1,4-Butanediol (1,4-BD)
Pre-Review Report

Expert Committee on Drug Dependence
Thirty-fifth Meeting
Hammamet, Tunisia, 4-8 June 2012
35th ECDD (2012) Agenda item 5.5

1,4-Butanediol (1,4-BD)
Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Medicines Access and Rational Use Unit. The WHO Secretariat would like to thank the following people for their contribution in producing this pre-review report: Prof. Louis Harris and Dr. Laura Johnson, United States of America (literature review and drafting), Dr Caroline Bodenschatz (editing) and Mr Kamber Celebi, France (questionnaire report).
1,4-Butanediol (1,4-BD)
Contents

SUMMARY ............................................................................................................. 7

1. Substance Identification .................................................................................. 8
   A. International Non-proprietary Name (INN) ..................................................... 8
   B. Chemical Abstract Service (CAS) Registry Number ....................................... 8
   C. Other Chemical Names ................................................................................. 8
   D. Trade Names .................................................................................................. 8
   E. Street Names .................................................................................................. 8
   F. Physical properties .......................................................................................... 8
   G. WHO Review History .................................................................................... 8

2. Chemistry .......................................................................................................... 8
   A. Chemical Name .............................................................................................. 8
   B. Chemical Structure ........................................................................................ 9
   C. Stereoisomer .................................................................................................... 9
   D. Synthesis .......................................................................................................... 9
   E. Chemical description ....................................................................................... 10
   F. Chemical properties ....................................................................................... 10
   G. Chemical identification .................................................................................. 10

3. Convertibility into controlled substances .......................................................... 10

4. General pharmacology ..................................................................................... 10
   4.1. Pharmacodynamics .................................................................................... 10
   4.2. Route and dose of administration ................................................................ 11
   4.3. Pharmacokinetics ....................................................................................... 11

5. Toxicology ......................................................................................................... 12

6. Adverse reactions in humans ............................................................................. 15

7. Dependence potential ....................................................................................... 15

8. Abuse potential .................................................................................................. 16

9. Therapeutic applications, therapeutic use and epidemiology of medical use .......... 16

10. Listing on the WHO Model List of Essential Medicines ................................... 17

11. Marketing authorizations (as a medicine) .......................................................... 17
12. Industrial use .................................................................17
13. Non-medical use, abuse and dependence ................................17
15. Licit production, consumption and international trade .........................19
16. Illicit manufacture and traffic and related information ..................................19
17. Current international controls and their impact ........................................20
18. Current and past national control .......................................................20
19. Other medical and scientific matters relevant for a recommendation on the scheduling of the compound .............................................................21

References ..........................................................................................22

Annex 1: WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: 1,4-Butanediol (1,4-BD) ..............................................................................................................29
Summary

1,4-butanediol (1,4-BD) is an industrial chemical presenting good environmental characteristics and involving minimal health risks to workers. 1,4-BD is an important kind of raw material to both the organic chemical and fine chemical industries. (1) It is widely used in the medicine industry, the chemical industry, the textile industry, the paper making industry, the automobile industry, and the daily-using chemical industry.

Since the end of the 1990s, 1,4-BD is also ingested by certain individuals for the purpose of intoxication. The epidemiology of the use and abuse of 1,4-BD is intrinsically linked to that of gamma-hydroxybutyrate (GHB). It is rapidly metabolized to and reported forensically as GHB - there is no need first to convert it chemically into some other substance. Deaths have been documented, but owing to this metabolism it is difficult to establish whether the deceased person had consumed GHB or 1,4-BD. Indeed, forensic samples of blood and other tissues are generally analyzed for GHB not its precursor. 1,4-BD appears to be mainly used and abused in the United States, Europe and Australia.

The amount needed to be taken in order to produce intoxication varies slightly among the substances; GHB is more potent than gamma-butyrolactone (GBL), another GHB precursor, which is more potent than 1,4-BD. On the substance market, the substance is usually sold mixed with distilled water at different concentrations. The doses of abuse are small: 100-200 ml, usually mixed with a taste-giver, such as a soft drink. Margins are small between normal and excess doses, entailing great overdose risks. Visually, the substances are very similar. It is difficult to tell them apart and to identify a sample with the naked eye.

In March 2001, GHB was added to Schedule IV of the 1971 UN Convention on Psychotropic Substances. Therefore, all Member States were bound to control it under their legislation addressing psychotropic substances. 1,4-BD is not subject to the 1988 UN Convention that covers precursor chemicals. This legal loophole is exploited by the users as possession and consumption of 1,4-BD is legal in most of the countries.

In view of concerns about the diversion of 1,4-BD from the domestic distribution channel and illicit trade of 1,4-BD, some Member States have chosen to control one or both precursors under drug control or equivalent legislation. Furthermore, the European Community and the Member States have taken additional voluntary measures to prevent its diversion. This includes guidance for operators to be vigilant when placing this substance onto the international market.

However, the crucial issue remains how to do this without affecting industrial use. 1,4-BD is used in tons in the industry, while the doses for abuse are very small. Still, even if supervision of 1,4-BD was to be reinforced through its listing in the 1988 Convention, it would remain available to most citizens.
1. Substance Identification

A. International Non-proprietary Name (INN)
   Not applicable.

B. Chemical Abstract Service (CAS) Registry Number
   110-63-4
   55-98-1  dimethylsulfonate (busulfan)
   2425-79-8  diglycidyl ether

C. Other Chemical Names
   1,4-Butylene glycol; 1,4-Dihydroxybutane; BDO; Butanediol-1,4; Tetramethylene glycol; 1,4-BD; 1,4-BDO; 1,4-Tetramethylene; 1,4-Tetramethylene glycol

D. Trade Names
   No medical use

E. Street Names
   1,4-BD has been associated with street names including:

F. Physical properties
   1,4-BD is a colorless, waxy solid to viscous liquid depending on temperature (melting point 20.1°C and boiling point of 230°C).

G. WHO Review History
   During the discussion of gamma-hydroxybutyric acid (GHB) at the 34th Meeting of the WHO Expert Committee on Drug Dependence, the Committee “noted information relating to the abuse of 1,4-BD itself (convertible to GHB in the body) and suggested this substance for pre-review.” (2)

2. Chemistry

A. Chemical Name
   IUPAC Name:  1,4-butanediol
   CA Index Name:  1,4-butanediol
B. Chemical Structure

\[
\text{HO} \quad \text{HO}
\]

**Molecular Formula:**
- \( \text{C}_4\text{H}_{10}\text{O}_2 \)
- \( \text{C}_6\text{H}_{14}\text{O}_6\text{S}_2 \) (dimethylsulfonate)
- \( \text{C}_{10}\text{H}_{18}\text{O}_4 \) (diglycidyl ether)

**Molecular Weight:**
- 90.12 g/mol
- 246.3 g/mol (dimethylsulfonate)
- 202.25 g/mol (diglycidyl ether)

**Melting point:**
- 20 °C
- 114-117 °C (dimethylsulfonate)
- 116-119 °C (diglycidyl ether)

**Boiling point:**
- 230 °C
- no data (dimethylsulfonate)
- 266 °C (diglycidyl ether)

**Fusion point:**
- 135 °C
- no data (dimethylsulfonate)
- no data (diglycidyl ether)

C. Stereoisomer

None.

D. Synthesis

In its industrial synthesis, acetylene reacts with two equivalents of formaldehyde to form 1,4-butynediol, also known as but-2-yn-1,4-diol. This type of acetylene-based process is illustrative of what is known as "Reppe chemistry", after German chemist Walter Reppe. Hydrogenation of 1,4-butynediol gives 1,4-butanediol.

LyondellBasell manufactures 1,4-BD in a proprietary, multi-step process without the use of acetylene. First, propylene oxide is converted to allyl alcohol. The allyl alcohol is then hydroformulated to 4-hydroxybutyaldehyde. Hydrogenolysis of the 4-hydroxybutyaldehyde yields 1,4-BD. (3)

It can also be manufactured on an industrial scale by the vapour phase hydrogenation of the esters and anhydrides of maleic acid and succinic acid. Genomatica (a San Diego-based company) has genetically engineered *E. coli* to metabolize sugar into 1,4-butanediol. They expect to build and begin operating a pilot plant by the end of 2009. Genomatica CEO Christopher Gann said the
process consumes 32,000 BTU per pound of 1,4-butanediol (75 MJ/kg), far less than the acetylene-based process, and does not have any by-products. (4,5)

E. **Chemical description**

1,4-Butanediol is the organic compound with the formula HOCH₂CH₂CH₂CH₂OH. This colorless viscous liquid is derived from butane by placement of alcohol groups at each end of the chain. It is one of four stable isomers of butanediol.


F. **Chemical properties**

1,4-BD is soluble in water, dimethylsulfoxide, acetone, 95% ethanol and insoluble in ether.

G. **Chemical identification**

Early GC and GC-MS methods (6,7) have been replaced with newer methodology which have increased sensitivity and specificity. (8,9,10)

3. **Convertibility into controlled substances**

1,4-BD is readily converted both chemically and in the body to GHB, a controlled substance. GHB is placed in Schedule IV of the 1971 Convention

4. **General pharmacology**

4.1. **Pharmacodynamics**

Early in the investigation of 1,4-BD, it became evident that most of its pharmacological and toxicological effects were mediated through a metabolite, GHB. (11,12) In comparisons with other alcohols, it was occasionally reported to have similar effects unrelated to its conversion to GHB. (13) Further research activity was sporadic until concern arose in the late 1990s about the widespread abuse of GHB, especially in young people. National and international controls of GHB prompted substitution of 1,4-BD and gammabutyrolactone (GBL), the GHB metabolites for GHB, by young abusers. This popular trend paralleled the rise in the use of the internet for the exchange of information. Thus, at the request of the WHO, the College on Problems of Drug Dependence initiated comprehensive studies on both 1,4-BD and GBL, which, in turn, aroused interest by other investigators. These are detailed below:

At the 2002 CPDD Meeting, Aceto *et al.* (14) reported that 1,4-BD was inactive as an analgesic in a variety of mouse models and neither substituted for morphine nor
exacerbated withdrawal in the morphine-dependent rhesus monkey. At the same meeting, preliminary drug discrimination results were presented. These were later published as full papers. For instance, McMahon et al. (15) reported that in monkey self-administration studies, 1,4-BD was not self-administered. In drug discrimination studies 1,4-BD did not substitute for pentobarbital, midazolam or flumazenil.

As it would be expected from its rapid conversion to GHB, 1,4-BD produces mixed depressant and stimulatory effects in a wide variety of tests in rodents. (16-22) Increases in blood pressure and heart rate have been noted (20) as has a mechanistic relationship to the GABAB receptor system. (16,17,20) Of particular interest was the recent report that 1,4-BD given to rats directly to the brain (ICV) lacked the typical behavioral response seen with GHB. (20)

Until recently, there were no double-blind placebo controlled human clinical pharmacology studies of 1,4-BD. This was addressed by the study by Thai et al. (23) They compared the pharmacology of 1,4-BD and GHB after oral administration of 25 mg/kg 1,4-BD in a single dose to healthy volunteers. Vital signs were monitored and subjective mood and symptoms were assessed using a visual analog scale (VAS). Serial blood samples were taken over a 24-hr period and analyzed by GC/MS for 1,4-BD and GHB levels. Results were summarized as follows: “1,4-BD was quickly absorbed and cleared, with time to maximal plasma concentration of 24±12 min, and elimination half-life (T1/2) of 39.3±11 min. 1,4-BD was extensively converted to GHB, with a mean maximum GHB concentration of 45.6±19.7mg/l reached 39.4± 11.2 min after 1,4-BD ingestion. GHB T1/2 averaged 32.3±6.6 min. Some subjects exhibited slow oral clearance of 1,4-BD, which tended to correlate with a variant haplotype of the alcohol dehydrogenase gene ADH-1B variant G143A. Mean clearance (CL/F) was 151.5 ± 176.5 ml/min/kg for four subjects with variant haplotype versus 598.8 ± 446.6 ml/min/kg for four wild-type subjects (P= 0.061). Subjects reported feeling less awake and alert, less able to concentrate, and more lightheaded in the first 90 min after 1,4-BD ingestion. Pulse oximetry readings were lower 45 min after 1,4-BD dosing with a mean oxygen saturation of 98.5% with 1,4-BD versus 99.6% with placebo (P= 0.031). Transient increases in mean systolic and diastolic blood pressure were observed, but other vital signs remained unchanged. 1,4-BD was extensively converted to GHB after oral administration, but significant inter-individual variability in the rate of metabolism, possibly related to variants in ADH-1B, was observed. At the modest dose studied, significant clinical effects were not seen.

4.2. Route and dose of administration

There are no therapeutic uses. Doses used in abuse are discussed in section 13 below.

4.3. Pharmacokinetics

1,4-BD is converted into GHB by the enzymes alcohol dehydrogenase and aldehyde dehydrogenase and differing levels of these enzymes may account for differences in effects and side effects between users. (24) Because these enzymes are also responsible for metabolizing alcohol there is a strong chance of a dangerous drug interaction. (24-25) Emergency room patients who overdose on both alcohol and 1,4-BD often present with symptoms of ethanol intoxication initially and as the ethanol is metabolized the 1,4-
butanediol is then able to better compete for the enzyme and a second period of intoxication ensues as the 1,4-BD is converted into GHB. (24)

5. Toxicology

Toxicity in animals

1,4-BD was selected for evaluation by the U.S. National Toxicology Program (NTP) “because of high production volume, the potential for worker exposure, the lack of adequate toxicological characterization and the lack of evaluation for carcinogenic potential.” A summary report was issued in 1996. (26) This report contains an extensive review of literature on the pharmacology metabolism and disposition, toxicity, carcinogenicity of 1,4-BD, GBL and GHB. Much of the following material is quoted from this source. They studied only the metabolism and disposition of 1,4-BD in male rats and cite an earlier study of the survival and mean body weight in mice and rats after 16-day and 13-week oral gavage with GBL. They also cite a carcinogenic study of GBL carried out by the NTP. (27)

The acute toxicity studies are summarized in Table 1. The results were unremarkable except for the relatively low lethal potency of the substance.

Table 1
Acute Toxicity Values for 1,4-BD

<table>
<thead>
<tr>
<th>Species</th>
<th>Number</th>
<th>Route</th>
<th>LD$_{50}^a$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat/Albino</td>
<td>25 Male</td>
<td>Oral</td>
<td>1,550 mg/kg</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>25 Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat/Wistar</td>
<td>30 Male</td>
<td>Oral</td>
<td>1,830 mg/kg</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>30 Female</td>
<td></td>
<td>2,000 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Rat/— b</td>
<td>—</td>
<td>Oral</td>
<td>1,525 mg/kg</td>
<td>30</td>
</tr>
<tr>
<td>Rat/Wistar</td>
<td>18 Male</td>
<td>Intraperitoneal</td>
<td>1,070 mg/kg</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>18 Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat/Albino</td>
<td>88 Male</td>
<td>Intraperitoneal</td>
<td>1,000 mg/kg</td>
<td>32</td>
</tr>
<tr>
<td>Rat/Albino</td>
<td>88 Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat/Sprague-Dawley</td>
<td>—</td>
<td>Intraperitoneal</td>
<td>1,328 mg/kg</td>
<td>33</td>
</tr>
<tr>
<td>Mouse/— b</td>
<td>—</td>
<td>Oral</td>
<td>2,180 mg/kg</td>
<td>34</td>
</tr>
</tbody>
</table>
In dermal irritancy studies, 1,4-BD when applied neat to the intact or abraded back skin of New Zealand white rabbits did not produce any indication of primary irritancy after 72 hours. (28,29) Intraocular administration of 0.1 ml of 1,4-BD was considered non-irritating (7) or slightly irritating (29) to the eyes of New Zealand white rabbits. Hartley guinea pigs sensitized with 1,4-BD exhibited no contact dermatitis upon rechallenge. (29)

Repeated-dose studies have been conducted in animals using gavage administration (35) and inhalation exposure. (34) Groups of eight male and eight female Wistar rats were administered 1,4-BD by gavage at doses of 5, 50, or 500 mg/kg for 28 days. There were no deaths during the study. Mean body weights, organ weights, and feed consumption of the different dose groups were similar to those of the controls. Hematology parameters determined from blood samples obtained at necropsy indicated some potential differences between dosed and control groups; however, the differences were small and not indicative of chemical-related toxicity and thus were considered of questionable toxicologic significance. Mild-to-moderate inflammation of the liver was observed in some dosed animals, primarily from the 500 mg/kg group, but the increased severity compared to that in the controls was not statistically significant in males or females. (35)

Groups of 10 male Crl:CD rats were exposed nose only to an aerosol containing 0.2, 1, or 5 mg/L of 1,4-BD for 6 hours per day, 5 days per week for 2 weeks. (34) After the ninth exposure, overnight urine samples were collected from all animals. Five rats per exposure group were killed after the tenth exposure, and the five remaining rats in each group were killed at the end of a 14-day recovery period, which immediately followed the 14-day exposure period. Prior to necropsy, blood samples were collected from all rats for hematology and clinical chemistry evaluations. No effects associated with chemical exposure were observed in rats exposed to 0.2 or 1 mg/L 1,4-BD. Rats exposed to 5 mg/l exhibited lower (7% to 9%) mean body weights than air-exposed controls. Rats receiving 10 exposures had slight atrophy of the lymphoid cells of the thymus. After 14 days of recovery, mean body weights returned to control values and no indication of thymic atrophy was reported. (34)

The developmental toxicity of 1,4-BD was evaluated by gavage with the administration of 1, 100, 300, or 600 mg/kg in water to timed-pregnant Swiss albino mice on gestation days 6 through 15. (36) No maternal deaths occurred during the study; however, signs of acute CNS intoxication including: hypoactivity, immobility, and loss of righting reflex occurred after dosing in the 300 and 600 mg/kg groups, but usually resolved within 4 hours after dosing. No apparent tolerance was noted during the 10-day dosing period. Other indications of maternal toxicity included body and liver weights and feed consumption that were lower than those of the controls in the 300 and 600 mg/kg groups and kidney weight lower than that of controls in the 600 mg/kg group. Significant reductions in live fetal weight occurred in the 300 and 600 mg/kg groups. The incidence of resorptions was not increased by chemical exposure, and the percentage of litters with one or more late fetal deaths was
1,4-BD has not been evaluated for chronic toxicity or carcinogenicity; however, γ-butyrolactone was evaluated in animals in 2-year studies by the NTP. (29) During the 2-year studies, γ-butyrolactone was administered by gavage in corn oil 5 days per week for 102 weeks. Male rats received 0, 112, or 225 mg/kg, female rats received 0, 225, or 450 mg/kg, and male and female mice received 0, 262, or 525 mg/kg. Exposure to γ-butyrolactone caused no adverse effects in rats or female mice. Focal hyperplasia of the adrenal medulla was increased in male mice in the 262 mg/kg group but not in 525 mg/kg males, and pheochromocytomas were present in the adrenal medulla of two control, six 262 mg/kg males, and one 525 mg/kg male. Although the incidence of pheochromocytomas in the 262 mg/kg group was not significantly increased compared to the control group, focal hyperplasia and pheochromocytoma of the adrenal medulla are considered a morphological and biological continuum. The increased incidence in the 262 mg/kg group is suggestive of a proliferative response associated with exposure to γ-butyrolactone. The incidence of proliferative lesions was not increased in the 525 mg/kg group of males. However, reduced survival as a result of deaths that occurred during the first year of the study may have reduced the sensitivity of this group for experiencing a carcinogenic response. Therefore an association between γ-butyrolactone exposure and hyperplasia and pheochromocytoma of the adrenal medulla on male mice in the 262 mg/kg group was considered uncertain.

A structural isomer, 1,3-butanediol, has also been evaluated in a chronic exposure study. (37) In this study, Sprague-Dawley rats (30 males and 30 females per group) received 1%, 3%, or 10% 1,3-butanediol in feed, and dogs (four males and four females per group) received 0.5%, 1%, or 3% 1,3-butanediol in feed for 2 years. Blood and urine samples were collected from rats at six time points and from dogs at eight time points during the study. Blood samples were evaluated for hematology parameters, and urine was analyzed for specific gravity, pH, glucose, protein, and porphyrins. After 1 year of chemical exposure, ten rats and two dogs from each group were evaluated; after 2 years of chemical exposure, the surviving animals were evaluated. At necropsy, organ weights were taken and all major tissues were fixed and prepared for histopathological examination. No adverse effects were observed during the study, and there were no gross or microscopic lesions attributable to chemical exposure. (37)

No genetic toxicology studies of 1,4-BD were identified in literature.

None of the toxicology studies of 1,4-BD have identified organ-specific toxicity or other significant effects except for behavioral changes. 1,4-BD is rapidly metabolized to GBH and excreted via the Kreb cycle pathway. GBL shares a similar metabolic path. GBL was evaluated in 16-day, 13-week and 2-year studies in rats and mice. (28) The only toxic response in the 16-day and 13-week studies was behavioral arrest. This response was the basis for selecting doses for the 2-year studies. GBL exhibited no toxic or carcinogenic potential. Based on this common metabolic pathway, it was concluded that 1,4-BD would be unlikely to be carcinogenic in animals.
6. Adverse reactions in humans

For a number of reasons, one is unable to obtain precise data on the incidence of adverse effects of 1,4-BD in humans. This is primarily due to the fact most of the adverse effects reported are due to the rapid conversion of 1,4-BD to GHB. Secondarily, it has rarely been determined precisely what an individual has ingested (1,4-BD, GBL and GHB). In addition, recent survey data treat the three compounds as a single agent. Despite this, there are numerous published fatality case reports. (38-46) The general symptoms reported include: loss of consciousness, vomiting, urinary and fecal incontinence, agitation, convulsions, respiratory depression, coma and death. The number of adverse reports has declined over time and the incidence is currently low. One recent exception involved a toy called ‘Bindeez’. The toy consisted of plastic (magic) beads that, when sprayed with water, stuck to surfaces, resulting in the creation of colorful designs. Ingestion of these beads caused comatose states in children. Thanks to rapid diagnosis and the publication by Australian physicians and scientists of the issue, it was revealed that the toxic agent was 1,4-BD, which was rapidly metabolized to GHB and was responsible for the observed toxicity. (47) Widespread reporting of the findings led to further reports and an international recall of the toy. (48, 49)

7. Dependence potential

Animal Studies

No direct primary tolerance and withdrawal studies of 1,4-BD in animals have been reported. However, Columbo et al. (50,51) reported a reproducible withdrawal syndrome for GHB and its precursors, 1,4-BD and GBL, in alcohol-preferring rats. In the morphine-dependent rhesus monkey, 1,4-BD neither substituted for nor exacerbated withdrawal. (14) Finally, in a series of papers, Goodwin et al. (52, 53) examined the acute and chronic effects of GHB and GBL in the baboon. They clearly observed a spontaneous and precipitated withdrawal syndrome after chronic administration of both GHB and GBL and presented evidence that the GABA_B receptor system may be involved. Since 1,4-BD is metabolized to GHB, it could be postulated that its chronic administration might very well lead to tolerance and withdrawal.

Human Studies

Currently not much is known about 1,4-BD dependency syndrome and there is no direct evidence that 1,4-BD can produce tolerance and withdrawal as demonstrated by a withdrawal syndrome when the substance is abruptly discontinued following regular chronic use. However, since it can be converted to GHB metabolically, it can be inferred that features could be similar to GHB withdrawal. Several cases of withdrawal from GHB and its precursors have been documented (54-60) the clinical features of which have not been fully characterized. (61,62) The withdrawal syndrome appears to be similar to other CNS depressants such as alcohol and sedative hypnotics. Symptoms include insomnia, anxiety and tremor which usually resolve within 2 weeks. (63) These symptoms can progress to severe delirium with autonomic instability in frequent, heavy users (every 1-3
hours 24 hours per day). (57) One case of seizures related to GHB withdrawal (64) and one death due to complications of GHB withdrawal (57) have been reported. There is also some evidence that tolerance and withdrawal may occur in recreational users. (65,66) GHB withdrawal has recently been reviewed. (67,68,62)

8. Abuse potential

Animal Studies

Since it is generally agreed that 1,4-BD owes its central nervous system activity to its conversion to GHB (11-12,16,21), the abuse potential of the substance mimics that of GHB. Animal studies which contribute to the determination of abuse potential revolve around a compound’s pharmacological resemblance to substances with known abuse liability and the substance’s reinforcing or rewarding actions. The procedures used to provide this evidence most often include general pharmacology, drug discrimination studies, and self-administration studies. As indicated above, the general pharmacology of 1,4-BD most closely resembles that of GHB (see Section 4). Drug discrimination studies (15,69-71) indicate that 1,4-BD is not discriminated as pentobarbital or midazolam but might share some properties with ethanol and some GABA-mimetic substances. Studies on the reinforcing effects of GHB are not indicative of a highly abused substance. Extensive self-administration studies in mice, rats and primates by both the oral and intravenous routes of administration indicate that GHB is not as reinforcing as other highly abused substances. Similarly, 1,4-BD showed little reinforcing properties when evaluated on intravenous self-administration in rhesus monkeys. (15)

Human Studies

The ability of a substance to produce reinforcing effects is the primary determinant of whether the substance will be abused. These effects may be described as positive reinforcers (e.g., producing pleasurable subjective effects) or negative reinforcers (e.g., alleviating negative states). For hypnotic substances, including GHB and 1,4-BD, some symptoms of withdrawal upon discontinuation (e.g., insomnia, anxiety), may accentuate the reinforcing effects of the substance. Also of importance is the adverse event (toxicity) profile of the substance. Both of these factors are used to determine relative abuse liability.

Such studies have been carried out with GHB (72), concluding that the profile of effects of GHB “only partially overlaps with that of triazolam and pentobarbital. Although the likelihood of GHB to be abused is intermediate to triazolam and pentobarbital, the possibility of accidental overdose (greater sedation than intended) with GHB appears to be greater.” No such studies exist for 1,4-BD. However, since 1,4-BD is rapidly converted to GHB in man, the abuse potential may be considered equivalent.

9. Therapeutic applications, therapeutic use and epidemiology of medical use
1,4-BD itself has no recognized therapeutic application. However, its dimethanesulfonate (busulfan, Myleran) is a bifunctional alkylating agent useful in the treatment of chronic myelogenous leukemia. (73) When given orally, except for seizures, there have been no reports of adverse central nervous system effects (i.e. CNS stimulations or depression). This would indicate that busulfan is not readily converted to GHB, at least in clinical doses up to those that produce severe toxic effects. (73).

10. **Listing on the WHO Model List of Essential Medicines**

1,4-BD is not listed.

11. **Marketing authorizations (as a medicine)**

1,4-BD itself is not authorized as a medicine. In the most recent (2008) WHO questionnaire for review of psychoactive substances, (Annex 1) not one of the 60 countries that responded authorized 1,4-BD as a medical or veterinary product.

12. **Industrial use**

The 2008 WHO questionnaire for review of psychoactive substances, (Annex 1) identified seven countries legitimated it for technical use. 1,4-BD is used in the production of a wide variety of polymers and as a solvent in various industrial processes. In Australia it is also used for forensic analysis. In Thailand it is used as a solvent in the laboratory.

13. **Non-medical use, abuse and dependence**

For the 2008 WHO questionnaire for review of psychoactive substances, (Annex 1), 7 countries reported on the use in a harmful way and 4 countries reported on the extent of the harmful use. When abused, 1,4-BD is administered orally.

1,4-BD starts to act after 5-20 min ingestion and lasts for about 2-3 hours. The actual effects are minted by an erotic, sensual warm sensation in the body, similar of those of “Ecstasy”, but also of alcohol. Withdrawal symptoms are accompanied with tremor (or shiver), sweating, nausea till delirium. They fade away after 3-5 days.

- A dose of 1-1.5 ml makes someone lose his inhibitions and acts as an aphrodisiac.
- A dose of 1.5-2 ml acts entactogen, euphoric and intensifies the senses (e.g. music).
- At a dose of 2-3 ml one can feel a strong euphoric “turn”.
- After a dose of 4 ml, 1,4-BD induces sleep (though the sedative effect can also be induced by lower doses. In some cases the sedative effect can lead to coma or even death).

However, the effect of 1,4-BD is different from individual to individual. Some people get nasty side effects already after an intake of 2 ml. Doses exceeding 6 ml induce heavy poisoning symptoms, leading to coma or death. (74)
The epidemiology of the use and abuse of 1,4-BD and GBL are intrinsically linked to that of GHB. They are both rapidly metabolized to and reported forensically as GHB. Indeed, forensic samples of blood and other tissues are generally analyzed for GHB not its precursors. 1,4-BD appears to be mainly used and abused in the United States, Europe and Australia. Some data from the Critical Review of GHB could be relevant to this pre-review of 1,4-BD.

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related emergency department (ED) visits for United States. For Q3-Q4, 2003 DAWN reports a total of 627,923 drug-related ED visits, of which only 990 involved GHB. Later DAWN data (75) indicates a continued low incidence of GHB ED visits and a continued downward trend. Thus, in 2004 there was a total of 1,253,956 misuse/abuse ED visits. Of these, 2340 were attributed to GHB (0.19%). In 2005, the total ED visits was 1’449’154. Of these, 1861 were attributed to GHB (0.13%).

Additional United States trend data can be found in the NIDA Proceedings of the Community Epidemiology Work Group. (76) In this data set, GHB/GBL are combined with MDMA and ketamine under the classification of “Club Drugs.” In general, the incidence of GHB/GBL use is low and has been trending down in recent years. This publication also includes DAWN ED, mortality and NFJLS data. In all categories, MDMA reports dominate with only a small number reported for GHB/GBL.

Reports to various substance monitoring centres indicate that the use and abuse of GHB or related products is far reaching across Europe. GHB continues to be monitored through the European early-warning system (EWS). The main aim of the EWS is the rapid collection, analysis and exchange of information on new synthetic substances as soon as they appear in Europe. Although indicators suggest that GHB use could spread significantly through recreational venues, there is insufficient data to establish prevalence or to identify trends at the EU level. Seizures of GHB, including its precursors GBL and 1,4-BD, have been reported in Belgium, the Czech Republic, Denmark, Estonia, France, the Netherlands, Sweden, Finland, the United Kingdom and Norway. (77) The latest report from this group (78) states that: “A lack of information makes trends in GHB use difficult to assess, although the available evidence suggests that use of GHB remains limited to some small subpopulation groups.” Data from dance music surveys from Belgium, the Netherlands, and the United Kingdom suggest that use of GHB may have peaked around 2000-2003 and declined subsequently. However, the extent to which this finding would apply to other subgroups is unclear. It might be noted that in 2005, substance telephone help lines in Finland reported telephone calls about GBL for the first time. The EMCDDA also recently published a thematic paper on “GHB and its precursor GBL: an emerging trend case study” which presents a comprehensive review of the status of this substance. (79)

It should be noted that prevalence of the use of GHB among Eight, Tenth, and Twelfth Graders, College Students and Young adults (Ages 19-28) in the United States over the years 2002-2006 was lower and trended down over time. (80) Equivalent data for 1,4-BD are not available.
14. **Nature and magnitude of public health problems related to abuse and dependence**

1,4-BD is a waxy solid to viscous liquid which is soluble in water. The material most often found on the street is as a solution in water and the primary route of administration is oral. Many of the dangers associated with illicit 1,4-BD are due to variances in the concentration of the solutions. Other routes of administration have rarely been reported. The compound is manufactured in ton quantities and is readily available in most countries and via the internet.

As discussed in Section 5, the incidence of adverse reactions to 1,4-BD are not available. However, some fatalities have been reported.

For the 2008 WHO questionnaire for review of psychoactive substances, (Annex 1), 3 countries reported on the extent of public health or social problems associated with the harmful use of 1,4-BD.

In summary, the nature and magnitude of public health problems related to the abuse and dependence on 1,4-BD has not reached those associated with GHB. Indeed, the magnitude of the problems appears to have decreased over the past several years.

15. **Licit production, consumption and international trade**

1,4-BD is an important kind of raw material to both the organic chemical and fine chemical industries. It is widely used in the medicine industry, the chemical industry, the textile industry, the paper making industry, the automobile industry, and the daily-using chemical industry. 1,4-BD can help produce THF, PBT, GBL, PU resin, dope, and plasticizer, etc., and can work as solvent or brightener for the electroplating industry.

World production of 1,4-Butanediol is reported as about one million metric tonnes per year and market price is about 2,000 USD per ton (2005). Almost half of it is dehydrated to tetrahydrofuran to make fibers such as Spandex. (81) The largest producer is BASF. (82)

The 2008 WHO questionnaire for review of psychoactive substances, (Annex 1) found that six countries import the substance.

16. **Illicit manufacture and traffic and related information**

A. **Reports of Illicit Activity and Seizures**

Based on the 2008 WHO questionnaire for review of psychoactive substances, (Annex 1), 4 countries have tracked illicit activities involving the substance. Clandestine manufacturing is reported once. Smuggling is reported two times and diversion is reported one time.

B. **1,4-BD Seized Material**
As found in 2008 WHO questionnaire for review of psychoactive substances, (Annex 1) two countries reported on the quantity of the seizures. In Norway there were 7 seizures with 7.4 L and in 2006 there were 10 seizures with 18.1 L. In 2007 there were no seizures reported. In the USA there were 46 seizures with 34533 g of powder and 26209 ml of liquid reported from System to Retrieve Information from Drug Evidence (STRIDE) data in 2007. National Forensic Laboratory Information System (NFLIS) showed 121 exhibits in 2007.

17. **Current international controls and their impact**

1,4-BD 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), subject to international controls in accordance with the 1971 UN convention on psychotropic substances.

18. **Current and past national control**

Only few States have declared 1,4-BD as a controlled substance as scheduling of 1,4-BD on a federal level seems difficult considering its legitimate industrial applications.

**Norway**

1,4-BD is controlled as a prescription drug under the Act on Medicinal Drugs (Legemiddeloven). Those wishing to use 1,4-BD have to submit a well-founded request to the Norwegian Medicines Agency, including information about their needs, storage arrangements, checks and controls, handling procedures and residuals management.

**US**

In May 1999, the USA FDA issued a public warning about products containing 1,4-BD 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-BD, when 1,4-BD 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.

In response to 2008 WHO questionnaire for review of psychoactive substances, (Annex 1), 4 countries reported 1,4-BD is controlled under legislation that is intended to regulate availability of substances of abuse.
19. Other medical and scientific matters relevant for a recommendation on the scheduling of the compound

Serious consideration should be given to whether 1,4-BD should be scheduled under the Psychotropic Convention (83) or controlled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988, New York, United Nations, 1991. (84)
References

1. Kajsa Mickelsson. Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) as industrial chemicals and drugs of abuse. Can they be regulated? National Institute of Public Health www.fhi.se.


11. R.H. Roth and N. J. Giarman. Evidence that central nervous system depression by 1,4-butanediol is mediated through a metabolite, gammahydroxybutyrate. Biochem. Pharmacol. 17, 735-739, 1968.


20. GAF Corporation. Summary of toxicity information for 1,4-butanediol. Pamphlet NO. 201-623, 3000.


28. GAF Corporation. Summary of toxicity information for 1,4-butanediol. Pamphlet NO. 201-623, 3000.


Annex 1: WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: 1,4-Butanediol (1,4-BD)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for 1,4-Butanediol (1,4-BD) by 60 countries.

**LEGITIMATE USE**

Not one of the 60 countries reported authorized 1,4-BD as a medical or veterinary product. 7 countries legitimated 1,4-BD for technical use. It is mostly used for the chemical industry in the Netherlands, Norway and the USA. The USA also uses 1,4-BD industrially as an intermediate in chemical synthesis of polymer, solvent and cleaner.

In Australia it is also used for forensic analysis. In Thailand it is used as a solvent in the laboratory. 4 countries authorized 1,4-BD for other legitimate use. In Denmark it is used as a cleaning chemical in the industry. In Australia and Thailand it is used industrially as a solvent and may be used in the manufacturing of some types of plastics and fibers. In Thailand it is also used as a solvent in the chemical and the pharmaceutical industry, in the process of shoe soles production, the process of car seat cover production, the paint industry, and electronic circuit industry.

6 countries indicated that they import the substance. In the USA 1,4-BD is manufactured and also imported in the country. Denmark noted that 1,4-BD is not controlled under legislation and the substance can be possessed and traded freely.

**ABUSE**

Of the 60 countries responding, 7 countries reported on the use of 1,4-BD in a harmful way and 4 countries reported on the extent of the harmful use.

When abused, 1,4-BD is administered orally.

In Australia, abuse of 1,4-BD is generally reported in relation to the abuse of GHB since it is a direct precursor to gamma-hydroxybutyric acid (GHB), being directly metabolised upon ingestion. Results from the 2004 and 2007 National Drug Strategy Household Surveys indicated that 0.1% of the general population of Australia had used GHB within the last twelve months. In the Czech Republic the use is very marginal and there are only several cases reported. Denmark considered the extent of the harmful use to be low.

In Australia it is usually ingested orally in the form of a dilute solution. In the Czech Republic it is used in a liquid form. In Denmark it is eaten and drunken and has the same effects as gamma-butyrolactone (GBL) and GHB. In Germany it is also used as a recreational substance. It exerts effects similar to GHB, which is a metabolic product of 1,4-BD and is once in a while used to avoid offences against the Narcotics Act. In the USA 1,4-BD containing products are available to the public for industrial purposes, it is sometimes substituted for GHB. After ingestion it is
metabolized to GHB, thus the route of administration is oral. It is toxic, addictive, and potentially lethal.

3 countries reported on the extent of public health or social problems associated with the harmful use of 1,4-BD.

According to Germany anecdotal reports on the Internet indicate that 1,4-BD produces a strong toxic feeling not present with GHB when ingested. These reports also indicate that it may cause damage to the liver as well as to other vital organs. Abuse has also resulted in dependence and possibly in death, but there is no official information about any death cases. Norway reported that the substance is rapidly converted to GHB and that it is difficult to detect in blood samples. The USA reported that 1,4-BD is converted to GHB after ingestion, the risks associated with its use mirror those associated with GHB administration. Side effects of 1,4-BD ingestion include vomiting, hypotonia, tremors, seizures, coma, respiratory depression, decreased body temperature, and decreased heart rate. Alcohol acts synergistically with the substance as a depressant on the central nervous system and respiration. Concurrent ingestion of alcohol also increases the duration of action of it. The enzyme which metabolizes 1,4-BD to GHB, alcohol dehydrogenase, also metabolizes alcohol, thus it remains in the system longer.

CONTROL

4 countries reported 1,4-BD is controlled under legislation that is intended to regulate availability of substances of abuse. In the USA 1,4-BD is not controlled. However, when the substance is intended for human consumption, it is also controlled as a schedule I controlled substance as an analogue to GHB. The Controlled Substances Act was amended in 1986 by the enactment of the Controlled Substance Analogue Enforcement Act. This law provides for controlled substance analogues, to the extent that they are intended for human consumption to be treated as schedule I controlled substances for the purposes of criminal prosecution.

In total 4 countries have tracked illicit activities involving the substance and one country reported that they have no confirmed data available. Clandestine manufacturing is reported once. Smuggling is reported two times and diversion is reported one time. Other illicit activities are not reported.

Two countries reported on the quantity of the seizures. In Norway there were 7 seizures with 7.4 l. and in 2006 there were 10 seizures with 18.1 l. In 2007 there were no seizures reported.

In the USA there were 46 seizures with 34533 g of powder and 26209 ml of liquid reported from System to Retrieve Information from Drug Evidence (STRIDE) data in 2007. National Forensic Laboratory Information System (NFLIS) showed 121 exhibits in 2007.

Brand Name
No information

Technical Use
- Forensic analysis
- Chemical industry
- Solvent in laboratory
- Industrially as an intermediate in chemical synthesis of polymer, solvent, cleaner

The following has been reported by countries as "other legitimate use"
Solvent in chemical and pharmaceutical industries
- In process of shoe soles production
- Process of car seat cover production
- Paint industry
- Electronic circuit industry
- Cleaning chemical in the industry
- Industrially as a solvent
- In the manufacturing of some types of plastics and fibers.