



NICNAS Existing Chemicals Information Sheet

1,4-Butanediol CAS No: 110-63-4

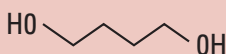
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Introduction

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 gamma-hydroxybutyrate (GHB), a neuromodulator that exerts potent depressant effects on the central nervous system.

Concerns regarding the toxicity of 1,4-butanediol have been 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. This Information Sheet presents the major findings of the health hazard assessment report available on the NICNAS website¹.

Chemical Identity

Common name:	1,4-Butanediol
Structural formula:	
CAS registry number:	110-63-4
IUPAC chemical name:	Butane-1,4-diol

1,4-Butanediol is a colourless, viscous and almost odourless liquid.

Import, Manufacture and Use of 1,4-Butanediol in Australia

1,4-Butanediol is listed on the NICNAS High Volume Industrial Chemicals List (HVICL). Over the year 2001-02, import volumes totalling greater than 1000 tonnes were reported. The major uses of 1,4-butanediol, as reported by the Plastics and Chemicals Industries Association (PACIA) 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 tetrahydrofuran². 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 http://www.nicnas.gov.au/Publications/CAR/Other/1,4-butandediol_Hazard_Assessment_PDF.pdf

² Personal communication, 5 December 2007

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1,4-Butanediol is also reportedly used as a solvent in cosmetic formulations and as a humectant in pharmaceuticals.

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.

Potential Exposure to 1,4-Butanediol

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. It is also used as a humectant, in pharmaceuticals and in cosmetic pencils (Household Products Database³).

The Hazardous Substances Databank (HSDB⁴) reports that 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.

Summary of Key Health Issues

The toxicity of 1,4-butanediol appears to be restricted to acute toxicity and slight skin, eye and respiratory tract irritation. 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 do not allow for the identification of a robust dose-response and No-Observed-Adverse-Effect-Level (NOAEL). There are no data to indicate that 1,4-butanediol is a skin sensitiser, genotoxic, carcinogenic, or a reproductive toxicant.

Current Regulatory Status

1,4-butanediol IS listed in:

- the Australian Inventory of Chemical Substances (AICS) and
- the National Drugs and Poisons Schedule Committee Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP⁵). The non-polymerised form of 1,4- butanediol for all domestic use (including toys) is listed in Appendix C. Appendix C lists substances, other than those included in Schedule 9 (prohibited substances), considered to be of such danger to health as to warrant prohibition of sale, supply and use.

1,4-butanediol IS captured by:

- the industry-based PACIA 'Code of Practice for Supply Diversion to Illicit Drug Manufacture'. This Code has been developed in consultation with law enforcement authorities to control supply of certain substances, including 1,4-butanediol now listed as an Illicit Drug Precursor (Category 1). Three Australian states (NSW, Qld and WA) have legislated to make elements of the PACIA Code mandatory and other states are also developing regulations.

³ <http://householdproducts.nlm.nih.gov>

⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

⁵ <http://www.tga.gov.au/ndpsc/susdp.htm#susdp>

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1,4-butanediol is NOT listed in:

- the Hazardous Substances Information System (HSIS), and
- the Australian Customs (Prohibited Imports) regulations which cover the import/export of drugs and certain precursor substances used in the manufacture of illicit drugs. However, GHB⁶ is classified as a psychotropic substance and listed as a prohibited import that requires import authorisation.

Health and Safety Information

The major source of the information about health effects is a report 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. A comprehensive literature search was carried out for data published since 1999 to ensure that those studies published after the last literature search conducted for the SIAR were also reviewed and summarised in the NICNAS report.

After oral or intravenous administration, 1,4-butanediol is rapidly and efficiently metabolised in the liver to form GHB. In humans, extensive conversion of 1,4-butanediol to GHB after oral dosing indicated that ingestion of 1,4-butanediol is essentially equivalent to GHB intake. Peak blood levels are achieved after 30 to 60 minutes.

No data are available on dermal absorption.

Animal Data

Acute Toxicity

1,4-Butanediol is considered to be moderately toxic by the oral route and has low toxicity by the dermal and inhalation routes. The lowest reported LD₅₀ (Lethal Dose, 50%; ie. the dose that is lethal for half of the animals tested) value is 1200 mg/kg bw (body weight) in guinea pigs. In rats and mice, reported values are in the range of 1525-1830 mg/kg bw and 2060 mg/kg bw respectively.

Irritation

Eyes and Skin – In rabbits, 1,4-butanediol is not irritating to the skin and at most considered only a slight irritant to the eyes.

Inhalation – Slight respiratory irritation has been observed in rats following exposure to an aerosol of 1,4-butanediol at concentrations higher than 4.6 mg/L.

Sensitisation

A study in guinea pigs showed no skin sensitising potential.

Repeated Dose Toxicity

In a 10-day oral (gavage) study in mice, a NOAEL of 100 mg/kg bw/day was established for signs of central nervous system intoxication including hypoactivity, immobility, loss of righting reflex and prone posture. Similar neurotoxicity was seen in rats in a 39 to 45-day gavage study from 200 mg/kg bw/day with full recovery noted within 5 hours of dosing. In an inhalation study, reduced body weight, increased erythrocyte counts and other blood values and slight atrophy of lymphoid cells in the thymus were seen from 5 mg/L (4h) with the body weights and thymic atrophy returning to normal during a 14-day recovery period.

⁶ Gamma-hydroxybutyrate, see Introduction, page 1.

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Neurotoxicity

Adverse effects of 1,4-butanediol on the nervous system have been observed in acute studies. The chemical appears to have dual toxicological actions: the major neurotoxic effects of 1,4-butanediol are attributable both to its conversion to GHB and its alcohol-like effect due to the diol itself. Administration of 496 mg/kg bw 1,4-butanediol to rats caused CNS⁷ depression and induced a state resembling sleep or anesthesia characterised by loss of righting reflex, struggle response and voluntary motor activity. Very similar neurotoxicologic responses were observed after administration of GHB.

Genotoxicity

1,4-Butanediol was negative in an Ames (bacterial mutation) test, a gene mutation and two chromosomal aberration tests in mammalian cells. The only *in vivo* study available was judged to be unreliable although a negative result was obtained. Overall, 1,4-butanediol is not considered to interact with DNA.

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. 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.

Reproductive Toxicity

No effect on fertility was seen in a study in male and female rats administered up to 800 mg/kg bw/day 1,4-butanediol. In a developmental toxicity study in the mouse using doses of 100 to 600 mg/kg bw/day, a slight reduction in live foetal weight was seen from 300 mg/kg bw/day in the presence of maternal toxicity. At 100 mg/kg bw/day no developmental toxicity was seen. Therefore, 1,4-butanediol is not considered a developmental toxicant, as the developmental effects seen were a secondary non-specific consequence of maternal toxicity.

Human Data

Acute toxicity

The critical toxic effect of 1,4-butanediol is neurotoxicity. Central nervous system disturbances including decreased alertness, dizziness and respiratory depression have been reported following oral dosing at 25 mg/kg bw. More significant effects occur at higher doses and by other routes of administration with sleep induction, restlessness and myoclonus (a quick, involuntary twitching of a muscle or muscle group) reported to occur following intravenous administration of 30 mg/kg bw and miosis (constriction of the pupil of the eye), areflexia (absence of reflexes), coma and death observed in patients after rectal administration of 15 or 30g 1,4-butanediol (estimated at 200 or 400 mg/kg bw).

Experience with human exposure – case studies

Numerous case reports are available that describe the neurological consequences (including agitation, combativeness, respiratory depression, a labile⁸ level of consciousness, vomiting, seizures and death) in patients known to have ingested illicit products containing 1,4-butanediol. 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.

⁷ Central nervous system

⁸ Imbalanced or unbalanced

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In late 2007 in Australia, four children were hospitalised after swallowing 'Bindeez' brand toy beads that were found to be coated with 1,4-butanediol, however quantification of the amount of 1,4-butanediol ingested was not reported.

International Regulatory Activities

USA

In May 1999, the USA Food and Drug Administration (FDA) issued a public warning about products containing 1,4 butanediol and declared the chemical to be a Class I Health Hazard (ie. potentially life-threatening). Although this classification imposes no legal restrictions on the manufacture, distribution or possession of 1,4 butanediol, when 1,4 butanediol is distributed for human consumption it meets the definition of a 'controlled substance analogue' and distributors can therefore be prosecuted for supplying a Schedule 1 substance.

New Zealand

The chemical has been classified as Class B1 (ie. a drug posing a high risk of harm) under the *Misuse of Drugs Act 1975*.

Other

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