

Existing Chemical Hazard Assessment Report



Australian Government
Department of Health and Ageing
NICNAS

1,4-Butanediol

March 2009

© Commonwealth of Australia 2009

ISBN 978-0-9803124-7-8

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, noncommercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at <http://www.ag.gov.au/cca>

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* (Cwlth) (the Act), which came into operation on 17 July 1990.

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

NICNAS assessments are carried out in conjunction with the Australian Government Department of the Environment, Water, Heritage and the Arts, which carries out the environmental assessment for NICNAS.

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

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia

For the purposes of Section 78(1) of the Act, copies of assessment reports for new and existing chemical assessments are freely available from the web. Hardcopies are available from NICNAS from the following address:

NICNAS
GPO Box 58
Sydney, NSW 2001
AUSTRALIA
Tel: +61 (2) 8577 8800
Fax: +61 (2) 8577 8888
Free call: 1800 638 528

Other information about NICNAS (also available on request and on the NICNAS web site) includes:

- NICNAS Service Charter;
- Information sheets on NICNAS Company Registration;
- Information sheets on the Priority Existing Chemicals and New Chemical assessment programs;
- Safety information sheets on chemicals that have been assessed as Priority Existing Chemicals;
- Details for the NICNAS Handbook for Notifiers; and
- Details for the *Commonwealth Chemical Gazette*.

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

<http://www.nicnas.gov.au>

Other information on the management of workplace chemicals can be found at the web site of the Australian Safety and Compensation Council

<http://www.ascc.gov.au>

Table of Contents

PREFACE	3
1. INTRODUCTION	7
1.1 Background	7
1.2 Sources of data	7
1.3 Chemical identity	7
1.3 Physical properties of 1,4-butanediol	8
1.4 Import, manufacture and use	8
1.5 Current regulatory status of 1,4-butanediol in Australia	9
1.6 Current international regulatory status of 1,4-butanediol	10
2. OCCUPATIONAL EXPOSURE	11
3. PUBLIC EXPOSURE	12
4. TOXICOLOGICAL INFORMATION	13
2.1 Toxicokinetics	13
2.2 Acute toxicity – oral, inhalation, and dermal	14
2.3 Skin irritation	15
2.4 Eye irritation	15
2.5 Respiratory irritation	15
2.6 Skin sensitisation – animal tests	15
2.7 Skin sensitisation – human studies	16
2.8 Repeated dose oral studies	16
2.9 Repeated dose inhalation studies	17
2.10 Neurotoxicity	17
2.10.1 Human studies	18
2.10.2 Experience with human exposure – case studies and media reports	18
2.11 Mutagenicity and genotoxicity	19
2.12 Carcinogenicity	19
2.13 Reproductive and developmental toxicity	19
2.14 Interactions with other chemicals	20
2.15 Conclusions	20
BIBLIOGRAPHY	22

1. Introduction

1.1 Background

1,4-Butanediol is an industrial solvent and intermediate used in the production of various plastics and polymers. When ingested, it is rapidly absorbed and metabolised to form γ -hydroxybutyrate (GHB), a neuromodulator that exerts potent depressant effects on the central nervous system.

In 2007, concerns regarding the toxicity of 1,4-butanediol were raised with NICNAS through public enquiries and the media after the hospitalisation of children who ingested toy beads that were found to contain 1,4-butanediol. These enquiries prompted NICNAS to investigate the use and safety of 1,4-butanediol in Australia and the adequacy of current regulatory controls. In April 2008, as a result of its investigations, NICNAS made recommendations to the National Drugs and Poisons Schedule Committee (NDPSC) on the scheduling of 1,4-butanediol in the Standard for the Uniform Scheduling of Drugs and Poisons. The NICNAS submission noted that given the pronounced neurotoxicity of GHB in animals and humans, there was concern about potential risks of adverse effects from exposures to 1,4-BD in domestic and cosmetic products. It also noted that a significant risk to children arises from intentional ingestion of toy products containing 1,4-BD. The NDPSC considered 1,4-butanediol scheduling in its 53rd meeting in June 2008, and resolved to include free form 1,4-butanediol in Appendix C for all domestic use (NDPSC, 2008). Appendix C comprises substances of such danger to health as to warrant prohibition of sale, supply and use.

1.2 Sources of data

To enhance efficiency and avoid duplication this assessment has utilised a report on 1,4-butanediol prepared under the Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) program. The SIDS Initial Assessment Report (SIAR) on 1,4-butanediol finalised in 2000 was the primary reference material. As a result, many primary references drawn from this document have not been sighted, and are indicated with an asterisk where quoted (*).

A comprehensive literature search was carried out for data published since year 1999 to ensure that those studies published after the last literature search conducted for the SIAR were covered.

1.3 Chemical identity

Common name: 1,4-Butanediol

Structural formula: 

Molecular formula: C₄H₁₀O₂

Molecular weight: 90.14 g/mol

CAS registry number:	110-63-4
IUPAC chemical name:	Butane-1,4-diol
Other names:	1,4-Butylene glycol; 1,4-Dihydroxybutane; Tetramethylene glycol; 1,4-Tetramethylene glycol; Tetramethylene-1,4-diol; Butylene glycol; Butanediol; Butane-1,4-diol

1.3 Physical properties of 1,4-butanediol

1,4-butanediol is a colourless, viscous liquid with a melting point of 20.1°C and a boiling point of 230°C (HSDB, 2003). It has a relatively low vapour pressure (1.9 Pa at 25°C), high water solubility (> 100g/L), and a low octanol/water partition coefficient ($\log K_{ow} = 0.50$) (OECD, 2000).

1.4 Import, manufacture and use

Australia

1,4-Butanediol is listed on the NICNAS High Volume Industrial Chemicals List (HVICL), a list of industrial chemicals that are manufactured and/or imported into Australia at volumes ≥ 1000 tonnes/year. Over the year 2001-2002, import volumes totalling 1200 tonnes were reported. 1,4-Butanediol is imported as a solid wax (99.5% purity) in 200L steel drums and also in formulated materials. It is onsold in the same drums, decanted in 20L containers or formulated into blends (in various pack sizes) from which the 1,4-butanediol can be readily recovered.

The major uses of 1,4-butanediol, as reported by the Plastic and Chemicals Industry Association in 2005, are as an intermediate and chain extender in the production of urethane prepolymers, polyether diols, polyester polymers (particularly polybutylene terephthalate) and in the manufacture of tetrahydrofuran. It is also used as a plasticiser (eg in polyesters and cellulose), as a carrier solvent in printing ink, a cleaning agent, an adhesive (in leather, plastics, polyester laminates and polyurethane footwear), in agricultural and veterinary chemicals and in coatings (in paints, varnishes and films). 1,4-Butanediol is also reportedly used as a solvent in cosmetic formulations and as a humectant in pharmaceuticals.

Worldwide

The major industrial uses are in the manufacture of tetrahydrofuran, γ -butyrolactone and derivatives and as a co-monomer in classical diol-condensation reactions to produce polyurethane elastomers and polybutylene terephthalate (Howe-Grant, 1998; HSDB, 2003). In 1994, the worldwide usage pattern of 1,4-butanediol comprised tetrahydrofuran, 48%; γ -butyrolactone and derivatives, 20%; polybutylene terephthalate resins, 23%; polyurethanes, 5%; other, 4% (HSDB, 2003). During 1978 to 1985, US production of 1,4-butanediol ranged from 63,000 to 161,000 tonnes annually – with 913 to 12,800 tonnes/year imported (Irwin, 2006) - while it was estimated that consumption during 2001 would be 387,000 tonnes (Hornfeldt et al., 2002). In Japan, the production volume was 29,717 tonnes in 1995 (OECD, 2000). In 2003, approximately 1,000,000 tonnes were consumed worldwide (Chemical Economics Handbook, 2007).

1.5 Current regulatory status of 1,4-butanediol in Australia

1,4-butanediol IS listed in:

- the Australian Inventory of Chemical Substances (AICS).
- the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) No. 23 (June 2008) (Amendment No. 3 of 2008). “1,4-BUTANEDIOL (excluding its derivatives) in non-polymerised form in preparations for domestic use” is listed in Appendix C of the SUSDP, being substances of such danger to health as to warrant prohibition of sale, supply and use.’

1,4-butanediol IS captured by:

- the NSW ‘Drug Misuse and Trafficking Regulations 2006’ as a Category 1 precursor, Victoria ‘Drugs, Poisons and Controlled Substances Act 1981’, Tasmania ‘Misuse of Drugs Act 2001-Part 4 Controlled Precursors’, Queensland ‘Drugs Misuse Regulation 1987-Schedule 6’, South Australia ‘Controlled Substances Regulations 1996-Schedule 3’, ACT ‘Criminal Code Regulation-Schedule 3’, Northern Territory ‘Misuse of Drugs Regulations-Schedule 2’ and Western Australia ‘Misuse of Drugs Amendment Act.
- the industry-based PACIA ‘Code of Practice for Supply Diversion to Illicit Drug Manufacture’ developed in consultation with law enforcement authorities to control supply of certain substances. Several Australian states (including NSW, QLD and WA) have legislated to make elements of the PACIA Code mandatory and a number of other states are also developing regulations.

Several states/territories have placed a permanent ban on the supply of any bead toys, including Bindeez, that contain 1,4 butendiol (e.g Northern Territory of Australia, 2007; NSW Department of Commerce, 2007; Government of Victoria, 2007; Government of Western Australia, 2008)

1,4-butanediol is NOT listed in:

- the Hazardous Substances Information System
<http://hsis.ascc.gov.au/Default.aspx>
- the Australian Customs regulations which cover the import/export of drugs and certain precursor substances used in the manufacture of illicit drugs. Although 1,4-butanediol is not currently treated as a prohibited import, in future it may be considered by the National Precursor Working Group which brings together a range of stakeholders looking at controls of substances that may be diverted to drug manufacture.

Any manufacturer or importer who supplies 1,4-butanediol for use at work is responsible for determining whether it is a hazardous substance in accordance with the National Occupational Health and Safety Commission’s Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. If hazardous, the manufacturer or importer has a responsibility to classify and label the substance appropriately.

1.6 Current international regulatory status of 1,4-butanediol

1,4-Butanediol is not restricted under the European legislation on cosmetics (EU, 1976), not classified as a dangerous substance in Annex I to Directive 67/548/EEC, and it is not listed in a priority list (under Council Regulation EEC No. 793/93) on the evaluation and control of the risks of existing substances.

The chemical is not subject to the key UN convention that covers precursor chemicals; however its metabolite, γ -hydroxybutyrate (GHB), is subject to international controls in accordance with the 1971 UN convention on psychotropic substances.

In May 1999, the USA FDA issued a public warning about products containing 1,4 butanediol and declared the chemical to be a Class I Health Hazard (i.e. potentially life-threatening). Although this classification imposes no legal restrictions on the manufacture, distribution or possession of 1,4 butanediol, Garcia and Catterton (2003) state that when 1,4 butanediol is distributed for human consumption it meets the definition of a 'controlled substance analogue' and can therefore be prosecuted as a Schedule 1 substance. This definition is supported by the US Court as at least 3 people have been prosecuted and found guilty of distributing a controlled substance analogue of GHB in violation of the Controlled Substance Analogue Enforcement Act of 1986 ("the Analogue Act"), 21 U.S.C. §§ 802 and 813. Others have concluded that the extensive industrial use of 1,4 butanediol, in combination with anonymous marketing via the Internet (see 'Public Exposure'), ensures a continued supply that is almost impossible to regulate (Zvosec et al., 2001).

2. Occupational exposure

Workers may be exposed to 1,4-butanediol through inhalation of vapours and through eye and skin contact. No exposure standard for vapour concentration in Australian workplaces has been established. As a raw material in the production of thermoplastic polyesters used in construction materials, 1,4-butanediol was identified at a high concentration in the indoor air of new and recently renovated buildings in Switzerland. Therefore, people living and working in new buildings may be exposed to the chemical through inhalation of contaminated air (HSDB, 2003).

3. Public exposure

Limited information about the presence of 1,4-butanediol in consumer products was found in the literature. In Europe, 1,4-butanediol is used as an ingredient in deodorants and listed as a solvent in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck & McEwen, 2006) 2006). It is also used as a humectant and in pharmaceuticals (Lewis, 1997) and in 'Cover Girl Eyeslicks Gel Eyecolor' cosmetic pencils (Household Products Database, consulted November 2007). In the US, 1,4-butanediol has been used as a so-called 'natural' or 'non-toxic' ingredient in dietary, health, sleep aid or bodybuilding supplements and is also being marketed worldwide on the Internet and in underground markets for purposes of illicit abuse (Garcia and Catterton, 2003).

People living in new buildings may be exposed to 1,4-butanediol through inhalation of contaminated air.

4. Toxicological Information

Table 1: Summary of toxicology data for 1,4-butanediol

Toxicological parameter	Result
Acute oral toxicity	Rat: LD50 1525-1830 mg/kg bw. Mouse: LD50 2060 mg/kg bw. Rabbit: LD50 2531 mg/kg bw. Guinea pig: LD50 1200 mg/kg bw.
Acute inhalation toxicity	Rat: LC50 > 5.1 mg/L (4 hour). Slight altered respiratory function (5.1 mg/L, 4 hours).
Acute dermal toxicity	Rat: LD50 >5000 mg/kg bw.
Acute human toxicity (studies and case reports)	Unconsciousness, miosis, areflexia, renal failure and death (210-430 mg/kg per rectum). Restlessness, clonic spasms of extremity muscles, sleep (30 mg/kg bw i.v.).
Skin irritation (rabbit)	No reaction observed on intact or abraded skin (24 hour exposure).
Eye irritation (rabbit)	Slight irritant.
Respiratory irritation (rat)	Slight irritant
Skin sensitisation	Guinea pig: Not sensitising.
Respiratory sensitisation	No data.
Repeated dose oral toxicity	Mouse: NOAEL 100 mg/kg bw/day (F) Rats: LOAEL 200 mg/kg bw/day (hyperactivity observed)
Repeated dose inhalation toxicity	Rat: NOAEC (systemic) 1.1 mg/L. Reduction in heart and body weight and serum cholesterol; increase in RBCs and haematocrit; atrophy in thymus lymphoid cells (5.2 mg/mL).
Neurotoxicity	Rat: CNS depression, anaesthesia, loss of righting reflex and voluntary motor activity. Neurotoxic in human case reports.
Mutagenicity	No evidence of genotoxicity
Carcinogenicity	No data.
Reproductive toxicity	Rat: NOAEL 800 mg/kg bw/day
Developmental toxicity	Mouse: NOAEL 600 mg/kg bw/day (not teratogenic).

2.1 Toxicokinetics

Overall, the toxicokinetics of 1,4-butanediol are similar between man and experimental animals. After oral or intravenous administration, it is rapidly and efficiently metabolised in the liver to form GHB which is eliminated via the tricarboxylic acid cycle as CO₂. In a well-conducted oral metabolism and disposition study (NTP, 1989), male F344/N rats were gavaged with 1-[¹⁴C]-1,4-butanediol at single doses of 4, 40, 120, or 400 mg/kg bw. Within the first 2 h after administration of 4, 40, or 120 mg/kg, approximately 50% of the administered radiolabel was eliminated as exhaled ¹⁴CO₂ and 85% eliminated within 72 h. The kidney and gastrointestinal tract were minor routes of excretion with approximately 4% and 0.6% of the administered radioactivity (94% as ¹⁴CO₂) excreted over 72 h

in the urine and the faeces respectively. There was no evidence of bioaccumulation in any tissue. Seventy-two hours after administration, a total of 2.3% of the dose remained in the carcass, with the greatest concentrations present in liver and skin. In animals and humans, the major biotransformation pathway of 1,4-butanediol in the brain, liver, kidney and heart is oxidation to GHB (Roth and Giarman, 1966*; Maxwell and Roth, 1972*; Vree et al., 1978*). Following intravenous administration to humans, the conversion of 1,4-butanediol occurs rapidly with the plasma concentration-time profile of GHB as a metabolite very similar to that obtained after intravenous injection of GHB itself (Vree et al., 1978*) however an equivalent oral study oral has not been conducted.

In a further study in humans, Thai et al. (2007) demonstrated extensive conversion of 1,4-butanediol to GHB after oral administration indicating that ingestion of 1,4-butanediol is essentially equivalent to GHB intake. The average maximum plasma concentration of GHB following administration to eight subjects of 25 mg/kg bw 1,4-butanediol was found to be 45.6 ± 19.7 mg/L, comparable to the maximum plasma concentration of GHB following oral administration of 25 mg/kg bw of GHB itself to eight volunteers under similar conditions of 39.4 ± 25.2 mg/L (Brenneisen et al., 2004). On a molar basis, 25 mg/kg bw 1,4-butanediol is equivalent to 28.9 mg/kg bw GHB assuming complete conversion. The rate of metabolism was variable and appeared to correlate with the class IB-alcohol dehydrogenase genotype. Additionally, the time taken to achieve maximal GHB plasma concentration (T_{max}) in this study is consistent with T_{max} values reported in other oral studies of GHB (Borgen et al., 2004; Brenneisen et al., 2004; Scharf et al., 1998 all cited in Thai et al., 2007). *In vitro*, alcohol dehydrogenase from rat liver or brain catalyses the oxidation of 1,4-butanediol to GHB via the intermediate aldehyde, γ -hydroxy-butyraldehyde, with ethanol a competitive inhibitor (Poldrugo & Snead, 1986*).

2.2 Acute toxicity – oral, inhalation, and dermal

Oral LD50 values for 1,4-butanediol have been reported in rats (1525-1830 mg/kg bw), in mice (2060 mg/kg bw), in guinea pigs (1200 mg/kg bw) and rabbits (2531 mg/kg bw) (Jedrychowski et al., 1990a*; Knyslova, 1968*). The most common signs of toxicity were lateral posture, an irregular decreased rate of respiration and catalepsy. At necropsy in rats, congestion of internal organs was observed in animals that died.

In an inhalation study conducted according to OECD TG 403 (BASF, 1991*), Wistar rats were exposed to 5.1 mg/L of a liquid aerosol of 1,4-butanediol for 4 h. No deaths were seen, and slight respiratory distress (accelerated and shallow respiration) that was observed in animals during and immediately after exposure had resolved by day 1. On gross pathological examination, no abnormalities could be detected.

Male rats were exposed, nose only, to 4.6, 9.4 or 15.0 mg/L of an aerosol of 1,4-butanediol for 4 h (Kinney et al., 1991*). All rats survived at 4.6 or 9.4 mg/L up to 14 days after exposure, but 1/10 rats at the top dose died 1 day post exposure. After exposure, rats at 4.6 and 9.4 mg/L were lethargic with labored breathing. At 15.0 mg/L, a red discharge was observed in the perineal area and a few rats at 9.4 and 15.0 mg/L had lung noise and dry red nasal discharge lasting 1-9 days. Rats in all treated groups displayed dose-related slight to severe weight loss for 24 h post exposure, followed by resumption of normal rate of weight gain.

The dermal LD50 value of 1,4-butanediol in rats (under occlusive conditions) has been reported as >5000 mg/kg body weight (Jedrychowski et al., 1990a*). Histopathological changes were limited to the skin and liver although no further details were reported.

Overall, 1,4-butanediol is of moderate acute toxicity by the oral route and of low acute toxicity following inhalation or dermal application.

2.3 Skin irritation

In a study investigating the short-term dermal irritation potential of 1,4-butanediol (Jedrychowski et al., 1990a*), groups of White Vienna rabbits were topically administered gauze patches with undiluted 1,4-butanediol for 24 h under occlusive dressing to intact or abraded skin. Adjacent areas of untreated and water treated skin of each animal served as a control. No skin reactions were seen at 1, 24, 48 and 72 h after patch removal. In a second experiment, the internal areas of the right ears of rabbits were painted with either 100 % or 50 % 1,4-butanediol in water for 10 consecutive days. The left ear of each rabbit painted with water served as a control. After 10 days of exposure, a minimal reddening was observed in the 100 % 1,4-butanediol treated group.

In a poorly reported study in rabbits (Knysnova, 1968*), repeated application of 1,4-butanediol to both intact and abraded skin resulted in no appreciable irritation and no evidence of absorption of acutely toxic amounts. Volume and concentration of the test substance and exposure time were not reported.

No skin irritation was seen in 200 human volunteers following treatment with 1,4-butanediol however no other details were reported (GAF Corporation, 1967*).

Therefore, the data indicate that at most 1,4-butanediol possesses a very weak skin irritation potential.

2.4 Eye irritation

Slight reddening of the conjunctivae and small amounts of discharge were observed in 4 rabbits, 1 h after ocular application of a single dose of 0.1 mL undiluted 1,4-butanediol (Jedrychowski et al., 1990a*). The effects diminished after 24 and 48 h and no abnormalities were observed at 72 h. A similar result was obtained in a briefly reported rabbit study where there was very slight conjunctival irritation but no corneal injury (Cavender & Sowinski, 1994).

Overall, evidence is available that 1,4-butanediol is a slight irritant to eyes.

2.5 Respiratory irritation

Respiratory irritation has been observed in rats exposed to 5.1 mg/L (BASF, 1991*) and 4.6-15 mg/L (Kinney et al., 1991*) 1,4-butanediol for 4 h as described in the acute toxicity section above. Based on these studies, 1,4-butanediol is considered a slight respiratory irritant.

2.6 Skin sensitisation – animal tests

In a briefly reported Maximisation test (Jedrychowski et al., 1990a*), 1,4-butanediol was applied at a concentration of 10 % (intradermal injections) and 30 % (topical application) at induction to test groups of Hartley guinea-pigs.

Challenge was conducted with 10 % and 30 % 1,4-butanediol. No allergic contact dermatitis was reported.

2.7 Skin sensitisation – human studies

No skin sensitisation was reported in 200 humans following patch testing with 1,4-butanediol but details of the study were not reported (GAF Corporation, 1967*).

2.8 Repeated dose oral studies

In a 28-day gavage study (Jedrychowski et al., 1990b*), 8 Wistar rats per sex per dose received 0, 5, 50 or 500 mg/kg bw/day 1,4-butanediol 7 times per week. There were no deaths during the study. Mean body weights, organ weights, and feed consumption of dosed groups were similar to those of the controls. Slight changes to haematology parameters were judged to be not treatment related. Only 5/8 animals per group were histopathologically examined. Mild to moderate inflammation of the liver and proliferation of bile ducts observed in both sexes was dose-related in females. However, the incidence of proliferation of the bile ducts at the top dose was only statistically significant when both sexes were pooled. Therefore, the NOAEL was determined to be 50 mg/kg bw/day in both sexes based on effects on the liver, though the absence of neurotoxicity described in other oral studies limits the significance that can be attached to the data from this study and the derived NOAEL value.

In a combined repeat dose and reproductive toxicity study in SD rats conducted according to OECD TG 422 (Japan Ministry of Health and Welfare, 1999*), males were gavaged with 0, 200, 400 or 800 mg/kg bw/day 1,4-butanediol for 45 days and females the same doses from 14 days prior to mating to day 3 of lactation. All dosed groups showed transient behavioral signs of hyperactivity through hypoactivity to coma with severity related to dose level. All animals showed full recovery by 5 h post exposure. Body weight gains were reduced at 400 and 800 mg/kg bw/day with an associated decrease seen in food consumption. In contrast to the Jedrychowski et al. (1990b) study above, histopathologic findings were limited to diffuse transitional epithelial hyperplasia and fibrosis of the lamina propria of the urinary bladder at 400 and 800 mg/kg bw/day. Overall, it was considered that neurotoxicity was observed at the lowest dose level tested and a LOAEL of 200 mg/kg bw/day for both sexes was identified based on the dose-related trend in central nervous system effects.

In an NTP-sponsored developmental toxicity study (Price et al., 1993*), pregnant Swiss (CD-1) mice were administered 0, 100, 300 or 600 mg/kg bw/day 1,4-butanediol by gavage on gestation days 6 -15. Symptoms of acute CNS intoxication (including hypoactivity, immobility, and loss of righting reflex) occurred at 300 and 600 mg/kg bw/day, but usually resolved within 4 h after dosing. In the same groups, other indications of maternal toxicity included body and liver weights and feed consumption that were lower than those of the controls and reduced kidney weights in the top dose group only. Therefore, 100mg/kg bw/day was determined as the NOAEL for maternal toxicity in this study.

Overall, 1,4-butanediol is of moderate toxicity in repeated dose oral studies.

2.9 Repeated dose inhalation studies

Groups of male rats were exposed to an aerosol of 1.5-2.0 mg/L 1,4-butanediol for 2 h/day (calculated dose: 85 – 110 mg/kg bw/day) for 4 months (Stasenkova, 1965*). Clinical signs of toxicity, such as inactivity and sleepiness, were observed after the first 3 or 4 weeks of the study however these signs were reversible within 10 to 20 minutes after the exposure. Histopathological examination revealed extensive pulmonary emphysema, mild lung oedema and, in a few animals, inflammatory changes of single alveolar cells and weak hyperplasia of alveolar septum with proliferation of lymphocytes and histiocytes were seen. These changes were considered to be local irritant effects and were not accompanied by treatment related pathological changes in other organs. A LOAEC of 1.5 mg/L (85 mg/kg bw/day) was determined in male rats as signs of clinical toxicity immediately following exposure were seen at all doses. In a further study, male rats were exposed to an aerosol of 0.3-0.5 mg/L 1,4-butanediol for 2 h per day, 6 d per week (calculated dose: 15 – 24 mg/kg bw/day) for 4 months (Stasenkova, 1965*). No clinical signs of toxicity were observed following exposure, and body weight, nervous system function (neuromuscular response), haemogenesis, liver function and kidney function were not changed. Consequently, the NOAEC is determined to be 0.5 mg/L (equivalent to 24 mg/kg bw/day) in this briefly reported study.

In a more recent study, groups of 10 male Crl:CD rats were exposed nose-only to an aerosol of 0, 0.2, 1.1 or 5.2 mg/L 1,4-butanediol for 6 h per day, 5 d per week for 2 weeks (Kinney et al., 1991*). Five rats per group were killed after the tenth exposure, and the five remaining rats per group were killed at the end of a 2 week recovery period. Compared to controls, lower (7% to 9%) mean body weights, increased erythrocyte counts and haematocrit were seen in rats at the top dose. Slight atrophy of the lymphoid cells of the thymus was seen in 3/5 rats receiving 10 exposures. Body weights and thymic changes had returned to normal during the recovery period. As no adverse effects were observed in rats exposed to 0.2 or 1.1 mg/L 1,4-butanediol, the NOAEC, based on haematology parameters, was determined to be 1.1 mg/L (calculated to be 134 mg/kg bw/day).

2.10 Neurotoxicity

Adverse effects of 1,4-butanediol on the nervous system have been observed, although the data is limited. 1,4-Butanediol appears to have dual pharmacological actions: the major neurotoxic effects of 1,4-butanediol are attributable both to its conversion to GHB and another alcohol-like effect due to the diol itself (Poldrugo & Snead, 1984*). Administration of 496 mg/kg bw 1,4-butanediol to male Sprague-Dawley or Holtzman rats caused CNS depression and induced a state resembling sleep or anesthesia characterized by loss of righting reflex, struggle response, and voluntary motor activity, but retention of the ability to respond to pain and tactile stimuli (Sprince et al., 1966*). Very similar neuropharmacologic responses were observed after administration of GHB (dose not reported) except that sleep induction time and duration of sleep are longer after 1,4-butanediol administration. In contrast, no clinical or pathological changes were observed in central and peripheral nervous systems of Sprague-Dawley rats given 0.5 % 1,4-butanediol in drinking water (approx. 508 mg/kg/day) daily for 10 days (Spencer et al., 1978*).

In a 6-month oral study investigating the influence of 1,4-butanediol on conditioned reflexes and biochemical profile (Knyshova et al., 1968*), 6 male rats

per group were given 0, 0.25, 3.0 or 30 mg/kg bw/day 1,4-butanediol. The animals at 30 mg/kg lagged with respect to the appearance and fixation of the reflex and had a longer latent period before responding to the stimulus. At the top dose there were also changes to clinical chemistry parameters and histopathological changes were noted in the brain and liver. Overall, the limited reporting of experimental details and results mean no reliable conclusions can be drawn from the data and this study is not discussed further.

A fall in body temperature of 1.0-2.0°C was measured in Wistar rats from 0.5 to 4 h after intraperitoneal administration of 500 mg/kg bw 1,4-butanediol (Taberner & Pearce, 1974*). The fall coincided with a loss of righting reflex and was considered to be a result of the CNS depressant action of the 1,4-butanediol although a direct hypothermic action could not be excluded.

2.10.1 Human studies

In an old study (Hinrichs et al., 1948*), 15 or 30 g of 1,4-butanediol was rectally administered to 7 patients (body weights not reported). After 10 to 20 min, the patients became deeply comatose with miosis and complete areflexia observed over 1 to 16 h following administration. Five patients recovered fully (some after treatment with analeptic) however 2 died within 72 h. Unspecified renal disorder was found in the 2 dead patients.

It was reported that sleep is induced by intravenous administration of 30 mg/kg bw 1,4-butanediol or by infusion of 15 to 22 mg/kg bw/h for about 38 to 68 h with restlessness and clonic spasms of the muscle of the extremities also seen (Toxikologische Bewertung, 1993*).

In a combined pharmacokinetics and clinical effects study (Thai et al., 2007), 8 healthy human volunteers (5 male) were administered a single oral dose of 25 mg/kg bw 1,4-butanediol. Pre- and follow up checks comprised of vital signs (heart rate, blood pressure and respiratory rate), a cognitive battery and subjective mood assessment. Subjects reported feeling less awake and alert, less able to concentrate and more light-headed within 90 min of 1,4-butanediol ingestion. Mild respiratory depression and transient increases in blood pressure were also observed however, overall, the changes were judged as unlikely to have serious clinical consequences.

2.10.2 Experience with human exposure – case studies and media reports

Numerous case reports are available that describe the neurological consequences (including agitation, combativeness, respiratory depression, a labile level of consciousness, vomiting, seizures and death) in patients known to have ingested illicit products containing 1,4-butanediol (Dyer et al., 1997*, Zvosec et al., 2001; Theron et al., 2003; Caldicott et al., 2004; Strickland et al., 2005). The inability to accurately determine the dose of 1,4-butanediol ingested - and the co-exposure to other chemicals present at unreported concentration in these products in many cases - means that it is not possible to correlate the degree of 1,4-butanediol exposure with the severity of neurotoxicity from these reports.

During early November 2007, a 2-yr-old boy and a 10-yr-old girl presented to the ICU at Children's Hospital Westmead with a decreased level of consciousness and the girl also displaying persistent vomiting and a 4-minute generalised seizure. Upon toxicological screening, γ -hydroxybutyrate (GHB) was identified in the urine of both children. The source of the GHB was subsequently identified as its metabolic precursor, 1,4-butanediol, which was present in 'Bindeez' brand toy

beads that had been ingested by both children (Gunja et al., 2007). Quantification of the amount of 1,4-butanediol ingested was not reported. During the same period, media sources reported that an 18-month-old NSW boy and a 19-month-old Queensland boy had both become ill after allegedly swallowing the same beads. The NSW Division of Analytical Laboratories tested six sets of 'BindeeZ' beads provided by the Office of Fair Trading (purchased 6th November at retailers) and confirmed the presence of 1,4-butanediol in all samples (Environmental Health Branch, NSW Department of Health). The Chinese manufacturer of the 'BindeeZ' beads does not list 1,4-butanediol as an ingredient, however 1,5-pentanediol was included on the formulation list. There was speculation in the media that the more toxic 1,4-butanediol may have been substituted for 1,5-pentanediol.

2.11 Mutagenicity and genotoxicity

1,4-butanediol was negative in a bacterial reverse mutation test conducted according to OECD guidelines (Japan MHW, 1997*) and also failed to induce clastogenicity or polyploidy in CHL/IU cells (Japan MHW, 1997*) and Chinese hamster V79 cells (Hüls AG, 1993a*) in chromosome aberration tests. Similarly, in gene mutation assay using CHO cells, 1,4-butanediol did not induce any significant increase in the mutant frequency of the HPRT (hypoxanthine-guanine phosphoribosyl transferase) locus with and without metabolic activation (Hüls AG: 1993b*).

In vivo, the reliability of a negative result in a *Drosophila melanogaster* sex-linked recessive lethal assay (Roehrborn, 1959*) is questionable because of inadequate sample size (as reported by Lee et al., 1983*). Overall, 1,4-butanediol is not considered to be mutagenic.

2.12 Carcinogenicity

Although 1,4-butanediol has not been evaluated for carcinogenicity, γ -butyrolactone which, like 1,4-butanediol, is rapidly converted to GHB, has shown no carcinogenic response in rats and mice over a 2 year period (NTP, 1992*). Based on the absence of evidence for genotoxicity of 1,4-butanediol and the negative result of the carcinogenicity bioassay for a related compound, 1,4-butanediol is not considered to be carcinogenic in animals.

2.13 Reproductive and developmental toxicity

Only limited data is available regarding any 1,4-butanediol-induced impairment of fertility. In a combined repeat dose and reproductive toxicity study in SD rats conducted according to OECD TG 422 (Japan MHW, 1999*), males were gavaged with 0, 200, 400 or 800 mg/kg bw/day 1,4-butanediol for 45 days and females the same doses from 14 days prior to mating to day 3 of lactation. The parental animals exhibited no alteration in the reproductive parameters. A slight, but significant, reduction in pup body weight seen at 800 mg/kg bw/day was considered as attributable to maternal toxicity (reduced food consumption and body weight gain).

In an NTP-sponsored developmental toxicity study (Price et al., 1994*), pregnant Swiss (CD-1) mice were administered 0, 100, 300 or 600 mg/kg bw/day 1,4-butanediol by gavage on gestation days 6 -15. Signs of CNS depression (including hypoactivity, immobility, and loss of righting reflex) occurred at 300 and 600 mg/kg bw/day, but usually resolved within 4 h after dosing. In the same groups, other indications of maternal toxicity included body and liver weights and feed

consumption that were all lower than those of the controls. Reduced kidney weights were seen in the top dose group only. A significant reduction in live foetal body weight at 300 and 600 mg/kg bw/day (8 and 17% respectively) and an increasing trend (not statistically significant) towards skeletal malformations (missing or branched ribs and fused thoracic vertebrae) were considered as secondary, non-specific consequences of maternal toxicity. The NOAEL for maternal toxicity is 100 mg/kg bw/day based on central nervous system effects at higher doses and the NOAEL for developmental toxicity is the highest dose of 600 mg/kg bw/day. Thus, 1,4-butanediol is not determined to have developmental toxicity.

2.14 Interactions with other chemicals

Several studies describe the interaction of 1,4-butanediol with ethanol. Simultaneous ingestion of 1,4-butanediol and ethanol increased the mortality rate and both renal and hepatic damage in rats (Poldrugo et al., 1985*). The action of ADH from rat liver or brain in the conversion of 1,4-butanediol to GBH was competitively inhibited by ethanol (Poldrugo & Snead, 1986*). Pyrazole, an inhibitor of ADH, blocked the reaction catalyzed by the liver enzyme *in vitro*, and *in vivo* antagonised the pharmacologic response (induction of sleep or sedation) to administered 1,4-butanediol in rodents (Poldrugo & Snead, 1986*; Taberner & Pearce, 1974*)

2.15 Conclusions

Acute toxicity data shows moderate toxicity by the oral route, with the most common clinical signs being depressed respiration, lateral posture and catalepsy, and low toxicity by dermal and inhalation routes. 1,4-butanediol is considered at most a slight irritant to the eyes, skin and respiratory tract but shows no evidence of skin sensitisation. In animals and humans, 1,4-butanediol is rapidly absorbed and metabolized to γ -hydroxybutyric acid, and therefore the CNS depressant activity of 1,4-butanediol is considered to be predominantly caused by the metabolite, γ -hydroxybutyric acid. 1,4-Butanediol shows a competitive inhibition of alcohol dehydrogenase and concurrent consumption with ethanol may increase the risk of death or organ damage and potentiate the effects of ethanol.

There are no long-term data on the chronic effects of 1,4-butanediol. In an oral, 45 day combined repeat dose and reproductive/developmental screening study in rats, neurobehavioral toxicity and histopathological changes in the bladder were observed. Transient neurotoxicity, resolved within 5 h after dosing, was observed at the lowest dose of 200 mg/kg bw/day. A similar neurotoxic profile was also observed in an oral, 10-day developmental toxicity study of mice at doses of 300 and 600 mg/kg bw/day, but not at 100 mg/kg/day, and therefore a NOAEL of 100 mg/kg/day for oral repeat dose toxicity is considered to be reliable. Systemic adverse effects in rats after a 2-week (6 h/day) inhalation exposure were reduced body weight and thymic atrophy at 5.2 mg/L with both effects reversible during the recovery period. The NOAEC was determined to be 1.1 mg/L. From repeated dose studies, it is evident that the most sensitive adverse effect is neurotoxicity. Overall, the short duration and nature of the available studies does not allow for the identification of a robust dose-response and NOAEL.

The limited available data in animals provides no evidence that 1,4-butanediol has a direct effect on reproduction or development. In a reproductive toxicity study in

rats and a developmental study in mice, a reduction in fetal body weight was the only definitive adverse effect observed. In both studies this effect was considered to be secondary to maternal toxicity with NOAELs for reproductive toxicity in rats and developmental toxicity in mice the highest doses tested of 800 and 600 mg/kg bw/day respectively. The chemical is not considered to be genotoxic based on negative results of a bacterial mutation test and chromosomal aberration tests *in vitro* conducted according to OECD guidelines.

Bibliography

BASF (1991) Study on the acute inhalation toxicity LC50 of 1,4-Butanediol as a liquid aerosol in rats 4-hour exposure. (unpublished report submitted by BASF).

Borgen LA, Okerholm RA, Lai A, & Scharf MB (2004) The pharmacokinetics of sodium oxybate oral solution following acute and chronic administration to narcoleptic patients. *J. Clin. Pharmacol.*; 44: 253-257.

Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, & Watson DE (2004) Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J. Anal. Toxicol.* **28**:625-630.

Caldicott DG, Chow FY, Burns BJ, Felgate PD, & Byard RW (2004) Fatalities associated with the use of γ -hydroxybutyrate and its analogues in Australasia. *Med J Aust*, **181**(6): 310-313.

Cavender FL & Sowinski EJ (1994) Butanediols. In: Clayton GD & Clayton FE ed., *Patty's industrial hygiene and toxicology*, 4th ed. New York, John Wiley & Sons Inc., vol 2, part F, pp 4692-4693.

Chemical Economics Handbook (2007) 1,4-Butanediol marketing research report. . Menlo Park CA, Stanford Research Institute.

Dyer JE, Galbo MJ, & Andrews KM (1997) 1,4-Butanediol, "Pine Needle Oil": overdose mimics toxic profile of GHB. *Journal of Toxicology Clinical Toxicology*, **35**(5): 554.

EU (1976). Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. *OJ L262*, 169–200, 27 September 1976. <http://europa.eu.int/eur-lex/en/consleg/main/1976/en_1976L0768_index.html> (consulted Nov 2007).

GAF Corporation (1967) Technical Bulletin, 7543-077.

Garcia AD & Catterton AJ (2003) 1,4-Butanediol (BD)-forensic profile. *Microgram Journal*, **1**(1-2): 44-54.

Gottschalek TE & McEwen GN ed. (2006) *International cosmetic ingredient dictionary*, 11th ed. Washington D.C. The Cosmetic, Toiletry and Fragrance Association, vol 1, p 276.

Government of Victoria (2007) Fair Trading Act 1999 - Order prohibiting the supply of dangerous goods and revoking previous order. *Victoria Government Gazette*, No. S359, Monday 24 December 2007.

Government of Western Australia (2008) Consumer Affairs Act 1971 section 23r(2) Order prohibiting supply of goods. *Western Australia Government Gazette*, Perth, Tuesday 8 January 2008, No. 5, Special.

Gunja N, Doyle E, Carpenter K, Chan OT, Gilmore S, Browne G, & Graudins A. γ -Hydroxybutyrate poisoning from toy beads eMJA Rapid Online publication 19 November 2007.

HSBD (Hazardous Substances Data Bank) [Internet]. Bethesda (MD): National Library of Medicine (US); 1,4-Butanediol; Hazardous Substances Databank Number: 1112. Available from: <http://toxnet.nlm.nih.gov/> Accessed Nov 2007

- Hazardous Substances Information System (<http://www.nohsc.gov.au/applications/hsis/>), Office of the Australian Safety and Compensation Council © Commonwealth of Australia.
- HPD (Household Products Database) [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <http://toxnet.nlm.nih.gov/> Accessed Nov 2007.
- Hinrichs A, Kopf R, Loeser A (1948) Zur Toxicologie des 1,4-Butanediol. *Pharmazie*, **3**: 110-112.
- Hüls AG (1993a) Unpublished report. Department of Toxicology, Final Report, CA-93/0089
- Hüls AG (1993b), Unpublished report. Department of Toxicology, Final Report, HP-93/0089
- Irwin RD (2006) A review of evidence leading to the prediction that 1,4-butanediol is not a carcinogen. *J Appl Toxicol.*, Jan-Feb; **26**(1): 72-80.
- Japan Ministry of Health and Welfare (1997) Toxicity testing reports of environmental chemicals, **5**:429-442
- Japan Ministry of Health and Welfare (1999) Toxicity testing reports of environmental chemicals, **7**:371-385.
- Jedrychowski RA, Stetkiewicz J, & Stetkiewicz I (1990a) Acute toxicity of 1,4-butanediol in laboratory animals. *Pol. J. Occup. Med.*, **3**:415-420.
- Jedrychowski RA, Gorny R, Stetkiewicz J, & Stetkiewicz I (1990b) Acute toxicity of 1,4-butanediol in laboratory animals. *Pol. J. Occup. Med.*, **3**:421-428.
- Kinney LA, Burgess BA, Stula EF, & Kennedy GL (1991) Acute and subchronic inhalation toxicity of 1,4-butanediol in rats. *Inhalation Toxicology*, **3**(4): 379-388.
- Howe-Grant M ed. (1998) Kirk-Othmer encyclopedia of chemical technology, 4th ed., Vol. 9, p. 245; Vol.19, p.655; Vol.23, p.551. John Wiley and Sons, New York.
- Knyshova SP (1968) Biological effect and hygienic significance of 1,4-butanediol and 1,4-butanediol. *Gig. Sanit.*, **33**: 41-47.
- Lee WR, Abrahamson S, Valencia R, von Halle ES, Würzler FE, & Zimmering S (1983) The sex-linked recessive lethal test for mutagenesis in *Drosophila melanogaster*. A report of the U.S. Environmental Protection Agency Gene-Tox Program. *Mutat. Res.*, **123**:183-279.
- Lewis RJ (1997) Hawley's condensed chemical dictionary. 13th ed. New York, John Wiley & Sons Inc., p 178.
- Maxwell R & Roth RH (1972) Conversion of 1,4-butanediol to -hydroxybutyric acid in rat brain and in peripheral tissue. *Biochem. Pharmacol.*, **21**:1521-1533.
- National Drugs and Poisons Schedule Committee (September 2007) Standard for the Uniform Scheduling of Drugs and Poisons. Canberra, Australian Government Publishing Service.
- National Toxicology Program (NTP) (1989) Project report: Absorption, disposition, metabolism and excretion of 1,4-butanediol in rats after oral administration. (Appendix to NTP, 1996).

National Toxicology Program (NTP) (1992) Toxicology and carcinogenesis studies of γ -butyrolactone (CAS No. 96-48-0) in F344/N rats and B6C3F₁ mice (gavage studies). Research Triangle Park, North Carolina, US Department of Health and Human Services, (NTP Technical Report Series No. 406), 232 pp, NIH Publication 92-3137.

National Toxicology Program (NTP) (1996) Summary report on the metabolism, disposition and toxicity of 1,4-butanediol (CAS No. 110-63-4). Research Triangle Park, North Carolina, US Department of Health and Human Services (NTP Toxicity Report Series No. 54) 41 pp, NIH Publication 96-3932.

NDPSC (2008) Record of reasons, 53rd meeting, 17-18 June 2008. National Drugs and Poisons Schedule Committee. <http://www.tga.gov.au/ndpsc/record/rr200806.htm>

NOHSC (1999) List of designated hazardous substances. National Occupational Health and Safety Commission. Canberra, Australian Government Publishing Service.

NOHSC (2004) Approved criteria for classifying hazardous substances [NOHSC:1008(2004)] (3rd Edition). National Occupational Health and Safety Commission, http://www.ascc.gov.au/NR/rdonlyres/C3F31984-D009-415E-A5BA-F6CD5638A7EF/0/approved_criteriaNOHSC1008_2004.pdf

Northern Territory of Australia (2007) Government Gazette, No. S41, 24 December 2007. Darwin, NT. <http://www.nt.gov.au/ntg/gazette/2007/s41.pdf>

NSW Department of Commerce, Office of Fair Trading (2007) Bindeez update – 19 December 2007. http://www.fairtrading.nsw.gov.au/About_us/News_and_events/Media_releases/2007_media_releases/20071219_bindeez_update.html

OECD (2000) 1,4-Butanediol (SIDS Initial Assessment Report for 10th SIAM – Tokyo, March 15-17, 2000), UNEP Publications <http://www.inchem.org/documents/sids/sids/110634.pdf>

Poldrugo F & Snead OC III (1984) 1,4 Butanediol, GHB and ethanol: relationships and interactions. *Neuropharmacology*; **23**(1): 109-113.

Poldrugo F. & Snead OC III (1986) 1,4 Butanediol and ethanol compete for degradation in rat brain and liver in vitro..*Alcohol*, **3**(6): 367-370.

Poldrugo F, Barker S, Basa M, Mallardi F, & Snead OC III (1985) Ethanol potentiates the toxic effects of 1,4-butanediol. *Alcohol Clin. Exp. Res.*; **9**(6): 493-497.

Price CJ, Marr MC, Myers CB, Heindel JJ, & Schwetz BA. (1994 Jun) Final report on the developmental toxicity of 1,4-butanediol (CAS no. 110-63-4) in Swiss (CD-1) mice on gestational days 6 through 15--final report and appendices. Springfield: National Technical Information Service (Technical Report NTIS/PB94-195831) 193 pp.

Roehrborn G (1959) Studies on the problem of the genetic effectiveness of myleran on *Drosophila melanogaster* *Zeitschrift f. Vererbungslehre*, **90**(1): 116-131.

Roth RH, & Giarman NJ (1966) -Butyrolactone and -hydroxybutyric acid — I. Distribution and metabolism. *Biochem. Pharmacol.*, **15**: 1333-1348.

Scharf MB, Lai AA, Branigan B, Stover R, & Berkowitz DB (1998) Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. *Sleep*, **21**:507-514.

- Spencer PS, Bischoff MC, & Schaumburg HH (1978) On the specific molecular configuration of neurotoxic aliphatic hexacarbon compounds causing central-peripheral distal axonopathy. *Toxicol. Appl. Pharmacol.*, **44**(1): 17-28.
- Sprince H, Josephs JA, & Wilpizeski CR (1966) Neuropharmacological effects of 1,4-butanediol and related congeners compared with those of γ hydroxybutyrate and γ -butyrolactone. *Life Sci.*, **5**: 2041-2052.
- Stasenkovna KP (1965) *Toksikol. Novykh. Prom. Khim. Veshchestv.* **7**:5-13.
- Strickland RM, Felgate P, & Caldicott DG (2005) Survival of massive γ -hydroxybutyrate/1,4-butanediol overdose. *Emerg Med Australas.*, **17**(3): 281-283.
- Taberner PV & Pearce MJ (1974) Hypothermic and toxic actions of 2-butyne-1,4-diol and other related diols in the rat *J. Pharm. Pharmacol.*, **26**(8): 597-604.
- Thai D, Dyer JE, Jacob P, & Haller C (2007) Clinical pharmacology of 1,4-butanediol and gamma-hydroxybutyrate after oral 1,4-butanediol administration to healthy volunteers. *Clinical Pharmacology & Therapeutics*, **81**(2): 178-184.
- Theron L, Jansen K, & Skinner A (2003) New Zealand's first fatality linked to use of 1,4-butanediol (1,4-B, Fantasy): no evidence of coingestion or comorbidity. *NZ Med J*, **116**(1184): U650.
- Toxikologische Bewertung, Heidelberg, Berufsgenossenschaft der chemischen Industrie, 1993; 99: 29 p.
- Vree TB, Van Dalen R, van der Kleijn , & Gimbrere JSF (1978) Pharmacokinetics of 1,4-butanediol and 4-hydroxybutyric acid in man, rhesus monkey, and dog. *Anesthesiol. Intensivmed*, **110**: 66-73.
- Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ, & Peacock EA (2001) Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med.*, Jan 11; **344**(2): 87-94.