidance material, MSDS and labels. Where appropriate, measures for managing risks from exposure to 1,4-dioxane are dealt with separately for specific Australian workplace scenarios.

Relevant information was provided by manufacturers of ethoxylated chemicals, users of products (containing 1,4-dioxane as an ingredient) in the optical lens manufacturing and film processing industries, as well as suppliers and users of 1,4-dioxane for research, development and analysis. Information was also obtained from site visits.

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

• workplace control measures;

• hazard communication (including training and education);

• monitoring and regulatory controls; and

• emergency procedures.

11.1 Workplace control measures

According to the NOHSC *National Model Regulations for the Control of Workplace Substances* (NOHSC, 1994c), exposure to hazardous substances should be prevented or, where this is not practicable, adequately controlled, so as to minimise risks to health and safety. The NOHSC *National Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) provides further guidance in the form of a hierarchy of controls strategies, namely:

• elimination;

• substitution;

• isolation;

• engineering controls;

• safe work practices; and

• personal protective equipment.

Control measures are not mutually exclusive and effective control usually requires a combination of these measures. In relation to 1,4-dioxane, particular attention needs to be given to control measures that minimise inhalation and dermal contact.

11.1.1 Elimination and substitution

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

1,4-Dioxane is an unwanted by-product in a number of substances formed via ethoxylation type reactions. Prior dehydration of starting materials reduces the prevalence of side reactions, including 1,4-dioxane formation.

Process controls have been implemented to minimise the amount of 1,4-dioxane formed in the production process and/or reduce the amount present in the final product. The following process controls and reactor conditions were reported to assist in minimising the formation of 1,4-dioxane during production of sulphated/sulphonated surfactants:

- controlled uniform SO_3 gas flow (SO_3 in air, 3% vol. max.);
- precise raw material delivery system (mole ratio of SO_3:ethoxylate of 1.01 to 1.03 yields low 1,4-dioxane levels of 20-50 ppm);
- organic feedstock temperature controlled at 30°C;
- cooling water temperature controlled at 30°C;
- throughput: 85% w/w of nominal for alkylbenzene;
- fast neutralisation (typically with sodium hydroxide or triethanolamine); and
- maintain pH at or above 7.

One manufacturer reported that for amine ethoxylate surfactant production the use of base catalysis instead of acid catalysis resulted in up to a 70% reduction in 1,4-dioxane formation. In addition, amine ethoxylates, ethoxylated alcohols, USP grade polyethylene glycol surfactants (PEGS) and ethoxylated sorbitan and fatty acid esters are produced at lower reaction temperatures and under 'nitrogen padding' of reactor headspace to further reduce 1,4-dioxane formation.

1,4-Dioxane content of the final product may be further reduced by 'dioxane stripping', using either steam distillation or vacuum de-aeration techniques (Milwidsky, 1988). In practice, the 'stripping unit' operates as an in-line process step between the neutralisation stage and blending, but may be bypassed where 1,4-dioxane levels in the final product are not critical. Information provided by surfactant manufacturers in Australia indicates that the stripping systems used for their purposes are designed to achieve up to 95% removal of 1,4-dioxane, depending on the type of reactor used. Product analytical data supplied by one manufacturer indicated a reduction of 75 - 85%.

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

1,3-Dioxolane (CAS No. 646-06-0) has apparently been used as a substitute for 1,4-dioxane in a wide range of solvent applications (CWBG, 1993), however, its suitability for the applications assessed in this report is unknown. Evaluation of the health hazards of 1,3-dioxolane and other 1,4-dioxane alternatives is outside the scope of this report.

Little is known about suitable replacements for 1,4-dioxane in lens manufacture. However, one manufacturer recently reported that a suitable alternative product (KP-64 hard coating liquid) had been developed and would replace the existing use of a 1,4-dioxane-containing product. The potential health hazards of this 'substitution product' were not assessed.

Alternative cements (using increasing concentrations of dichloromethane or acetone to replace 1,4-dioxane) have apparently been tried in film processing. Apparently, if 1,4-dioxane is omitted, the glued celluloid becomes more brittle and is subject to 'cracking'.

With regard to surfactants, alternatives that are free of 1,4-dioxane precursors (e.g., alkylpolyglucosides (Bernadi et al., 1996)) are available, however, their suitability as replacements for surfactants in use is unknown.

Little information was available for assessment regarding alternatives for 1,4-dioxane in solvent or analytical reagent applications. However, due to its diversity of applications it is unlikely that any one substance would be a suitable substitute. Some users have reported that 1,4-dioxane has unique solvent properties which are essential for certain laboratory applications.

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

Substitutes for 1,4-dioxane should be of a lower toxicity and thoroughly tested.

11.1.2 Isolation

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

There is limited scope for isolation of workers from potential exposure to 1,4-dioxane during laboratory applications as such applications usually require manual handling. Although not strictly defined as isolation, exposures may be significantly reduced by storage and use in fume cupboards/hoods.

At one site visited, isolation of the optical lens coating process was achieved by housing the solvent baths and drying ovens in a separate workshop, with solvent baths situated in airtight cabinets. However, exposure to 1,4-dioxane was possible as lenses were loaded and removed manually in this process.

The manufacture of ethoxylated surfactant products is essentially a closed process, where products are handled in sealed or contained plant systems.

11.1.3 Engineering controls

Local exhaust ventilation is the most common practicable engineering control for 1,4-dioxane exposure.

In the optical lens coating process at one site visited local (mechanical) exhaust ventilation was installed with cabinets containing solvent baths. Solvents, including 1,4-dioxane, were stored in a fume cupboard.

No exhaust ventilation was employed during film splicing at one workshop visited, apart from standard air conditioning.

It is anticipated that most laboratories using 1,4-dioxane would be equipped with both exhaust (mechanical) ventilation and fume cupboards/hoods. Australian Standard AS 2982.1 (Standards Australia, 1997b) provides information on laboratory construction and Australian Standards AS 2243.8 (Standards Australia, 1992) and AS 2243.9 (Standards Australia, 1991a) provide information on fume cupboards.

No local exhaust ventilation was used at a surfactant manufacturing plant, in view of low level emissions during production. However, extractor fans were used in the sulphonation plant[1] building to provide general dilution ventilation.

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[1] The sulphonation process reportedly gives rise to the highest 1,4-dioxane impurity levels.

11.1.4 Safe work practices

A number of appropriate safe work practices have been recommended for handling 1,4-dioxane. Apart from the normal provisions for handling carcinogens and flammable chemicals, the following practices have been recommended for 1,4-dioxane:

- small quantities (< 50 L) to be kept in workrooms, provided they are contained in closed vessels and stored in cupboard/bin made of fire-resistant materials;

- use in well ventilated area;

- storage away from incompatible materials (e.g., oxidising agents; Raney nickel; nitromethane);

- storage and bulk containers[2] to be earthed to prevent static charge before 1,4-dioxane is removed;

- use non-sparking tools and footwear in storage area;

- no smoking in storage or work areas. 'NO SMOKING' signs posted in appropriate areas; and

- local authorities (including fire service) to be informed if 1,4-dioxane enters surface drains.

With regard to the use of 1,4-dioxane in laboratory applications, the following practices have been recommended:

- avoid storage in bottles with ground glass stoppers to reduce explosion hazard (on opening) from peroxide deposits;

- peroxides to be decomposed before distillation to low volume;

- provision of clear safety instructions at entry points to work areas;

- warning signs (e.g., FLAMMABLE material, CARCINOGENIC CHEMICAL in use) posted in appropriate areas;

- pipetting 1,4-dioxane by mouth should not be carried out; and

- disposal carried out according to recognised procedures and, where relevant, by qualified chemical disposal company.

Australian Standards AS 1940 (Standard Australia, 1993a) and AS 2243.10 (Standards Australia, 1993b) deal with the storage and handling of flammable/combustible chemicals. For other relevant documentation relating to safe work practices in laboratories, see Appendix 2.

11.1.5 Personal protective equipment

Where other control measures are not practicable or adequate to control exposure, personal protective equipment (ppe) should be used. Appropriate ppe recommended for handling 1,4-dioxane include the following:

- overalls;

- safety glasses;

- appropriate footwear (non-sparking); and

- protective gloves.

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[2] Peroxide formation may be minimised by storing under nitrogen atmosphere or treating with reductants such as $SnCl_2$ or $FeCl_2$ or by addition of stabilisers (e.g., hydroquinone).

Permeation results for 1,4-dioxane (given as breakthrough times in minutes) were available for the following materials: butyl rubber (480 min); PVA (480 min); neoprene (16 min); nitrile (20 min). These results serve to question the suitability of neoprene and nitrile gloves for handling 1,4-dioxane (US EPA, 1996b).

Respiratory equipment is not normally required during routine use of 1,4-dioxane. However, during clean-up of large spills and fire fighting, appropriate respiratory protection should be worn.

NSW WorkCover has recently published a guidance document on the use of personal protective equipment (NSW WorkCover, 1996). Personal protective equipment should be selected according to manufacturers/suppliers recommendations, usually available in the MSDS. Personal protective equipment should also meet the appropriate Australian Standards (see information contained in sample MSDS at Appendix 3).

11.2   Emergency procedures

The availability of an emergency response plan to deal with unexpected releases of 1,4-dioxane, such as large spills, is good practice. All employees need to be trained in accident and emergency procedures. Although such plans were not available for assessment, the following emergency procedures have been described in available MSDS:

*   shut off all sources of ignition following spillage;
*   evacuate unprotected personnel from danger area following spillage;
*   notify emergency services in event of large fires or spills;
*   use water fog or fine water spray for fire fighting;
*   use alcohol-type or universal-type foams and SCBA for large fires; and
*   emergency shower facilities to be provided for employees where skin exposure is considered a possible hazard.

With regard to transport and storage of 1,4-dioxane, appropriate emergency procedures are contained in Australian/New Zealand Standard HB76 *'Dangerous Goods - Initial Emergency Response Guide'* (Standard Australia, 1997) which is endorsed in the ADG Code (FORS, 1998).

All plans/procedures should be fully documented and available to all workers. Local emergency services should be consulted on the appropriateness of emergency procedures developed.

11.3   Hazard communication

11.3.1 Assessment of Material Safety Data Sheets (MSDS)

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

A total of 5 MSDS for commercial grade 1,4-dioxane (undiluted) were provided for assessment, in addition to one for a product containing >20% 1,4-dioxane and several ethoxylated chemical products. Only MSDS for 1,4-dioxane and products containing 1,4-dioxane at concentrations above 1% (i.e., minimum concentration cut-off for

classification) were assessed. Hence, MSDS for ethoxylated products were not assessed, as in no case did levels of 1,4-dioxane exceed 3000 ppm (0.3%).

MSDS were assessed against the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994d). The most common deficiencies in the MSDS assessed were:

- no Australian emergency contact number;
- limited or no information on Australian regulations (e.g., ADG classification SUSDP or exposure standard);
- no 'statement of hazardous nature' at beginning of MSDS;
- incorrect hazard classification (i.e., not classified according to the NOHSC Approved Criteria (NOHSC, 1994a);
- insufficient supporting toxicological or environmental data; and
- no information on appropriate disposal.

11.3.2 Assessment of labels

Under the NOHSC *National Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers of industrial chemicals are obliged to provide labels in accordance with the NOHSC *Code of Practice for the Labelling of Hazardous Substances* (Labelling Code) (NOHSC, 1994e). Where products containing 1,4-dioxane are intended for domestic end-use, they need only comply with the SUSDP labelling requirements (Australian Health Ministers' Advisory Council, 1997).

Two labels were provided for assessment, comprising a label for commercial grade 1,4-dioxane and a label for a film cement product containing 1,4-dioxane as an ingredient. Both products are intended for industrial use and should be labelled in accordance with the Labelling Code (NOHSC, 1994e). In assessing these labels, account was given to the fact that the label for the film cement product was for a container < 500 ml capacity and as such may be labelled according to the 'reduced requirements' as stipulated in the Labelling Code (NOHSC, 1994e).

Deficiencies in labels included:

- no contact details for Australian supplier;
- no UN number;
- no information on emergency procedures;
- no information on ADG class;
- no reference to MSDS;
- incorrect 'signal' word;
- no risk phrases or not in accordance with correct hazard classification;
- no safety phrases; and
- proportion of 1,4-dioxane not stipulated.

Labelling of chemicals for use in laboratory applications should also be carried out in accordance with the Labelling Code (NOHSC, 1994e). In particular, hazardous substances which are decanted and not consumed immediately should be labelled with the product name, together with risk and safety phrases.

11.3.3 Education and training

Guidelines for the induction and training of workers potentially exposed to hazardous substances are provided in the NOHSC *Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c). Specifically, matters that need to be addressed for 1,4-dioxane include:

- the potential adverse health effects of 1,4-dioxane;

- flammability/explosion properties of 1,4-dioxane;

- specific protective equipment to be worn; and

- explanation of data contained in MSDS and labels.

No staff training material was provided by notifiers/applicants for assessment. With regard to laboratory safety, a number of relevant publications were identified and are listed in Appendix 2.

11.4 Other regulatory controls

The following sections comprise regulations/standards promulgated with the aim of protecting workers from adverse exposures to 1,4-dioxane in Australia. In some cases (e.g., SUSDP Code), these regulations/standards may also apply to consumer exposures.

11.4.1 Atmospheric monitoring

Under the NOHSC *Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), employees are required to carry out an assessment of the workplace for all hazardous substances, the methodology of which is provided in the NOHSC *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* (NOHSC, 1994f). When the assessment indicates that the risk of exposure via inhalation is significant, atmospheric monitoring should be conducted to measure 1,4-dioxane levels in the workplace as a precursor to the implementation of suitable control measures to reduce exposure. Subsequent monitoring will be required to ensure that such measures are effective.

It should be noted that atmospheric monitoring may not provide an accurate estimate of total exposure (i.e., body burden) in situations where significant dermal exposure occurs.

11.4.2 Occupational exposure standards

Australian atmospheric exposure standard

The current occupational exposure standard for 1,4-dioxane in Australia is 25 ppm (90 mg/m^3) TWA with a 'skin' notation (NOHSC, 1995). This standard was adopted from ACGIH, (1991).

Between 1974 -1981, the ACGIH standard was set at 50 ppm, based primarily on the lack of effects seen from animal inhalation studies in (i) rats, guinea pigs, rabbits and dogs exposed to 50 ppm 1,4-dioxane for up to 195 days and (ii) rats exposed to 111 ppm for 2 years. Subsequently, a reduction to 25 ppm was implemented following concerns that 50 ppm "might not adequately reflect the toxicity" of 1,4-dioxane. The

rationale for these concerns is not wholly transparent from the ACGIH documentation, but appears to be related to the following:

- a US NIOSH recommendation (based on potential carcinogenicity) for an exposure standard of 1 ppm (NIOSH, 1977); and

- the fact that the daily estimated intake (25 mg/kg 1,4-dioxane per day) for a worker exposed to 50 ppm, exceeded the chronic $NOAEL_{(oral)}$ (0.01% 1,4-dioxane in drinking water) determined in rats by Kociba et al. (1974).

The ACGIH documentation concluded that the TLV should be derived from the $NOAEL_{(oral)}$ determined by Kociba et al. (1974) for hepato- and nephrotoxic non-neoplastic effects, which occurred at a lower dose than that associated with tumour induction. The ACGIH documentation for 1,4-dioxane was recently revised (ACGIH, 1997) to incorporate an A3 'animal carcinogen' classification.

The adopted Australian occupational exposure standard of 25 ppm is consistent with the standard in several other countries, including the UK, USA, and Canada. However, some countries have a lower exposure standard, including Sweden, Germany, Holland, Denmark and Japan.

International exposure standards

Table 9 provides occupational exposure limits for 1,4-dioxane in other countries.

Table 9 - International occupational exposure standards

Country	Exposure limit		Source
	TWA	STEL	
Norway	5 ppm (18 mg/m^3)	-	Jorgensen (1995)
Denmark	10 ppm (36 mg/m^3)	-	Jensen & Niemela (1997)
France	10 ppm (35 mg/m^3)	40 ppm (140 mg/m^3)	ECDIN (1997)
Japan	10 ppm (35 mg/m^3)	-	Anon (1996)
Russia	10 ppm (35 mg/m^3)	-	ILO (1991)
Sweden	10 ppm (35 mg/m^3)	50 ppm (180 mg/m^3)	KEMI (1997)
Netherlands	12 ppm (40 mg/m^3)	24 ppm (80 mg/m^3)	IUCLID (1995)
Germany	20 ppm (72 mg/m^3)	40 ppm (144 mg/m^3)	DFG (1996)
Belgium	25 ppm (90 mg/m^3)	-	ILO (1991)
Canada	25 ppm (90 mg/m^3)	-	UNEP (1993)
Finland	25 ppm (90 mg/m^3)	40 ppm (135 mg/m^3)	ECDIN (1997)
New Zealand	25 ppm (90 mg/m^3)	-	OSH (1992)
Switzerland	25 ppm (90 mg/m^3)	50 ppm (180 mg/m^3)	ILO (1991)
U.K.	25 ppm (90 mg/m^3)	100 ppm (360 mg/m^3)	HSE (1996)
USA (ACGIH)	25 ppm (90 mg/m^3)	-	ACGIH (1997)
USA (OSHA)	-	100 ppm (360 mg/m^3)	ACGIH (1997)
USA (NIOSH)	-	500 ppm (1800 mg/m^3)	UNEP (1993)
Austria	50 ppm (180 mg/m^3)	-	Kohlmann (1997)

TWA = Time weighted average   STEL = Short term exposure level

The current provisional German MAK of 20 mg/m^3 was apparently established to avoid eye irritation in workers, which is also expected to provide protection from cytotoxic/carcinogenic effects (Neumann et al. 1997). It is not clear how this level was derived, as the lowest exposure level reported in the literature for eye irritation in humans is 180 mg/m^3 1,4-dioxane (see Section 9.5.2).

The documentation to the Swedish occupational exposure standard indicates that the TWA standard is based on irritation to mucous membranes (Lundberg 1992), however it is not clear how the level of 35 mg/m^3 was derived. The STEL (adopted by Sweden) corresponds to the lowest exposure level reported (180 mg/m^3 1,4-dioxane) for eye irritation in humans (see Section 9.5.2).

The Dutch occupational exposure standard (TLV) of 40 mg/m^3, is apparently based on the NOAEL for chronic inhalation of 400 mg/m^3 derived by Torkelson et al. (1974). Uncertainty factors used in this derivation were a factor of 10 for interspecies differences and 1 for intraspecies variability (Van Koten, 1997).

The current Norwegian exposure standard (OEL) is apparently based on the NIOSH (NIOSH, 1977) criteria document (TLV of 1 ppm). No details of its derivation were provided, except that the OEL (18 mg/m^3), takes into account technical and economic considerations (Haug, 1997).

11.4.3 Health surveillance

In accordance with NOHSC *Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), employers have a responsibility to provide health surveillance in those workplaces where the workplace assessment indicates that exposure to a hazardous substance may lead to an identifiable substance-related disease or adverse health effect. 1,4-Dioxane is not listed in Schedule 3 (list of substances requiring health surveillance) and as such there are no formal requirements for health surveillance programs for exposed workers. Risk assessments for uses of 1,4-dioxane in Australia indicate that, under current conditions of use, risks of adverse occupational health effects are low (see Section 10.3.3).

The US NIOSH/OSHA Occupational Health Guidelines recommend liver function tests, urinalysis, chest X-ray and FEV/FVC lung function tests for employees exposed to hazardous levels of 1,4-dioxane (NIOSH/OSHA, 1978).

11.4.4 Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP)

1,4-Dioxane is listed (as 'Dioxane') in Schedule 6 of the Drugs and Poisons Schedule (SUSDP) in Australia (Australian Health Ministers' Advisory Council, 1997). Its availability is not restricted, but it must be labelled with the signal words 'POISON, NOT TO BE TAKEN' and 'KEEP OUT OF THE REACH OF CHILDREN' together with the following safety directions (SD) and first aid instructions, if it is likely to be used in the public domain:

Safety directions:
- Avoid contact with eyes (SD1);
- Avoid contact with skin (SD4); and
- Avoid breathing vapour or spray mist (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; and

- Remove from contaminated area. Apply artificial respiration if not breathing.

11.4.5 Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code)

1,4-Dioxane is listed (as 'Dioxane') in the ADG Code (FORS 1998). It is classified as a 'flammable liquid (Class 3)' and assigned to Packaging Group II, based on 'flash point (closed cup method)' and 'boiling point' criteria. The ADG Code also provides information for fire fighting and spillage dispersal, emergency procedures, packaging and storage requirements and road tank construction standards for 1,4-dioxane.

12. Public Health Assessment

1,4-Dioxane is listed in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (Australian Health Ministers' Advisory Council, 1997).

12.1 Public exposure

The general public may be exposed to 1,4-dioxane via skin absorption, inhalation and ingestion.

There is low potential for public exposure from research/laboratory use of small quantities of 1,4-dioxane. The notified flame retardant, containing up to 0.5% 1,4-dioxane, is applied by trades persons such as electricians and plumbers at the time of building construction or installation of pipes, cables etc and hence potential public exposure from such a use is negligible. Similarly, public exposure to 1,4-dioxane is unlikely from coated lenses or from film processing.

A survey undertaken by NICNAS indicated that widespread public exposure to 1,4-dioxane may occur from a variety of consumer products including cosmetics/toiletries, household detergents, pharmaceuticals, foods, agricultural and veterinary products, and ethylene glycol based antifreeze coolants.

There are no analytical data available for 1,4-dioxane levels in consumer products in Australia. The Cosmetic, Toiletry and Fragrance Association of Australia (CTFAA) have stated that the levels of 1,4-dioxane present in cosmetic/toiletry products are likely to be below 10 ppm, although some surfactant importers and manufacturers indicated that higher levels of 1,4-dioxane may be present in cosmetic/toiletry products (up to 30 ppm in hair and body cleaning liquids, liquid detergents and cosmetics). Based on published overseas analytical data, it appears that shampoo, hair conditioner, bath foam/liquid and body cleanser contain higher levels (see Table 10) of 1,4-dioxane than other cosmetic/toiletry products, such as skin cream/lotion, sun cream and after-shave. However, these data are limited in that it is now more than 5 years old and only represents a few countries and hence may be unrepresentative of the general marketplace and in particular the situation in Australia.

1,4-Dioxane has been detected in used ethylene glycol based antifreeze coolants (0.1 - 22 ppm) (Hartung, 1989). Some people may be exposed to 1,4-dioxane present in used antifreeze coolants during 'home maintenance' of automobiles. This would not be expected to occur more than once or twice a year and therefore exposure from this source should be negligible.

1,4-Dioxane is present in some pharmaceutical drugs and foods. Impurities in drugs and food products are regulated by the Drug Safety and Evaluation Branch of the Therapeutic Goods Administration and the Australia and New Zealand Food Authority (ANZFA), respectively. A number of ethoxylated products, such as polysorbates, are allowed for use in foods (National Food Authority, 1992). According to the US Food Chemicals Codex specifications, which are adopted by the ANZFA for polysorbates, the maximum level of 1,4-dioxane in these food additives is 10 ppm (Committee on Food Chemicals Codex, 1996). Therefore, the level of 1,4-dioxane in food products should be very low. 1,4-Dioxane has also been identified in a number of natural

products including shrimp, chicken, tomatoes, coffee and certain condiments (Hartung,

1989). Although the level of 1,4-dioxane in Australian food products has not been determined, it is expected to be extremely low.

The limit on the content of 1,4-dioxane in active raw pharmaceutical materials is 100 ppm (Anon, 1994a). However, there is no regulatory limit on 1,4-dioxane in drug products in Australia, although a limit of 380 ppm, equivalent to about 3.8 mg/day, was proposed by the International Conference on Harmonisation (European Agency for the Evaluation of Medicinal Products, 1996).

1,4-Dioxane may also be present in agricultural and veterinary products. A surfactant manufacturer indicated that the maximum level of 1,4-dioxane in ethoxylated amine surfactants used in such products is unlikely to exceed 10 ppm and considerably lower in the formulated product. It was also considered likely that the majority of 1,4-dioxane would evaporate to air following application. Residues in foods and hence Public exposure are therefore likely to be negligible from this source.

Most 1,4-dioxane for research/laboratory use or as a contaminant in ethoxylated surfactant (from manufacture and use) is disposed of into the sewer system. Considering the small quantities used in laboratories, lens coating and film processing and the low levels in ethoxylated chemicals and consumer products, disposal should result in little public exposure.

Table 10 - Monitoring data (1987-96) for 1,4-dioxane in consumer products

Product type	1,4-Dioxane (ppm)*	Reference
Shampoos	< 50 - 300	Rusenapp & Hild (1987)
Shampoos and bath foams (in Netherlands)	≤ 200 in 90% of samples tested	Weyland and Rooselaar (1987)
Consumer products (household/cosmetics - 19 named products)	6 -160	US EPA (1989c)
Consumer products	< 1 - 96	Rastogi (1990)
Dishwashing products	< 2 - 65	Rastogi (1990)
Moisturising lotion	4	Scalia & Menegatti (1991)
Baby lotion	11	Scalia & Menegatti (1991)
Shampoos	11-45	Scalia & Menegatti (1991); Scalia (1992)
Bath foam	22-41	Scalia & Menegatti (1991); Scalia (1992)
Body gel	16	Scalia (1992)
Hair lotion	47-108	Scalia & Menegatti (1991); Scalia (1992)
Liquid soap	7	Scalia (1992)
Cosmetics (variety) including: creams, lotions, shampoos, conditioners and cleansers	≤ 4	Song et al (1996)

* As well as quoted values, 1,4-dioxane was not detected in some samples.

12.1.1 Assessment of public exposure to 1,4-dioxane in cosmetics, toiletries and detergents

The main potential source of exposure of the general public to 1,4-dioxane is likely to be from exposure to consumer products, in particular, cosmetics/toiletries and detergents. Although oral intake of certain products is possible during normal use, the main routes of exposure to such products are inhalation and dermal contact.

There are a wide range of cosmetics/toiletries, which are either rinse-off or stay-on products. The most frequently used 'rinse-off' cosmetics/toiletries with relatively high levels of 1,4-dioxane may include hair shampoo and lotions, bath gel/foam and body cleanser, while skin cream/lotion may be the most widely and frequently used stay-on product.

Because of the large variety of cosmetics/toiletries used by the public, quantitative exposure assessment for 1,4-dioxane from all possible cosmetic/toiletry products is impractical. As such, consumer exposure to 1,4-dioxane in shampoo and skin lotion/cream has been evaluated, as representative of 'rinse-off' and 'stay-on' products, respectively, as such products may contain higher 1,4-dioxane levels.

Exposure to shampoo products

Based on the following assumptions: 30 ppm 1,4-dioxane present in shampoo, 10% of the product remaining on the skin following rinsing, 12 g used per application and one application per day, the estimated dermal contact with 1,4-dioxane for a 60 kg person is 0.6 µg/kg/day 1,4-dioxane (see Appendix 1, calculation 2).

Assuming a room volume 2 m^3 (adjusted for immediate vicinity of users) and 50% evaporation, the air level would be 0.09 mg/m^3 1,4-dioxane (see Appendix 1, calculation 3). Assuming 3% dermal absorption and 100% absorption by inhalation, 15 min per shower and a respiration rate of 0.9 m^3/h, the systemic exposure (body burden) is 0.36 µg/kg/day (for a 60 kg person), comprising: 0.02 µg/kg/day (6%) from dermal absorption and 0.34 µg/kg/day (94%) from inhalation

Exposure to body lotion/cream

For body lotion/cream, also assuming a 1,4-dioxane level of 30 ppm, 8 g used per application and 2 applications per day, the dermal *contact* would be 0.008 mg/kg/day (for a 60 kg person) equivalent to a systemic exposure of 0.24 µg/kg/day (see Appendix 1, calculation 4).

Exposure to household detergents

The 'worst case' exposure scenario among household detergents may be from hand dishwashing liquid because the uses of hand dishwashing liquid are frequent and a large number of homes do not have dishwashing machines. Since hand dishwashing liquid is normally diluted when used, dermal exposure should be lower than that from shampoo. However, using the same exposure model as for shampoo and assuming a 1,4-dioxane level of 30 ppm and 2 washes per day, the systemic exposure from hand dishwashing liquid is 0.72 µg/kg/day.

Other minor exposures may also occur, but would be only a fraction of the above exposures. Assuming that a person might use up to 10 consumer products per day, as the worst case scenario, with systemic exposure levels of 0.72 µg/kg/day from each product, the daily exposure would be about 7 µg/kg/day.

12.2 Assessment of public health risks

The health effects of 1,4-dioxane are described in Section 9.

In humans, acute health effects include hepatic and renal necrosis and irritation to the skin, eyes and respiratory tract via dermal and/or inhalation routes. However, acute public health risks are extremely unlikely from the exposure scenarios detailed in the previous section.

A number of epidemiological studies have been carried out for occupational exposures to 1,4-dioxane, however, none have conclusively demonstrated a causal relationship with adverse effects. Limited human data exist to suggest an association with 1,4-dioxane exposure and increased incidence of liver cancers.

Chronic effects in animals include hepatic, renal and lung effects and hepatic and nasal tumours. In rat studies (Section 9.2.5) the overall chronic NOAEL was 10 - 40 mg/kg/day (0.01 - 0.02% 1,4-dioxane in drinking water).

Compared with a NOAEL of 10 mg/kg/day, the above worst case assumption of a systemic exposure of 7 µg/kg/day (from consumer products) would represent a safety margin (MOS) of about 1500. The presence of 1,4-dioxane (up to 30 ppm) as an impurity in consumer products is therefore not considered to pose a significant health risk to the general public.

13. Recommendations

13.1　NOHSC hazard classification

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1994a) and based on an assessment of health hazards, the recommended classification for 1,4-dioxane is:

- **R36/37　　　Irritating to eyes and respiratory system**
- **R40　　　　Possible risk of irreversible effects**

Consistent with this classification, the *overall classification* for products or preparations containing *≥ 20% 1,4-dioxane*, is:

- **Harmful / Irritant : carcinogen (category 3)**

and for products or preparations containing *≥ 1% 1,4-dioxane < 20%*, is:

- **Harmful : carcinogen (category 3)**

Products or preparations containing other hazardous substances should be classified by taking into account the health effects of all ingredients.

The above classification is in agreement with the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1994b).

13.2　Hazard communication

As 1,4-dioxane is a hazardous substance, employers and suppliers should be aware of their obligations to provide information, such as MSDS and labels, about the hazards of the chemical. Details of these obligations, consistent with employers' general duty of care, are provided in the NOHSC *National Model Regulations to Control Workplace Hazardous Substances* (NOHSC, 1994c).

13.2.1　Material Safety Data Sheets

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

1,4-Dioxane is regulated for transport (FORS, 1998) and scheduled as a poison available to the public (Australian Health Ministers' Advisory Council, 1997) and has an Australian exposure standard. As such, specified information should appear in the MSDS under the relevant sections i.e., 'Identification', 'Precautions for use' and 'Safe handling information'.

In order to rectify the deficiencies identified in this assessment, it is recommended that suppliers amend their MSDS where necessary and in particular attention should be given to the following:

- inclusion of a statement of hazardous nature;
- appropriate risk and safety phrases;
- inclusion of an Australian emergency contact number;
- inclusion of Australian exposure standard; and
- information on appropriate disposal procedures.

A sample MSDS for 1,4-dioxane (commercial grade) is provided at Appendix 3.

13.2.2 Labels

It is recommended that labels be updated by suppliers of 1,4-dioxane, taking into account the deficiencies identified in this assessment. The labelling requirements are outlined below:

NOHSC requirements

The NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994e) provides guidance for the labelling of workplace hazardous substances (i.e., industrial chemicals). Requirements for 1,4-dioxane are as follows:

Ingredient disclosure

1,4-dioxane is a 'Type I' hazardous ingredient and as such, should be disclosed on the label (together with the concentration present) when present in a mixture above 1% w/w.

Risk and safety phrases

Consistent with its classification, the following NOHSC risk phrases are recommended for 1,4-dioxane:

R11*   **Highly flammable**

R19   **May form explosive peroxides**

R36/37   **Irritating to eyes and respiratory system**

R40   **Possible risk of irreversible effects**

(*this risk phrase need not be included if the ADG Code class (class 3) appears on the label)

The recommended safety phrases for 1,4-dioxane prescribed in the *List of Designated Hazardous Substances* (NOHSC, 1994b) are:

S16   **Keep away from sources of ignition - no smoking**

S36   **Wear suitable protective clothing**

S37   **Wear suitable gloves**

Safety phrases equivalent to **S23, S24, S25, S27 and S28** have also been recommended by the SUSDP (Australian Health Ministers' Advisory Council, 1997) - *see under 'SUSDP requirements' below*. Safety phrases should be chosen as considered appropriate.

1,4-Dioxane products containing other hazardous ingredients should be classified and labelled accordingly.

Signal word (hazard category)

In accordance with NOHSC requirements (NOHSC, 1994e), a 'signal word' should be used in the labelling of hazardous substances. For 1,4-dioxane the signal words 'HARMFUL' or 'HAZARDOUS' are appropriate for workplace chemicals (see also *SUSDP requirements*).

Decanted substances

Of particular relevance to the laboratory uses of 1,4-dioxane is the requirement for labelling of decanted (hazardous) substances which are not consumed immediately. Minimum labelling requirements are: *product name, risk and safety phrases.*

Dangerous goods requirements

The following information should also appear on the label for 1,4-dioxane in order to comply with the requirements of the ADG Code (FORS, 1998):

* **United Nations Number - UN 1165***

* **Dangerous Goods Class - Class 3**

*need only be included on labels for containers with capacity of > 500 ml (g).

SUSDP requirements

In accordance with the SUSDP (Australian Health Ministers' Advisory Council, 1997), the signal words 'POISON, NOT TO BE TAKEN and KEEP OUT OF REACH OF CHILDREN' should be used for 1,4-dioxane products used by the general public. In addition, the following safety directions and first aid instructions should also appear on the label:

Safety directions:

SD1   **Avoid contact with eyes.**

SD4   **Avoid contact with skin.**

SD8   **Avoid breathing vapour or spray mist.**

First aid instructions:

(a)   **If poisoning occurs, contact a doctor or Poisons Information Centre.**

(f)   **If skin contact occurs, remove contaminated clothing and wash skin thoroughly.**

(g)   **Remove from contaminated area. Apply artificial respiration if not breathing.**

According to instructions for *'modified first aid instructions for dilute preparations'* (SUSDP - Appendix E), only statement (a) needs be used at 1,4-dioxane concentrations less than 70 g/L (i.e., 7%).

13.2.3 Training and education

Guidelines for the induction and training of workers potentially exposed to hazardous substances are provided in the NOHSC *National Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

Workers potentially exposed to 1,4-dioxane need to be trained in safe handling, storage, transportation and disposal of the chemical. Training should provide information on the health and safety hazards of 1,4-dioxane and should address appropriate control and safety measures required to minimise both occupational and environmental exposure. As 1,4-dioxane is highly flammable (with potential explosive properties), workers should also be trained and equipped to fight fires.

The following publications provide comprehensive guidance on the safe handling and disposal of toxic/carcinogenic chemicals (applicable to 1,4-dioxane) in laboratory use:

- National Health and Medical Research Council (NHMRC), *Guidelines for laboratory personnel working with highly toxic chemicals* (Haski & Stewart, 1990);

- Queensland Division of Workplace Health and Safety, *Elements of a Laboratory Health and Safety Management System* (Anon, 1994b);

- *CCH Laboratory Safety Manual 1994* (Bartolo et al., 1994);

- *Laboratory Chemical Hygiene* (AIHA, 1995);

- Australian standard 2243.2: *Safety in laboratories - chemical aspects* (Standards Australia, 1997); and

- IARC publication no 33: *Handling chemical carcinogens in the Laboratory* (IARC, 1979).

Other relevant publications are listed in Appendix 2. It is recommended that relevant information is made available to laboratory safety officers and to other laboratory personnel directly handling 1,4-dioxane.

For storage and transport emergencies, it is recommended that reference is made to the *Dangerous Goods Initial Emergency Response Guide Number 14* (which may be obtained from State or Territory WorkCover Authority or Standards Australia).

MSDS for 1,4-dioxane and/or 1,4-dioxane containing products should be made freely available to all workers with potential exposure.

13.3 Occupational control measures

Under the NOHSC *National Model Regulations and Code of Practice to Control Workplace Hazardous Substances* (NOHSC, 1994c) control measures must be implemented to minimise health risks during handling and use of hazardous substances. With regard to 1,4-dioxane, control measures should be implemented to minimise worker exposure via inhalation and skin absorption.

13.3.1 Transport and storage

With regard to worker exposure during transport and storage of 1,4-dioxane, it is recommended that:

- adequate ventilation is provided in accordance with the relevant Australian Standards, in particular AS 1668.2 (Standards Australia, 1991b);

- exhaust ventilation is non-sparking and grounded;

- stored and bulk containers are earthed before 1,4-dioxane is decanted;

- decanting of 1,4-dioxane from drums or other storage containers is automated (where possible);

- flame arresters are fitted in storage area;

- 1,4-dioxane is *not* decanted into bottles with ground glass stoppers;

- gloves are worn during manual handling of containers;

- non-sparking footwear is worn in storage areas;

- clean-up of leaks and spills is in accordance with local regulations;

- local authorities (including fire service) are informed if 1,4-dioxane enters surface drains; and

- emergency shower facilities are provided at storage site.

13.3.2 Laboratory operations

With regard to worker exposure to 1,4-dioxane during laboratory (research/development and analysis) operations, it is recommended that:

- adequate ventilation is provided in accordance with the relevant Australian Standards, in particular AS 1668.2 (Standards Australia, 1991b);

- exhaust ventilation is non-sparking and grounded;

- operations using 1,4-dioxane are carried out in a fume cupboard or hood (flame proof) where possible;

- fume cupboards/hoods are serviced according to manufacturers recommendations;

- should distillation of 1,4-dioxane be necessary, that peroxides are decomposed before distillation (due to explosion hazards);

- 1,4-dioxane is *not* stored in bottles with ground glass stoppers;

- gloves, protective clothing and safety glasses are worn where potential exposure to 1,4-dioxane exists;

- doors into areas where 1,4-dioxane is being used should be marked "CARCINOGENIC CHEMICALS IN USE"; and

- regular OHS audits be carried out to ensure maintenance of laboratory safety standards.

13.3.3 Film processing

With regard to worker exposure to 1,4-dioxane during film (splicing operations) processing, it is recommended that:

- adequate ventilation is provided in accordance with the relevant Australian Standards, in particular AS 1668.2 (Standards Australia, 1991b);

- that cement is *not* stored in bottles with ground glass stoppers; and

- that gloves are worn during cement application.

13.3.4 Optical lens manufacture

With regard to worker exposure to 1,4-dioxane during optical lens (coating) manufacture, it is recommended that:

- all reagents used in the coating process are isolated by storing in separate room (preferably in a fume cupboard) from general workplace;

- that 1,4-dioxane is *not* stored in bottles with ground glass stoppers;

- adequate ventilation is installed to void fumes emitted from coating and drying processes in accordance with the relevant Australian Standards, in particular AS 1668.2 (Standards Australia, 1991b);

- exhaust ventilation is non-sparking and grounded; and

- gloves, protective clothing and safety glasses are worn where potential exposure to 1,4-dioxane exists.

13.3.5 Ethoxylated chemicals (manufacture and formulation)

With regard to worker exposure to 1,4-dioxane during ethoxylated chemical (e.g., surfactant) manufacture and formulation, it is recommended that:

- adequate plant ventilation should be provided (in particular, extraction fans should be installed in potential hot spots e.g., sulphonation plant);

- cleaning of plant and equipment is carried out prior to maintenance operations being carried out; and

- gloves and protective clothing are worn where potential exposure to 1,4-dioxane exists.

13.4   Exposure standard

It is recommended that the occupational exposure standard (TWA) be based on the $NOAEL_{(inhal)}$ of 111 ppm (0.4 mg/L^3) 1,4-dioxane in rats.

The hazard assessment concluded that:

- the critical effects from repeated exposure to 1,4-dioxane in animals and humans are eye irritation, liver and kidney damage;

- eye (mild) irritation was experienced in humans at 50 ppm;

- the $NOAEL_{(inhal)}$ in rats (for chronic neoplastic and non-neoplastic effects) is 111 ppm, estimated at 105 mg/kg/day;

- the $LOAEL_{(oral)}$ in rats (for chronic neoplastic and non-neoplastic effects) is 0.1% (in drinking water), estimated at 90 - 150 mg/kg/day;

- 1,4-dioxane is not extensively absorbed by unoccluded skin (see Section 9.1.1);

- absorption via inhalation may be significantly lower in human than in rats;

- metabolism and plasma half-life for 1,4-dioxane are similar in rats and humans;

- a threshold dose may exist for effects in rats associated with metabolic saturation. Such a dose corresponds to a plasma level of around 100 μg/ml 1,4-dioxane;

- no evidence of metabolic saturation was seen in humans exposed to 50 ppm 1,4-dioxane (for 6 hours). Steady state plasma levels in this study were 10μg/ml 1,4-dioxane (and 8μg/ml HEAA); and

- 1,4-dioxane should be classified as a carcinogen (Category 3).

It is recommended that NOHSC provide documentation (currently adopted from ACGIH) to reflect the above information and assess the appropriateness of the current exposure standard for 1,4-dioxane.

13.5   Public health

Currently there are no analytical data for levels of 1,4-dioxane in Australian end use products. Public exposure and risk estimates in this report were based on advice that the upper limit of 1,4-dioxane as a by-product in consumer products is 30 ppm (30 mg/kg or mg/L). While it is desirable that the level of 1,4-dioxane in consumer products be limited to 30 ppm, a level of 100 ppm in consumer products is considered toxicologically acceptable (providing an MOS of around 500, without considering food and therapeutic drugs). If the conditions of use are varied or the levels of 1,4-dioxane in consumer products exceed 100 ppm, reassessment of the hazards to public health may be required (see Section 14).

The current poison schedule classification, first aid instructions and safety directions for 1,4-dioxane are appropriate. However, it is recommended that consideration be given to allocating a concentration limit of 20% (for irritation effects) to the entry for 'Dioxane' in Appendix F (Part 3), in order to harmonise the SUSDP labelling of 1,4-dioxane with the Approved Criteria (NOHSC, 1994a) and the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994e). It is also recommended that entries for 'Dioxane' in the SUSDP be clarified as to whether they apply to all isomers of dioxane or specifically to 1,4-dioxane.

There are regulatory mechanisms in place to assess the public health impact of the presence of 1,4-dioxane in pharmaceuticals and food. It is recommended that the findings of this report be forwarded to the Drug Safety Evaluation Branch of the Therapeutic Goods Administration (TGA) and the Australia New Zealand Food Authority (ANZFA) for their consideration.

13.6   Data gaps and further studies

This report identified a number of gaps in the available information/data for 1,4-dioxane, the most important of which are:

• an animal skin irritation test (carried out according to recognised guidelines);

• adequate data on reproductive (fertility) effects;

• data on metabolic saturation levels for 1,4-dioxane in animals and humans and relationship(s) to specific toxic endpoints; and

• data (monitoring) on levels of 1,4-dioxane in Australian consumer products.

It is recommended that air monitoring studies be carried out to quantify levels of 1,4-dioxane in the breathing zone of workers engaged in optical lens coating.

14. Secondary Notification

Under Section 65 of the Act, the secondary notification of 1,4-dioxane may be required, where an applicant or other introducer (importer) of 1,4-dioxane, becomes aware of any circumstances which may warrant a reassessment of its hazards and risks. Specific circumstances include:

a) the function or use of 1,4-dioxane has increased, or is likely to change, significantly;

b) the amount of 1,4-dioxane introduced into Australia has increased, or is likely to increase, significantly;

c) manufacture of 1,4-dioxane has begun in Australia;

d) additional information has become available to the applicant/notifier as to the adverse health and/or environmental effects of 1,4-dioxane; and

e) levels of 1,4-dioxane in consumer products exceed 100 ppm.

The Director must be notified within 28 days of the applicant/notifier becoming aware of any of the above circumstances.

Appendix 1

Details of calculations cited in the report

1. Calculation (theoretical) of absorption rate (AR) for human skin[1]

a) Permeability coefficient (Kp) for 1,4-dioxane

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

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

$$\log Kp = -6.3 + (0.71 \times -0.27) - 0.0061 \times 88.12$$

$$\log Kp = -6.3 - 0.192 - 0.5904$$

$$\log Kp = -7.0824$$

$$Kp = 8.272 \times 10^{-8} \text{ cm/sec}$$

$$= 5 \times 10^{-6} \text{ cm/min} = 3 \times 10^{-4} \text{ cm/hr}$$

b) Absorption rate (AR) for 1,4-dioxane

$$AR = Kp \times \text{dose conc.}$$

at a concentration of 100% 1,4-dioxane (i.e., 1.036 g/cm^3)

$$AR = \frac{3 \times 10^{-4} \text{ cm/hr} \times 1.036 \text{ g}}{1 \text{cm}^3}$$

$$= 3 \times 10^{-4} \text{ g/cm}^2\text{/hr} = 0.3 \text{ mg/cm}^2\text{/hr}$$

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[1] Potts & Guy (1992).

2. Calculation of dermal exposure to 1,4-dioxane from shampoo use

$$E_{derm} = \frac{W \times Q \times F \times N}{BW} \quad [mg/kg/day]$$

E_{derm}	=	dermal exposure (amount of substance on skin)
W	=	amount of product used (mg)
Q	=	weight fraction of 1,4-dioxane in product (30 ppm)
F	=	fraction of substance remaining on skin (after rinsing)
N	=	number of applications per day
BW	=	average human body weigh (60 kg)

$$E_{derm} = \frac{12,000 \times 0.003\% \times 10\% \times 1}{60}$$

$$E_{derm} = 0.036 \text{ mg or } 0.6 \text{ μg/kg bw per day}$$

3. Calculation of airborne levels of 1,4-dioxane from shampoo use

$$C_{air} = \frac{W \times E \times Q}{V} \quad [mg/m^3]$$

W	=	weight of product used per event (mg)
E	=	evaporation of 1,4-dioxane (%)
Q	=	weight fraction of 1,4-dioxane in product (30 ppm)
V	=	room volume (m^3)

$$C_{air} = \frac{12,000 \times 50\% \times 0.003\%}{2} = 0.09 \text{ mg/m}^3$$

4. Calculation of dermal exposure to 1,4-dioxane from skin cream/lotion use

$$E_{derm} = \frac{W \times Q \times N}{BW} \quad [mg/kg/day]$$

E_{derm}	=	dermal exposure (amount of substance on skin)
W	=	amount of product used (mg)
Q	=	weight fraction of 1,4-dioxane in product (30 ppm)
N	=	number of applications per day
BW	=	average body weight (human) (60 kg)

$$E_{derm} = \frac{8,000 \times 0.003\% \times 2}{60} = 8 \text{μg/kg/d}$$

Thus, assuming 3% dermal absorption, the systemic dose = 0.24 μg/kg bw per day

Appendix 2

Publications of relevance to the safe handling and use of 1,4-dioxane in the laboratory

- Australian Standard 2982: Laboratory construction (Standard Australia/Standard New Zealand, 1997);

- Use of personal protective equipment at work (NSW WorkCover, 1996);

- Management challenges in laboratory safety (Fraci, 1996);

- Laboratory chemical hygiene (AIHA, 1995);

- NATA guide to the development of a quality system for a laboratory (NATA, 1995);

- CCH laboratory safety manual (Bartolo et al., 1994);

- Elements of a laboratory health and safety management system (Anon, 1994b);

- National Health & Medical Research Council (NHMRC), 'Guidelines for laboratory personnel working with carcinogenic or highly toxic chemicals' (Haski & Stewart, 1990);

- Hazards in the chemical laboratory (RSC, 1986);

- RACI laboratory safety booklet (RACI, 1986);

- Safe use of solvents (Grasso, 1982);

- IARC publication no 33: Handling chemical carcinogens in the laboratory (IARC, 1979);

- The lab creates special control challenges (Ettinger et al., 1977); and

- Australian Standard 2243.2: Safety in laboratories - chemical aspects (Standard Australia, 1997).

Appendix 3

Sample Material Safety Data Sheet
for 1,4-Dioxane

Date of issue	24 April 2000		Page	1	of Total	6

1,4-Dioxane is classified as Hazardous according to the National Occupational health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1994)].

Company details

Company name

Address

		State	Postcode

Telephone number   **Emergency telephone number**

Facsimile number   **Telex number**

Identification

Product name

1,4-Dioxane

Other names

Dioxane; *para*-dioxane; dioxan; diethylene dioxide; diethylene ether; 1,4-dioxacyclohexane; glycol ethylene ether; tetrahydro-*para*-dioxin

Manufacturer's product code

UN number

UN 1165

Dangerous goods class and subsidiary risk

Class 3

Hazchem code

3YE

Poisons Schedule number

Schedule 6

Use

Solvent (various applications)

UN number

UN 1165

Dangerous goods class and subsidiary risk

Class 3

Hazchem code

3YE

Poisons Schedule number

Schedule 6

Use

Solvent (various applications)

Physical description and properties

Appearance
Colourless liquid (@25°C)

Boiling point
101.1°C (214°F)

Freezing point
No data

Vapour pressure
4.9 kPa (@25°C)

Specific gravity
1.036 (@20°C)

Flashpoint
12°C (54°F) (closed cup); 23°C (73°F) (open cup)

Flammability limits
Highly flammable

Solubility in water
Miscible in all proportions

Other properties

Odour: Mild ethereal odour.

Odour threshold: 6.5 - 9.8 mg/m^3

Density: 1.034 kg/L (@20°C)

Vapour density: 3.0 (relative to air)

Evaporation Rate: 7.3 (relative to diethyl ether)

Partition Co-efficient: log $K_{o/w}$ = - 0.27 to - 0.49

Explosive Limits:

Lower limit: 2% v/v

Upper limit: 22% v/v

Reactivity: Hygroscopic and reacts with water to form explosive peroxides (in the presence of air).

Does not polymerise.

The following form explosive mixtures with 1,4-dioxane:

hydrogen (plus hot Raney nickel)

silver perchlorate

sulphur trioxide

nitromethane

boron trifluoride

decaborane

Ingredients/impurities

Chemical entity	CAS Number	Proportion
1,4-Dioxane	123-91-1	

Health hazard information

HEALTH EFFECTS

Acute

<u>Inhalation</u>: Low acute toxicity in animal studies. At high concentrations may cause liver, kidney and nerve fibre damage. Fatalities (preceded by epigastric pain, convulsions and coma) have been reported following short-term repeated exposure to high doses. Vapour irritating to respiratory system (including nose and throat) at 200-300 ppm for 15 min.

<u>Skin</u>: Low acute dermal toxicity in animal studies. Animal and human evidence indicate liquid is not irritating to skin. 1,4-Dioxane has a degreasing action on skin.

<u>Eye</u>: Liquid and vapour cause eye irritation and transient corneal injury in animals. Vapours cause slight eye irritation in humans.

<u>Swallowed</u>: Low acute oral toxicity in animal studies. No evidence for humans.

Chronic

<u>Skin</u>: Repeated or prolonged exposure may cause dermatitis. No evidence of sensitisation in animals.

<u>Systemic</u>: Has been shown to cause cancer in animals (in oral studies). Limited evidence of hepatocarcinogenicity in humans.

Contraindications

Breathing of vapour/mist may aggravate asthma and inflammatory or fibrotic pulmonary disease. Because of its degreasing properties, may aggravate existing skin disease (eg. dermatitis).

Alcohol consumption may increase the risk of toxicity (particularly liver damage) caused by 1,4-dioxane.

FIRST AID

<u>Inhalation</u>: Remove from exposure. Keep warm and at rest until fully recovered. If breathing laboured and patient cyanotic give oxygen. Apply artificial respiration if not breathing. Call a doctor.

<u>Skin</u>: Remove contaminated clothing. Wash immediately with copious quantities of water. Call a doctor if considered necessary.

<u>Eye</u>: Irrigate immediately with copious quantities of water for at least 15 minutes. Call a doctor if irritation persists.

<u>Swallowed</u>: Give water to drink and induce vomiting. Call a doctor.

Contact a *Poisons Information Centre* for further information.

First aid facilities:

ADVICE TO DOCTOR

Treat symptomatically. No specific antidote.

Precautions for use

EXPOSURE STANDARD

Australian Exposure Standard: 25 ppm (90 mg/m^3) TWA with a 'skin notation'.

[The skin notation indicates that absorption through the skin may be a significant source of exposure].

ENGINEERING CONTROLS

Control airborne concentrations below the exposure standard.

Use only with adequate ventilation.

Local exhaust ventilation (non-sparking and grounded) and/or fume cupboards/hoods may be necessary for some operations.

PERSONAL PROTECTION

Wear overalls, rubber footwear, safety glasses and gloves in accordance with manufacturer's recommendations.

SCBA and complete protective clothing should be worn during large spills and fire fighting.

Ensure that all personal protective equipment complies with Australian Standards.

Ensure good personal hygiene.

FLAMMABILITY

Highly flammable liquid. Anhydrous 1,4-dioxane may form explosive peroxides on exposure to light and air.

Use in well ventilated area.

Bulk containers to be earthed to reduce possibility of sparks.

Do not wear nailed footwear in storage area.

Do not store in bottles with ground glass stoppers.

Safe handling information

STORAGE and TRANSPORT

1,4-Dioxane is non-corrosive and may be stored/transported in iron, mild steel, copper or aluminium containers.

Store in a cool place and out of direct sunlight.

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

Drums should be grounded and equipped with self-closing valves, pressure vacuum bungs and flame arresters.

Peroxide formation may be minimised by storing under nitrogen atmosphere or by addition of reducing agents.

Classified as a dangerous good and should be stored and transported in accordance with ADG Code requirements:

Correct shipping name: DIOXANE

Packaging group: II

Emergency procedure guide: 3A1

SPILLS and DISPOSAL

Evacuate unprotected personnel from danger area following spillage.

Shut off all possible sources of ignition following spillage.

Contain spill with soil/sand absorbent (and collect for disposal).

Clean-up of leaks/spills and disposal in accordance with local regulations. Local authorities (including fire service) to be informed if 1,4-dioxane enters surface drains.

Empty containers to be incinerated.

FIRE/EXPLOSION HAZARD

Vapour may travel considerable distance to source of ignition and flash back.

Distillation accelerates formation of explosive peroxides. 1,4-Dioxane should *not* be distilled to dryness because of the potential for explosion of non-volatile peroxides.

Incompatible materials: organic peroxides and strong oxidising agents, nitromethane, Raney nickel.

Toxic and irritant gases and vapours, including carbon dioxide and carbon monoxide, may be released in a fire involving 1,4-dioxane.

Fire fighting:

- wear SCBA and complete protective clothing
- use water fog (or fine water spray) for small fires
- use alcohol-type or universal-type foams for large fires

Other information

Animal toxicity data:

Acute (oral) LD_{50} 5400-7300 mg/kg bw (rat).

Acute (dermal) LD_{50} 7600 mg/kg (rabbit).

Acute (inhalation) LD_{50} (2hr)   12,780 ppm (46 g/m^3) (rat).

Chronic (inhalation) - NOAEL   400 mg/m^3 (111 ppm) (rat).

Environmental data:

The majority of 1,4-dioxane emissions will partition to water.

Bioaccumulation is estimated as being negligible.

1,4-Dioxane is classified as practically non-toxic to aquatic microorganisms, plants, invertebrates and fish.

Relevant Australian Standards:

Respiratory protection (including SCBA) - refer to AS1319; AS 1715 and AS 1716).

Clothing/overalls - refer to AS 3765.1 and AS 3765.2.

Gloves - refer to AS/ANZ 2161.

Safety glasses - refer to AS 1336 and AS 1337.

Storage and handling of flammable and combustible liquids - refer to AS 1940.

Storage of chemicals - refer to AS 2243.10.

Further information:

National Industrial Chemicals Notification and Assessment Scheme, Full Public Report - Priority Existing Chemical No.7 - 1,4-Dioxane, NOHSC, 1998.

Australian Dangerous Goods Code (FORS, 1998).

CCH Laboratory Safety Manual 1994 (Bartolo et al., 1994).

Contact point

Contact name	Telephone number

Position title

Address

State	Postcode	Country

Appendix 4

ORDER FORM FOR NICNAS PRODUCTS

I wish to purchase: *Quantity*

NICNAS "Handbook for Notifiers"   @ AUD $200.00 each   ....

Copy/s (free) of Full Public Report/s for the following
new chemical assessment/s: Please indicate NA /_____   ....
                                                      NA /_____
       ....   NA /_____
              ....

Copy/s of Full Public Report/s for the following
priority existing chemical (PEC) assessment/s:
       PEC/7 - 1,4-Dioxane   @ AUD $25.00 each   ....
       PEC/8 - 1,1,1-Trichloroethylene @ AUD $30.00 each
       ....

All prices include postage and packaging within Australia and by SEAMAIL
overseas. For AIRMAIL please include an additional $50.00 for each Handbook
and $10.00 for each other NICNAS product.

Overseas only: Please send by AIRMAIL.   YES / NO

ALL ORDERS MUST BE ACCOMPANIED BY PREPAYMENT IN AUSTRALIAN DOLLARS
PURCHASE ORDERS NOT ACCEPTED

I enclose $**...................**   cheque/money order payable to Worksafe Australia
drawn on an Australian bank in Australian dollars
OR   Bankcard [   ]   Visacard [   ]   Mastercard [   ]
Card Number:_____Expiry Date:_____
Name of Card
Holder:_____Signature:_____
Name of
Recipient:_____
Position: _____
Company:_____
Address:_____
_____Postcode_____
Telephone: (___)_____Fax:(___)_____

Send this order to :   **Worksafe Australia**
                              Finance Section
                              GPO Box 58
                              Sydney NSW 2001
                              Australia

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