

1,4-Butanediol (I,4 BD)

Critical Review Report

Agenda item 4.4

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014



**World Health
Organization**

Acknowledgments

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Policy Access and Rational Use Unit. The WHO Secretariat would like to thank the following people for their contribution in producing this critical review report: Prof. Patrick Beardsley, USA (literature review and drafting), Dr Louis S. Harris, USA (pre-review report for the 35th ECDD), Dr Caroline Bodenschatz, Switzerland (editing) and Mr David Beran, Switzerland (questionnaire report drafting).

Contents

Summary.....	7
1. Substance identification	8
A. <i>International Nonproprietary Name (INN)</i>	8
B. <i>Chemical Abstract Service (CAS) Registry Number</i>	8
C. <i>Other Names</i>	8
D. <i>Trade Names</i>	8
E. <i>Street Names</i>	8
F. <i>Physical properties</i>	8
G. <i>WHO Review History</i>	8
2. Chemistry.....	9
A. <i>Chemical Name</i>	9
B. <i>Chemical Structure</i>	9
C. <i>Stereoisomers</i>	9
D. <i>Synthesis</i>	9
E. <i>Chemical description</i>	10
F. <i>Chemical properties</i>	10
G. <i>Chemical identification</i>	10
3. Ease of convertibility into controlled substances	10
4. General pharmacology	10
4.1. Pharmacodynamics.....	10
4.2. Routes of administration and dosage	12
4.3. Pharmacokinetics.....	12
5. Toxicology	13
6. Adverse reactions in humans.....	15
7. Dependence potential.....	16
8. Abuse potential.....	18
9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use	19
10. Listing on the WHO Model List of Essential Medicines	20
11. Marketing authorizations (as a medicine)	20
12. Industrial use	20
13. Non-medical use, abuse and dependence	20
14. Nature and magnitude of public health problems related to misuse, abuse and dependence	22
15. Licit production, consumption and international trade.....	23
16. Illicit manufacture and traffic and related information	23
17. Current international controls and their impact	24
18. Current and past national controls.....	25
19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance	26

References..... 27
Annex 1: Report On WHO Questionnaire For Review Of Psychoactive Substances for the 36th ECDD
1,4-Butanediol..... 32

Summary

1,4-butanediol (1,4-BD) is a colorless, viscous liquid derived from butane by placement of alcohol groups at each end of its molecular chain and is one of four stable isomers of butanediol. 1,4-BD has widespread industrial use. It is used in the production of spandex fibers, urethane elastomers, and copolyester ethers. Sizable quantities of 1,4-BD are also used to make gamma-butyrolactone (GBL), which has outlets in electronics, pharmaceuticals, and agrochemicals, as well as high-performance polymers. Miscellaneous uses include its use in solvents, coating resins, and as pharmaceutical intermediates. Worldwide production capacity for 1,4-BD is measured in the millions of metric tons/year.

1,4-BD is a precursor to gamma-hydroxybutyric acid (GHB), and is readily converted to GHB upon its ingestion producing clinical effects identical to GHB. 1,4-BD appears not to have behavioral effects of its own because its direct CNS administration is without effects. 1,4-BD's biotransformation to GHB involves enzymes also involved in alcohol's metabolism, and co-ingestion with ethanol can alter the time course and magnitude of 1,4-BD's toxicity.

GHB was marketed to bodybuilders in the 1980s as a purported aid to muscle building and fat loss. Because of its euphoric and sexual effects, it became a drug of abuse. Reports of the drug's toxicity resulted in warnings about health risks. Subsequently, 1,4-BD and GBL, another precursor to GHB, began to be marketed as a "natural," "nontoxic" dietary supplement, and as a substitute for GHB for its intoxicating effects.

1,4-BD is used as a liquid and a few milliliters would be a typical recreational dose. There is a steep dose-effect curve between doses producing desired and excessive effects, and there have been published reports of adverse reactions to 1,4-BD including fatalities. Signs and symptoms can include: euphoria, relaxation, reduced inhibition and sedation, progressing to vomiting, urinary and fecal incontinence, agitation, convulsions, bradycardia, respiratory depression, coma and death.

Because of 1,4-BD's rapid conversion to GHB, the epidemiology of their use and abuse is intrinsically linked. Also, forensic samples of blood and other tissues are not analyzed for GHB's precursors and not routinely even for GHB. These observations, coupled with the fact that most surveys treat incidences of GHB's, GBL's and 1,4-BD's use as if they were one drug, makes accurately estimating the incidence, prevalence and societal harm produced *specifically* by 1,4-BD impossible at present.

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 it 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.

1,4-BD has the capacity to produce a state of dependence, and can produce similar effects as GHB that is in Schedule II of the 1971 Convention. However, the prevalence and magnitude of the public health and social problems its use specifically creates is difficult to accurately estimate. Coupled with the appreciation that 1,4-BD is used as an industrial chemical with production and trade in the millions of metric tons, controlling it as a psychotropic substance equivalent to GHB would not likely result in benefits sufficient to justify the burdens such controls would impose.

1. Substance identification

A. *International Nonproprietary 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 Names*

1,4-Butanediol; Butane-1,4-diol; 1,4-Butylene glycol; Tetramethylene glycol; 110-63-4; 1,4-Dihydroxybutane; 1,4-Tetramethylene glycol; BDO; Butanediol-1,4; 1,4-BD; 1,4-BDO; 1,4-Tetramethylene

D. *Trade Names*

No approved medical use, although a dimethanesulfate (1,4-butanediol dimethanesulfonate) is available in oral (Busulfan; Myleran, GlaxoSmithKline) and intravenous (Busulfex IV, Otsuka America Pharmaceutical, Inc.) forms for the treatment of chronic myeloid leukemia (CML) ¹.

E. *Street Names*

1,4-BD has been associated with street names including:

"BlueRaine", "Dream On", "Fubar", "Pine Needle Oil", "Rejuv@Nite", "Thunder", "Cleaner", "Enliven", "Inner G", "One Comma Four", "One Four Bee", "One Four B-D-O", "Revitalize Plus", "Serenity", "SomatoPro", "Soma Solution", "Sucol B", "Thunder Nectar", "Weight Belt Cleaner", "White Magic".

F. *Physical properties*

1,4-BD is a colorless, almost odorless, waxy solid to oily liquid depending on temperature (melting point 20.4°C and boiling point of 235°C).

G. *WHO Review History*

During the pre-review 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-butanediol itself (convertible to GHB in the body)...", and suggested this substance for pre-review ². Based on the evidence presented in the pre-review of 1,4-BD during the 35th Meeting of the WHO ECDD, given its close association with GHB, and the recommendation made by the Expert Committee to reschedule GHB from Schedule IV to Schedule II of the 1971 Convention, the Committee recommended that a critical review of 1,4-BD be undertaken ³.

2. Chemistry

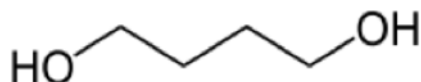
A. *Chemical Name*

IUPAC Name: 1,4-butanediol

CA Index Name: 1,4-butanediol

B. *Chemical Structure*

Free base:



Molecular Formula:

C₄H₁₀O₂

C₆H₁₄O₆S₂ (dimethylsulfonate) C₁₀H₁₈O₄ (diglycidyl ether)

Molecular Weight:

90.12 g/mol

246.3 g/mol (dimethylsulfonate)

202.25 g/mol (diglycidyl ether)

Melting point:

20.4 °C

114-117 °C (dimethylsulfonate) 116-119 °C (diglycidyl ether)

Boiling point:

235 °C

no data (dimethylsulfonate)

266 °C (diglycidyl ether)

C. *Stereoisomers*

None

D. *Synthesis*

Methods of manufacturing:

The most prevalent 1,4-BD production route worldwide is BASF's Reppe process, which reacts acetylene and formaldehyde. Acetylene reacts with two equivalents of formaldehyde to form 1,4-butynediol, also known as but-2-yne-1,4-diol. Hydrogenation of 1,4-butynediol gives 1,4-butanediol. 1,4-BD is also made on a large industrial scale by continuous hydrogenation of the 2-butyne-1,4-diol over modified nickel catalysts. The one-stage flow process is carried out at 80 - 160 deg C and 300 bar. Mitsubishi uses a three-step process: (1) the catalytic reaction of butadiene and acetic acid yields 1,4-diacetoxy-2-butene; (2) subsequent hydrogenation gives 1,4-diacetoxybutane; and (3) hydrolysis leads to 1,4-butanediol.⁴

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

Readily soluble in water (1.0x10⁶ mg/L at 20 deg °C), alcohols, ketones, glycol ethers, and glycol ether acetates; less soluble in diethyl ether and esters; not miscible with aliphatic and aromatic hydrocarbons and chlorinated hydrocarbons.

G. Chemical identification

In general, the available methods for detecting 1,4-BD in body fluids are costly and dependent on targeted analysis; "this fact adds to its attractiveness for recreational use, because it is not detected by standard screening tests for drugs" ⁵.

A rapid (<12 min) method of determining levels of 1,4-D (including GHB and GBL) in urine has been developed using liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis ⁶. In addition, a sensitive measure for determining these levels in whole blood has also been developed using LC–MS/MS analysis with a limit of detection of 0.02 mg/L for 1,4-BD in ante mortem blood ⁷. Other methods are available for determining levels of 1,4-BD in both blood and urine using GC–MS and HPLC ^{8, 9} or using a micellar electrokinetic chromatography (MEKC) method ¹⁰.

3. Ease of convertibility into controlled substances

1,4-BD is readily converted both chemically and in the body to GHB ^{11, 12} with a T_{max} of conversion to GHB following oral administration of 39.4 (±11.2) min in humans ¹². GHB is currently placed in Schedule II of the 1971 Convention.

4. General pharmacology**4.1. Pharmacodynamics**Receptor activity:

1,4-BD is a colorless viscous liquid that is derived from butane by placement of alcohol groups at each end of the chain. It is one of four stable isomers of butanediol. 1,4-BD (and GHB) occur endogenously in humans in trace amounts ¹³. 1,4-BD has no remarkable binding affinity for CNS receptors, at least given what is known, and does not bind to high-affinity GHB sites, GABA-A, or GABA-B receptors ^{14, 15, 16}. Because of its lack of affinity at these suspect receptor sites, and because 1,4-BD is behaviorally inactive if injected directly into the brain ¹⁷, and because its effects are similar to, if not identical with those of GHB (e.g., ^{12, 18}), 1,4-BD is believed to exert its behavioral effects by conversion to GHB ^{15, 16, 17, 18, 19, 20}.

Gross behavior:

1,4-BD has marked CNS effects. Administration of 500 mg/kg 1,4-BD (5.5 x 10⁻³ mols/kg) to male Sprague-Dawley or Holtzman rats causes CNS depression and induces 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 stimuli²¹. Very similar neuropharmacologic responses are observed after administration of GHB, except that sleep induction time (1.94x) and sleeping time (1.43x) are longer after administration of 1,4-BD than after administration of GHB²¹. The LD50 via intraperitoneal injection for 1,4-BD is ~ 1 g/kg, and more potent than the LD50 of 1.7 g/kg for GHB²¹. Effects on EEG tracings are identical between 1,4-BD and GHB except for variations in time of onset, time of maximal effect, and duration of the anesthetic response²¹. Administering 3 g/kg ethanol before, but not 30 min after administration of 1 g/kg 1,4-BD blocks the EEG effects induced by 1,4-BD¹⁸. Administering ethanol with 1,4-BD also attenuates the rate-decreasing effects of 1,4-BD on operant responding maintained by food delivery in rats²². The ability of ethanol to attenuate the effects of 1,4-BD on the EEG and on operant behavior suggests that conversion of 1,4-BD to GHB is required considering that both drugs compete for the same metabolic enzyme during their biotransformation (alcohol dehydrogenase)²³.

The induction of sleep by 1,4-BD in rats appears to track the emergence of GHB in the brain¹⁵. Roth and Giarman¹⁵, reported that within 15 min of being administered 520 mg/kg 1,4-BD i.v. significant increases in blood and brain concentrations of GHB occur in Sprague-Dawley rats, and these concentrations continued to increase to a maximum at approximately 60 min (blood) or 90 min (brain) after administration. These increases in GHB blood and brain concentrations were accompanied by sleep onset 30 min after administration, and sleep continued until GHB levels returned to normal (approximately 150 min after administration)¹⁵.

Consistent with a general depressant effect, 1,4-BD produces a dose-dependent loss of the righting reflex in rats, with a single 1 g/kg i.p. dose sustaining a loss of this reflex for nearly 5.3 h²⁴. Significant disruption of rotorod performance is observed as low as 200 mg/kg of 1,4-BD, and virtually complete suppression of locomotor activity is observed at doses of 300 or 400 mg/kg²⁴.

1,4-BD dose-dependently suppresses locomotor activity, produces catalepsy and ataxia, and causes a loss of the righting reflex in mice, but at differing relative potencies to GHB²⁵. The potency to produce catalepsy following intraperitoneal injection in mice is similar between 1,4-BD (ED₅₀ 209.3 mg/kg) and GHB (ED₅₀ 221.0 mg/kg). 1,4-BD shows itself to be slightly more potent (ED₅₀ 177.6 mg/kg) than GHB (ED₅₀ 220.8 mg/kg) in suppressing locomotor activity. However, 1,4-BD is over twice as potent as GHB to produce loss of the righting reflex (ED₅₀ 839.4 vs. 1702.7 mg/kg), and nearly three times more potent to induce ataxia (ED₅₀ 197.7 vs. ED₅₀ 584.1 mg/kg)²⁵.

Pharmacodynamic effects related to abuse of 1,4-BD

Pharmacological effects related to the abuse potential of 1,4-BD are discussed below in Sections 7 and 8. In brief, 1,4-BD completely occasions the GHB discriminative stimulus in rats e.g.,^{26,27} and pigeons²⁸, but does not fully generalize to benzodiazepine or pentobarbital discriminative stimuli in rats, pigeons or rhesus monkeys^{29,30,31,32} or to phencyclidine or heroin stimuli in rats³³. 1,4-BD appears inactive as an analgesic in a variety of mouse models and neither substitutes for morphine nor exacerbates withdrawal in the morphine-dependent rhesus monkey³⁴.

Effects on respiration and cardiovascular function

Little information is available regarding the direct actions of 1,4-BD on respiration or cardiovascular function. Its metabolite, GHB, is a cardiovascular stimulant^{35, 36, 37}. GHB elicits marked and prolonged increases in mean arterial pressure and heart rate that are reversed by the intravenous and intracerebroventricular administration of the GABA-B receptor antagonist, CGP 35348³⁸. In another study using radio telemetry in conscious rats, 1,4-BD increased mean arterial pressure and heart rate²². These increases were attenuated by the concurrent administration of ethanol indicating that these cardiovascular effects of 1,4-BD required the conversion of 1,4-BD to GHB²².

Effects in humans under controlled conditions

Thai and colleagues 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 volunteers¹². 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 ($T_{1/2}$) 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 $T_{1/2}$ 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. Routes of administration and dosage

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

4.3. Pharmacokinetics

1,4-BD is quickly absorbed and cleared following oral administration to human subjects. Time to maximal plasma concentration is 24± 12 min with an elimination half-life ($T_{1/2}$) of 39.3 ± 11 min¹². The major biotransformation route of 1,4-BD is oxidation to GHB in rats^{11, 20, 23}, rhesus monkeys³⁹ and in humans^{12, 39}. Emergence of GHB following administration of 1,4-BD is rapid and can occur within 5 min of oral administration¹² and has a 2-min T_{max} after a single intravenous dose of 1,4-BD³⁹, although there can be considerable variability across subjects in these values¹². Following a 25 mg/kg oral dose of 1,4-BD, the average C_{max} for GHB was 45.6 mg/l, more than 10-fold higher than the C_{max} for 1,4-BD, which averaged 3.8 mg/l¹². The elimination half-life averaged 39.3 ±11.0 min for 1,4-BD and 32.3±6.6 min for GHB. Plasma levels of both substances were below the limit of quantitation of 1 mg/l by 4 h after dosing¹².

1,4-BD is first oxidized to gamma-hydroxybutyraldehyde by alcohol dehydrogenase. The intermediate aldehyde is oxidized by aldehyde dehydrogenase to GHB. GHB is subsequently oxidized to succinic semialdehyde by cytosolic and mitochondrial GHB dehydrogenases²³. Because the enzymes responsible for converting 1,4-BD are also responsible for metabolizing alcohol, alcohol can inhibit the biotransformation to GHB¹⁸. Inhibition can be mutual, and co-administration of alcohol and 1,4-BD may result in enhanced in vivo drug exposure to both⁴⁰.

5. Toxicology

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 1996²³. This report contains an extensive review of literature on the pharmacology, metabolism, disposition, toxicity, and carcinogenicity of 1,4-BD based upon the NTP's own studies and those of others up to the date of the report. Much of the following material referring to the NTP report is directly quoted from the NTP report itself.

The acute toxicity studies are summarized in Table 1. The results were unremarkable except for the relatively low lethal potency of the substance in that in no study involving the oral or intraperitoneal administration of 1,4-BD was the LD₅₀ lower than about 1 g/kg body weight in the rat, mouse or guinea pig²³.

Table 1: Results of acute and short-term studies involving oral and intraperitoneal administration to 1,4-butanediol

Acute Toxicity Values for 1,4-Butanediol (adapted with modification from Irwin 1996)

Species/Strain	Number	Route	LD ₅₀ ^a	Reference
Rat/Albino	25 Male 25 Female	Oral	1,550 mg/kg	41
Rat/Wistar	30 Male 30 Female	Oral	1,830 mg/kg 2,000 mg/kg	42
Rat/— ^b	—	Oral	1,525 mg/kg	43
Rat/Wistar	18 Male 18 Female	Intraperitoneal	1,070 mg/kg	44
Rat/Albino	88 Male ²¹	Intraperitoneal	1,000 mg/kg	
Rat/Sprague-Dawley	— ²⁴	Intraperitoneal	1,328 mg/kg	
Mouse/—	— ⁴⁵	Oral	2,180 mg/kg	
Guinea Pig	90 ⁴³	Oral	2,000 mg/kg	

^a LD₅₀ = median lethal dose^b Data not provided

Repeated-dose studies have been conducted in animals using gavage administration⁴² and inhalation exposure⁴⁵. 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. 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 females⁴².

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 weeks⁴⁵. 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 reported⁴⁵.

In a study sponsored by the NTP, the developmental toxicity of 1,4-butanediol was evaluated by administering 1, 100, 300, or 600 mg/kg by gavage in water to timed-pregnant Swiss albino mice on gestation days 6 through 15⁴⁶. 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 actually lower in the 300 and 600 mg/kg groups than in the control or 100 mg/kg groups. The incidence of fetuses with external or visceral malformations was similar in all groups; however, there was an increasing trend in skeletal malformations (missing or branched ribs and fused thoracic vertebrae), primarily in the 600 mg/kg group.

In genotoxicity and carcinogenicity studies, 1,4-Butanediol was negative in Salmonella mutagenicity tests^{47, 48} (as reported by Irwin, 2006⁴⁹). 1,4-BD also failed to produce clastogenicity or polyploidy in CHL/IU cells⁴⁸ (as reported by Irwin, 2006⁴⁹). 1,4-Butanediol has not been evaluated for chronic toxicity or carcinogenicity⁴⁹. However, Irwin in his review of the relevant literature for the NTP, and in light of the rapid conversion of 1,4-BD to GHB concluded, "Because of the absence of evidence for genotoxicity of 1,4-butanediol, coupled with the fact that the chronic toxicity and carcinogenicity of γ -hydroxybutyric acid was in effect fully evaluated in NTP prechronic and chronic studies with γ -butyrolactone, demonstrating a lack of organ specific toxicity or carcinogenic potential, it is concluded that 1,4-butanediol would be negative in a similar chronic toxicity and carcinogenicity study. For these reasons it is the opinion of the National Toxicology Program that 1,4-butanediol is not carcinogenic in animals (NTP, 1996), and no further cancer evaluation of this substance is needed."⁴⁹.

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. Consequentially, the signs and symptoms caused by GHB and 1,4-BD are similar or identical⁵⁰ (for a fuller discussion of *GHB*'s specific adverse effects, see the critical review of GHB⁵¹). Secondly, it has rarely been determined precisely what an individual has ingested (1,4-BD, GBL and GHB). In addition, recent survey data often treat the three compounds as a single agent. Qualified by these limitations, some description of the adverse effects produced by 1,4-BD can be described.

Zvosec and colleagues assessed nine episodes of toxic effects of 1,4-BD in eight patients, two of whom had died who had been given 15 g of 1,4-BD as a laxative⁵. GC-MS was used to measure concentrations of 1,4-BD and GHB in the body fluids of patients that had presented to the emergency department. Ingested doses of 1,4-BD were estimated on the basis of reports by the patients or by others who were presented at the time of ingestion, using the concentrations of 1,4-BD listed on the products packaging or detected by GC-MS in the un-ingested portions of the products. The clinical manifestations and adverse outcomes of the toxic effects of 1,4-BD in these patients included vomiting, urinary and fecal incontinence, confusion, ataxia, agitation, combativeness, an extremely labile level of consciousness, respiratory depression, and death⁵. The approximate doses of 1,4-BD ingested by the patients who died ranged from 5 to 20 g (88 to 300 mg/ kg of body weight) and were 1 to 14 g in those who survived. 1,4-BD was undetectable in the body fluids of the patients with nonfatal cases, presumably because of the smaller doses they ingested, the compound's rapid conversion to GHB, and the limits of detection of the assays used⁵.

Although major motor seizures have been inconsistently reported with 1,4-BD, intoxication, their direct induction by 1,4-BD ingestion was seen as unlikely given the primary pharmacological mechanism of 1,4-BD action was assumed to be GABA agonism, and given the irregularity of the reports⁵⁰. Mild hypothermia has been reported following the ingestion of 1,4-BD^{5, 52}. There does not appear to be strong myocardial depression from 1,4-BD⁵⁰. Miscellaneous adverse signs and symptoms include amnesia, diaphoresis, and myoclonus⁵.

A serious social health problem occurred in children following the unintentional ingestion of 1,4-BD^{53, 54, 55}. Aqua Dots (Spin Master Ltd.; Toronto, Canada) was a popular children's craft toy kit. The kits included small colored plastic beads that would fuse together when sprayed with water and then allowed to dry, forming various multidimensional designs⁵⁶. In 2007, Aqua Dots was named the "Toy of the Year" in Australia, where it was marketed under the name "Bindeez"⁵³. In late 2007, several reports of children, many of whom were toddlers, developed vomiting, ataxia, and self-limited coma after swallowing Aqua Dots beads, appeared in the Australian and American media^{53, 54} (and as reported in Suchard, 2009). GHB was detected in biologic samples from some of these children^{55, 57}, and thanks to the sleuthing of an Australian biochemical geneticist, Kevin Carpenter, it was discovered that 1,4-BD had been used during production to prevent the beads from getting sticky⁵⁵. Upon detailed analysis these beads contained 13.7% (\pm 2.4%, SD) 1,4-BD by weight, corresponding to a 1,4-BD content of 10.8 mg (\pm 1.9 mg, SD) per bead⁵⁶. It was suspected that for economic reasons 1,5 pentanediol was replaced with 1,4-BD during the bead's manufacture. Widespread reporting of the findings led to further reports and an international recall of the toy⁵⁸.

7. Dependence potential

Animal Studies

Studies have been conducted in rats and baboons investigating the ability of 1,4-BD to induce physical dependence. In Sardinian alcohol-preferring (sP) rats, which show a high sensitivity to the sedative/hypnotic and reinforcing effects of GHB^{59, 60}, were administered escalating b.i.d. doses of 1,4-BD (500–1000 mg/kg i.g.) for 9 consecutive days and then tested for audiogenic seizures⁶¹. Some rats were administered the selective GABA-B receptor antagonist, SCH 50911, prior to testing. One fourth of all 1,4-BD rats died during treatment. Significantly more 1,4-BD treated rats demonstrated seizure activity during testing. Administering SCH 50911 increased the proportion of 1,4-BD treated rats showing seizures, relative to control rats. These results indicate that 1,4-BD can induce physical dependence in rats particularly sensitive to the effects of GHB, and suggest that the GABA-B receptor may be involved in mediating this dependency. In contrast, in other studies by this laboratory neither 1,4-BD, gamma-butyrolactone, nor GHB were able to induce marked physical dependence effects in Sprague-Dawley or Wistar rats⁶².

Goodwin and colleagues evaluated the ability of 1,4-BD to induce physical dependence in male baboons⁶³. Subjects were given an escalating regimen of 1,4-BD from 100 to 600 mg/kg/day administered continuously through intragastric catheters and then were eventually maintained at 600 mg/kg/day for 3-4 weeks. Baboons were then tested for spontaneous withdrawal effects following abrupt termination of 1,4-BD administration, or were challenged for precipitated withdrawal with the GABA-B

receptor antagonist, SGS742 (3-aminopropyl-n-butyl-phosphinic acid; formerly CGP36742). At the end of chronic 1,4-BD dosing, the levels of GHB in plasma ranged from 1290 to 2300 $\mu\text{mol/L}$ and levels of 1,4-BD in plasma ranged from 13.1 to 37.9 $\mu\text{mol/L}$. Signs of physical dependence were observed following precipitated and spontaneous withdrawal tests, the most severe being tremor and jerks, although seizures were not observed. These results indicate that under the dosing regimen administered a mild to intermediate level of physical dependence is inducible in the baboon.

Human Studies

As has been mentioned previously, it is difficult to disentangle the effects of 1,4-BD from GHB, although evidence is emerging that 1,4-BD can initiate physical dependence in humans as it can in rats and baboons, albeit the evidence is mainly from case reports. Mycyk and colleagues were the first to report observations of subjects suffering withdrawal effects from 1,4-BD⁶⁴. In their study, a man and a woman who had been taking 1-oz doses of 1,4-BD nightly for five weeks for insomnia began developing abdominal cramps, palpitations, tremors and anxiety 6 h following cessation of the last ingestion of 1,4-BD. The patients had tried to relieve themselves of these discomforts by self-medicating with vodka for 4 days without success before presenting themselves for medical help. The patients displayed horizontal nystagmus, tongue tremors and upper extremity tremors. The patients were treated with lorazepam, and given a 5-day course of lorazepam treatment and released.

Another case report described the effects of withdrawal in a 29-year old male chemist that had been ingesting 1,4-BD daily as frequently as an hourly basis for 5 to 6 years at up to 250 ml per month⁶⁵. Three days following cessation of 1,4-BD ingestion the patient presented himself to the ED. He was discharged with a prescription for lorazepam but re-presented himself at a different ED two days later. The patient was mildly delirious with inattention and fluctuating orientation to person, place and time. He reported auditory hallucinations and required physical restraints for agitation. No tremor was noted, and the remainder of his physical examination was normal. The patient was subsequently admitted to the intensive care unit (ICU) with tachycardia, hallucinations and agitation where he was treated with lorazepam and haloperidol. By the fifth day of hospitalization his agitation, hallucinations and delirium had resolved and he was released after one additional day of hospitalization without medication. In a subsequent review of the literature involving withdrawal from GHB, GBL or 1,4-BD (only 3 cases of which involved 1,4-BD) the authors identified the most common withdrawal signs and symptoms were tremor (67%), hallucinations (63%), tachycardia (63%), insomnia (58%), anxiety (46%) and hypertension (44%). Other signs and symptoms included agitation (40%), diaphoresis (35%), paranoia (25%), confusion (21%), delusions (18%), delirium (12%), nystagmus (8%), rhabdomyolysis (7%) and seizures (7%). Of these only tremor, tachycardia, anxiety and hypertension were observed in $\geq 50\%$ of the specific cases involving 1,4-BD⁶⁵,

Other clinical reports mentioning the induction of physical dependence by 1,4-BD have included it by its association with GHB and GBL and not by its actual identification of usage. For a detailed review of physical dependence upon GHB the reader is referred to the critical review of GHB for the Thirty-fifth meeting of the ECDD⁵¹.

8. Abuse potential

Animal Studies

Since it is generally thought that 1,4-BD owes its central nervous system activity to conversion to GHB^{15, 21}, and it is behaviorally inactive when delivered directly into the CNS suggesting biotransformation is necessary to produce effects¹⁷, the abuse potential of 1,4-BD should mimic that of GHB to a great extent. Animal studies that contribute to our 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 kind of evidence most often include general pharmacology, drug discrimination studies, and self-administration studies. As indicated above, the general pharmacology of 1,4-BD closely resembles that of GHB, and there are no true pathognomonic signs or symptoms to separate 1,4-BD intoxication from poisoning due to GHB⁵⁰.

Carter and colleagues reported that 1,4-BD completely generalized to the GHB discriminative stimulus in rats with an ED₅₀ of 114±23.7 mg/kg i.p., which was similar to that of GHB itself of 139.9 ±11.2 mg/kg i.p.²⁷. Its onset of action was similar to that of GHB, but its duration of action was longer in that partial (~40%) generalization was still apparent 90 min after 1,4-BD administration, while the activity of GHB was already at near-zero levels by 60 min post-injection. 1,4-BD also completely occasioned the GHB discriminative stimulus in pigeons and with a longer duration of activity than GHB itself, however unlike in the rat⁶⁶, it did so with ~3-fold less potency²⁸. Baker and colleagues also reported that 1,4-BD completely occasioned the GHB discriminative stimulus using a procedure in which rats were trained in a three-way simultaneous discrimination involving GHB (300 mg/kg), ethanol (1.5 g/kg) and vehicle²⁶. In other studies by Carter and colleagues, 1,4-BD completely (>80%) occasioned the baclofen discriminative stimulus, but failed to produce more than 11% diazepam-appropriate responding⁶⁶. These latter results suggest that the discriminative stimulus effects of 1,4-BD involve GABA-B receptor activation and minimal GABA-A modulation.

In other drug discrimination studies involving rhesus monkeys, 1,4-BD did not occasion the discriminative stimulus effects of the barbiturate, pentobarbital, nor that of the benzodiazepine, midazolam, up to doses that suppressed responding maintained by the avoidance of shock³⁰. The failure of 1,4-BD to substitute for midazolam or pentobarbital suggests that it is not a high efficacy positive GABA-A receptor modulator, although as the authors warned, "...the present results cannot reject the possibility that direct stimulation of the GABAA receptor mediates the behavioral effects of BDL and GBL, perhaps by their eventual metabolism to GABA"³⁰. These results in rhesus monkeys, along with the results of Carter reviewed above in rats⁶⁶, suggest that the abuse-related effects of 1,4-BD are not identical to those of the benzodiazepines or of the barbiturates typified by pentobarbital, but are similar to those of GHB.

Rhesus monkeys trained to self-administer methohexital failed to self-administer 1,4-BD (0.1–3.2 mg/kg/injection) above saline-control levels when it was substituted for methohexital during 130 min test sessions except at one dose (0.32 mg/kg/injection) and by only one of four monkeys tested³⁰. When four baboons trained to self-administer 0.32 mg/kg/injection cocaine during 24-h test sessions (infusions limited to

8) were offered 1,4-BD (78-130 mg/kg/injection) instead of cocaine for at least 15 days, only two of four baboons self-administered it above vehicle levels⁶⁷. Intravenous self-administration of 1,4-BD produced ataxia, limb tremors, jerks, and vomiting/retching during the 3 h following injections⁶⁷. These self-administration results with 1,4-BD in rhesus monkeys and baboons indicate that it does not robustly reinforce behavior in the non-human primate, at least under the conditions tested.

In summary, drug discrimination studies indicate that 1,4-BD does not fully generalize to the benzodiazepines or pentobarbital in rats, pigeons or rhesus monkeys^{29,30,31,32} or to phencyclidine or heroin in rats³³. Studies on the reinforcing effects of GHB do not indicate it to be a robust reinforcer in that it is not self-administered by rhesus monkeys under conditions in which most drugs of abuse are^{29,30,33}, although it is self-administered by baboons when given extended access⁶⁸ and by mice⁶⁹. Similar to GHB, GBL was reported to be not self-administration by rhesus monkeys³⁰ although it was self-administered by baboons under extended access conditions⁶⁷.

Human Studies

Important determinants of the abuse potential of a substance is whether it produces subjective effects similar to a known drug of abuse, whether it produces positive reinforcing effects and is volitionally self-administered, and whether it induces physical dependence indicated by a withdrawal syndrome for which the user may relapse to self-medicate with the substance to alleviate withdrawal discomfort. Also of importance is the adverse event (toxicity) profile of the substance and whether it is a precursor or analogue to a known drug of abuse.

Controlled, laboratory-based evaluations of the pharmacological properties of 1,4-BD explicitly predictive of abuse potential have not been conducted. Such studies have been carried out with GHB, however⁷⁰, in which the authors concluded that the profile of effects of GHB in subjects with drug abuse histories: "... 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." In another laboratory-based examination of GHB's pharmacological effects the researchers concluded that in subjects without a sedative-abuse history, "... GHB produced dose-related increases in self-reported sedative-like and dissociative-like effects, and ratings of drug liking and high..."⁷¹. No such studies exist for 1,4-BD. Considering how rapidly 1,4 is converted to GHB in humans^{12,39}, these pharmacological predictors should apply to GBL. Considering there have been case studies that have reported that 1,4-BD can induce physical dependence by itself^{64,65}, along with the observation that 1,4-BD is a precursor and/or analog to GHB that is itself a Schedule II compound in the 1971 Convention, 1,4-BD likely has an abuse potential overlapping with GHB.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

1,4-BD itself has no recognized therapeutic application. However, the dimethanesulfate (1,4-butanediol dimethanesulfonate; busulfan) is available in oral (Busulfan; Myleran, GlaxoSmithKline) and intravenous (Busulfex IV, Otsuka America Pharmaceutical, Inc.) forms for the treatment of chronic myeloid leukemia (CML)¹. When given orally, except for seizures, adverse central nervous system effects (i.e. CNS stimulations or

depression) are not typically indicated^{1, 72, 73}. This suggests that busulfan is not readily converted to GHB, at least not at clinical doses up to those producing severe effects⁷⁴.

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 2008 WHO questionnaire for review of psychoactive substances, not one of the 60 countries that responded authorized 1,4-BD as a medical or veterinary product⁷⁴.

12. Industrial use

1,4-Butanediol's largest use is within tetrahydrofuran (THF) production, used to make polytetramethylene ether glycol, which goes mainly into spandex fibers, urethane elastomers, and copolyester ethers. The next largest outlet is engineering plastic polybutylene terephthalate (PBT). Sizable quantities of 1,4-BD are also used to make gamma-butyrolactone, which has outlets in electronics, pharmaceuticals, and agrochemicals, as well as high-performance polymers. Miscellaneous uses include solvents, coating resins, and pharmaceutical intermediates⁴. The 2008 WHO questionnaire for review of psychoactive substances, identified seven countries legitimated it for technical use⁷⁴. Sales in the United States alone in 1992 totaled 56,847,000 kg. Worldwide production capacities for 1,4-butanediol in 2006 were measured in millions of metric tons/year⁴. During 1978 to 1985 U.S. production of 1,4-butanediol reported in the Chemical Economics Handbook or to the U.S. International Trade Commission (USITC, 1981, 1982, 1983, 1984, 1985) ranged from 138.2 to 353.5 million pounds annually while the quantity imported for the same period of time ranged from 2.0 to 27.7 million pounds annually⁴⁹.

13. Non-medical use, abuse and dependence

GHB was marketed to bodybuilders in the 1980s as a purported aid to muscle building and fat loss⁵. Because of its euphoric and sexual effects, it became a drug of abuse. Reports of the drug's toxicity resulted in warnings about health risks. Subsequently, 1,4-BD (and GBL) began to be marketed as "natural," "nontoxic" dietary supplements⁵. Reports of toxic effects and deaths led the FDA to issue warnings about both compounds⁴. 1,4-BD was declared a class I health hazard, with toxic effects including vomiting, respiratory depression, loss of consciousness, seizures, and death⁵.

The following dosage and subjective effect reports are taken from the Pre-Review of 1,4-BD⁷⁴.

When abused, 1,4-BD is administered orally. 1,4-BD starts to act 5-20 min after 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, and 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.

The number of confirmed cases of 1,4-BD intoxication is relatively low compared to GHB. This is likely attributable to a several factors including the longer period of GHB availability, inaccurate or unknown identity of the substance ingested by intoxicated persons, similarity of symptoms, and perhaps most importantly, metabolic conversion of 1,4-BD to GHB⁵⁰. This latter factor is compounded by the fact that there is currently no readily available toxicological test to differentiate between the presence of GHB, GBL or 1,4-BD in patients presenting with self-reported ingestion of one of these drugs⁷⁵. One estimate of the relative proportion of GBL to GHB usage was provided in a retrospective review of cases of self-reported recreational GHB, GBL and 1,4-BD users in 2006 that were found in a toxicological database of a large inner city emergency department (ED) in London. There were a total of 158 ED presentations, of which 150 (94.9%) and 8 (5.1%) were GHB and GBL self-reported ingestions, respectively. Of the 418 samples seized, 225 (53.8%) were in liquid form; 85 (37.8%) contained GHB and 140 (62.2%) contained GBL. None of the seized samples contained 1,4-BD and there were no self-reported 1,4BD ingestions⁷⁵.

The epidemiology of the use and abuse of 1,4-BD is intrinsically linked to that of GHB. It is rapidly metabolized to and reported forensically as GHB. Indeed, forensic samples of blood and other tissues are not analyzed for GHB's precursors and not routinely even for GHB. Indicative of this regarding survey data, the European Monitoring Centre for Drugs and Drug Addiction stipulates, "Hence, when referring to prevalence and patterns of use, the term GHB/GBL may include known or unknown use of 1,4-BD or GBL, particularly in surveys conducted after GHB was placed under drug control and when it began to be substituted by GBL."⁷⁶ Compounding the difficulties of discriminating abuse of GBL from that of GHB or 1,4-BD there are no true pathognomonic signs or symptoms to separate 1,4-BD or GBL intoxication from poisoning due to GHB⁵⁰. Overall, accurate estimates of 1,4-BD's specific use are impossible to currently derive.

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related emergency department (ED) visits for the United States. In 2004 there was a total of 1,253,956 misuse/abuse ED visits. Of these, 2,340 were attributed to GHB (0.19%)⁷⁷. In 2005, the total number of ED visits was 1449154. Of these, 1861 were attributed to GHB (0.13%)⁷⁷. The most recent data are from 2011 in which total ED visits involving GHB was 2,406, which was 0.2% of all ED visits⁷⁸. Thus, in the United States the use of GHB leading to ED visits, and by inference, its precursors, was low and steady over a seven year span between the years of 2004 and 2011.

Additional United States trend data can be found in the National Institute of Drug Abuse Proceedings of the Community Epidemiology Work Group (CEWG) ⁷⁹. In its most recent review in January of 2013, GHB was identified among drug reports from forensic laboratories in 13 CEWG areas of the 25 reporting National Forensic Laboratory Information System data in the first half of 2012, including Chicago, Denver, Colorado, Los Angeles, Miami, Michigan, Minneapolis/St. Paul, New York City, San Diego, San Francisco, Seattle, Texas, and Washington, DC. Numbers were very low, and in no case did the percentage reach higher than 0.1 percent of total reports ⁷⁹. Seizures of illicitly marketed 1,4-BD in United States data can also be used to infer incidence and prevalence of its illicit use. Seizures of 1,4-BD intended for illicit use in the United States decreased from 189 to 152 seizures from 2011 to 2012, and gross amounts in those years changed from 14.25038 kg and 18.3224 l (2011) to 3.763292 kg and 25.96455 l (2012) ⁸⁰.

The European Monitoring Centre for Drugs and Drug Addiction's (EMCDDA) 2008 report on GHB treat GHB and its precursors as common entities and refer to them inclusively with the term "GHB/GBL" ("Hence, when referring to prevalence and patterns of use, the term GHB/GBL may include known or unknown use of GBL or 1,4-BD, particularly in surveys conducted after GHB was placed under drug control and when it began to be substituted by GBL." ⁷⁶. In this report the EMCDDA concluded, "Use of GHB/GBL is, generally, low in the EU..." (*sic*), but also observed that there was, "... evidence of some sub-populations, settings and geographical areas where it is commonly used, such as in gay nightclubs." ⁷⁶. For instance, among respondents sampled in 'gay' Amsterdam bars prevalence estimates for GHB/GBL use rise to 17.5% compared to less than 5% among respondents in the more mainstream or student pubs. Lifetime incidence was between 0.5% and 1.4% among 15-16 year old students in 12 EU countries. This estimate increases to between 3% and 19% of lifetime incidence when survey data are collected in dance music settings. At the time of the EMCDDA's report, no EU member state had reported any incidence of large-scale production, trafficking or distribution of GHB, and the proportion of reported seizures of GHB/GBL in the EU was referred to as "very small" compared to seizures of other synthetic illicit compounds ⁷⁶.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

It is extremely difficult to accurately assess the magnitude of public health problems related to the abuse and dependence upon 1,4-BD considering the near absence of data explicitly related to 1,4-BD. Most data are confounded by the inclusion of GHB and GBL with 1,4 BD. Seizures, of GHB and of 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 ⁸¹, and in Greece, Bulgaria, Italy, Hungary, Spain, and Austria ⁸². In Australia, overdose on GHB and its precursors is perceived to be a relatively common presentation to hospital by some ^{83,84}. Caldicott and colleagues concluded, "Because of the restrictions in obtaining GHB, it is probable that most of the "GHB" being consumed in Australia is now in the form of GBL or 1,4-BD.", and implied that many of the deaths associated with GHB are likely attributable to its precursors ⁸⁵.

The frequency of abuse and associated health problems of 1,4-BD, relative to many other drugs of abuse, is likely low in the EU⁷⁶ and in the United States (e.g.,⁷⁹), higher in some other countries such as Australia⁸⁵. Trends of GHB use, and by implication, 1,4-BD, were decreasing in the United States⁸⁶ while in New South Wales lifetime use increased from 0.5% to 0.8% during the years 2005 to 2010, although "recent use" held constant at 0.1%⁸⁷.

Because of the limited direct data with 1,4-BD itself, expressions of the nature and magnitude of public health problems related to its abuse and dependence is speculative. However, based upon the available data on 1,4-BD, and inferred from data with GHB, the use and abuse of 1,4-BD promotes serious health problems as discussed in the preceding sections above. However, 1,4-BD's use generally appears to be of a low prevalence to many other abused drugs, except perhaps in some isolated pockets of abuse, and the breadth of public health problems its abuse creates is comparatively likely limited and isolated.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

As identified in Section 12, 1,4-BD has widespread industrial applications and use. In fact, it has such world-wide usage and distribution that it has been considered by some⁸⁸ to be an environmental pollutant (as reported in Zabik 1968²⁴). It is an important intermediate chemical for tetrahydrofuran and polytetramethylene ether glycol (PTMEG), polybutylene terephthalate (PBT), gamma- butyrolactone (GBL), polyurethane (PU), and other solvents. These chemicals are widely used in fibers, engineering plastics, medicines, cosmetics, artificial leather, pesticides, plasticizers, hardener, solvent and rust remover, etc. Tetrahydrofuran is the largest application market for BDO, which has occupied largest percentage of the 1,4-BD market⁸⁹.

The global 1,4-BD market was 1,725.0 kilo tons in 2011 and is estimated to reach 2,548.5 kilo tons by 2017. Asia-Pacific is the prime user accounting for more than 55% of total volume consumed in 2011. Europe and North America constitute second and third largest market for 1,4-BD. The major chemical producers in the market are BASF SE (Germany), Dairen Chemicals (Taiwan), LyondellBasell Chemicals (The Netherlands), Shanxi Sanwei Group (China), International Specialty Products (U.S.), Invista (U.S.), and Mitsubishi Chemicals (Japan)

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

A. Reports of Illicit Activity and Seizures

There are instances of diversion of the raw substance, and trafficking in dietary supplements containing the compound e.g.,⁸⁰. Based on the 2008 WHO questionnaire for review of psychoactive substances, four countries had tracked illicit activities involving the substance. Clandestine manufacturing is reported once. Smuggling is reported two times and diversion is reported one time⁷⁴.

B. 1,4-BD Seized Material.

The U.S. Drug Enforcement Agency reported that there were 189 seizures in 2011 (14.25038 kg, 18.3223 l) and 152 seizures in 2012 (3.763292 kg, 25.96455 l)⁸⁰. In the most recently accessed report from the European Monitoring Centre for Drugs and Drug Addiction of 2011, Finland reported two seizures of 1,4-BD (228 ml) and Norway reported 1 seizure (0.07 l). No other countries were identified in this report that had seizures of 1,4-BD⁹⁰.

As reported in the 2008 WHO questionnaire for review of psychoactive substances, 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 2007⁷⁴.

The illicit distribution of 1,4-BD does not appear to be as prevalent as that of GHB and GBL given the data above and in light of some other studies. For example, all ED cases involving the recreational use of GHB, GBL and 1,4-BD between 1 January 2006 and 31 December 2006 were examined in a retrospective examination of a clinical toxicology database of a large inner city. There were a total of 158 ED presentations, of which 150 (94.9%) and 8 (5.1%) were GHB and GBL self-reported ingestions, respectively; 96.8% (153) were recreational use. Of the 418 samples seized, 225 (53.8%) were in liquid form; 85 (37.8%) contained GHB, and 140 (62.2%) contained GBL. None of the seized samples contained 1,4-BD and there were no self-reported 1,4-BD ingestions.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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 substances⁷⁴. 1,4-BD is not included in the Tables of the 1988 UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances⁷⁶. The chemical is not subject to the key UN convention that covers precursor chemicals; however its metabolite, γ -hydroxybutyrate (GHB), is currently in Schedule II of the 1971 Convention.

18. Current and past national controls

Only a few States have declared 1,4-BD as a controlled substance.

Bulgaria:

From April 2010 both GHB precursors (GBL and 1,4- BD) are enlisted in Schedule III - "Dangerous substances" ⁸²

Netherlands:

September 2011, based on the CAM advice, the Minister of Health has recently decided to promote GHB from class 2 to class 2 op the Opium law. It is now in the class of hard drugs.

It is advocated to place GBL and 1,4 BD in the highest class of the Wvmc (European trade treaty; 273/2004). ⁸²

Sweden:

February 1st, 2000 GHB was scheduled in Sweden.

Since 1 September 2005 GBL and 1,4-butandiole are also under control. ⁸²

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 ⁷⁴.

United Kingdom

In the United Kingdom, 1,4-butanediol was scheduled in December 2009 (along with GBL) as a Class C controlled substance.

United States

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 ⁷⁴.

In response to 2008 WHO questionnaire for review of psychoactive substances, 4 countries reported 1,4-BD is controlled under legislation that is intended to regulate availability of substances of abuse ⁷⁴.

The Scientific Committee of the EMCDDA, extended with experts from the Member States, and representatives of the Commission, Europol and the EMEA, recommended that the Drug Precursors Committee set up under Article 10 of Regulation 3677/90/EEC and Directive 92/109/EEC should strongly consider the inclusion of 1,4-butanediol within the monitoring system ⁹¹.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

None.

References

1. Buggia I, Locatelli F, Regazzi MB, Zecca M. Busulfan. *Ann Pharmacother*, 1994, **28**: 1055-1062.
2. World Health Organization. *WHO Expert Committee on Drug Dependence Thirty-fourth Report*. Geneva: World Health Organization; 2006. Report No.: 942 WHO Technical Report Series.
3. World Health Organization. *WHO Expert Committee on Drug Dependence Thirty-fifth Report*. Geneva: World Health Organization; 2012. Report No.: 973 WHO Technical Report Series.
4. Hazardous Substances Data Bank [Internet]. 1,4-Butanediol. Bethesda, MD: National Library of Medicine (US), Division of Specialized Information Services; 1986- [cited 2014 March 15].
5. Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ, Peacock EA. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med*, 2001, **344**: 87-94.
6. Wood M, Laloup M, Samyn N, Morris MR, de Bruijn EA, Maes RA, *et al*. Simultaneous analysis of gamma-hydroxybutyric acid and its precursors in urine using liquid chromatography-tandem mass spectrometry. *J Chromatogr A*, 2004, **1056**: 83-90.
7. Sorensen LK, Hasselstrom JB. A hydrophilic interaction liquid chromatography electrospray tandem mass spectrometry method for the simultaneous determination of gamma-hydroxybutyrate and its precursors in forensic whole blood. *Forensic Sci Int*, 2012, **222**: 352-359.
8. Duer WC, Byers KL, Martin JV. Application of a convenient extraction procedure to analyze gamma-hydroxybutyric acid in fatalities involving gamma-hydroxybutyric acid, gamma-butyrolactone, and 1,4-butanediol. *J Anal Toxicol*, 2001, **25**: 576-582.
9. Kankaanpaa A, Liukkonen R, Ariniemi K. Determination of gamma-hydroxybutyrate (GHB) and its precursors in blood and urine samples: a salting-out approach. *Forensic Sci Int*, 2007, **170**: 133-138.
10. Dahlen J, Vriesman T. Simultaneous analysis of gamma-hydroxybutyric acid, gamma-butyrolactone, and 1,4-butanediol by micellar electrokinetic chromatography. *Forensic Sci Int*, 2002, **125**: 113-119.
11. Snead OC, Furner R, Liu CC. In vivo conversion of gamma-aminobutyric acid and 1,4-butanediol to gamma-hydroxybutyric acid in rat brain. Studies using stable isotopes. *Biochem Pharmacol*, 1989, **38**: 4375-4380.
12. Thai D, Dyer JE, Jacob P, Haller CA. Clinical pharmacology of 1,4-butanediol and gamma-hydroxybutyrate after oral 1,4-butanediol administration to healthy volunteers. *Clin Pharmacol Ther*, 2007, **81**: 178-184.
13. Vayer P, Mandel P, Maitre M. Gamma-hydroxybutyrate, a possible neurotransmitter. *Life Sci*, 1987, **41**: 1547-1557.
14. Snead OC, 3rd, Liu CC. Gamma-hydroxybutyric acid binding sites in rat and human brain synaptosomal membranes. *Biochem Pharmacol*, 1984, **33**: 2587-2590.
15. Roth RH, Giarman NJ. Evidence that central nervous system depression by 1,4-butanediol is mediated through a metabolite, gamma-hydroxybutyrate. *Biochem Pharmacol*, 1968, **17**: 735-739.
16. Benavides J, Rumigny JF, Bourguignon JJ, Cash C, Wermuth CG, Mandel P, *et al*. High affinity binding sites for gamma-hydroxybutyric acid in rat brain. *Life Sci*, 1982, **30**: 953-961.
17. Carter LP, Koek W, France CP. Lack of effects of GHB precursors GBL and 1,4-BD following i.c.v. administration in rats. *Eur J Neurosci*, 2006, **24**: 2595-2600.
18. Poldrugo F, Snead OC. 1,4 Butanediol, gamma-hydroxybutyric acid and ethanol: relationships and interactions. *Neuropharmacology*, 1984, **23**: 109-113.
19. Carai MA, Colombo G, Reali R, Serra S, Mocchi I, Castelli MP, *et al*. Central effects of 1,4-butanediol are mediated by GABA(B) receptors via its conversion into gamma-hydroxybutyric acid. *Eur J Pharmacol*, 2002, **441**: 157-163.

20. Maxwell R, Roth RH. Conversion of 1,4-butanediol to gamma-hydroxybutyric acid in rat-brain and in peripheral tissue. *Biochemical Pharmacology*, 1972, **21**: 1521-.
21. Sprince H, Josephs Jr JA, Wilpizeski CR. Neuropharmacological effects of 1,4-butanediol and related congeners compared with those of gamma-hydroxybutyrate and gamma-butyrolactone. *Life Sciences*, 1966, **5**: 2041-2052.
22. Gerak LR, Hicks AR, Winsauer PJ, Varner KJ. Interaction between 1,4-butanediol and ethanol on operant responding and the cardiovascular system. *Eur J Pharmacol*, 2004, **506**: 75-82.
23. Irwin RD. NTP summary report on the metabolism, disposition, and toxicity of 1,4-butanediol (CAS No. 110-63-4). *Toxic Rep Ser*, 1996: 1-28, A21-28, B21-25.
24. Zabik JE, Vandam DP, Maickel RP. Pharmacological and toxicological Studies on 1,4-butanediol. *Res Comm Chem Path Pharm*, 1974, **8**: 83-90.
25. Carter LP, Wu H, Chen W, Matthews MM, Mehta AK, Hernandez RJ, *et al.* Novel gamma-hydroxybutyric acid (GHB) analogs share some, but not all, of the behavioral effects of GHB and GABAB receptor agonists. *J Pharmacol Exp Ther*, 2005, **313**: 1314-1323.
26. Baker LE, Searcy GD, Pynnonen DM, Poling A. Differentiating the discriminative stimulus effects of gamma-hydroxybutyrate and ethanol in a three-choice drug discrimination procedure in rats. *Pharmacol Biochem Behav*, 2008, **89**: 598-607.
27. Carter LP, Flores LR, Wu H, Chen W, Unzeitig AW, Coop A, *et al.* The role of GABAB receptors in the discriminative stimulus effects of gamma-hydroxybutyrate in rats: time course and antagonism studies. *J Pharmacol Exp Ther*, 2003, **305**: 668-674.
28. Koek W, Flores LR, Carter LP, Lamb RJ, Chen WB, Wu HF, *et al.* Discriminative stimulus effects of gamma-hydroxybutyrate in pigeons: Role of diazepam-sensitive and -insensitive GABA(A) and GABA(B) receptors. *Journal of Pharmacology and Experimental Therapeutics*, 2004, **308**: 904-911.
29. Woolverton WL, Rowlett JK, Winger G, Woods JH, Gerak LR, France CP. Evaluation of the reinforcing and discriminative stimulus effects of gamma-hydroxybutyrate in rhesus monkeys. *Drug Alcohol Depend*, 1999, **54**: 137-143.
30. McMahon LR, Coop A, France CP, Winger G, Woolverton WL. Evaluation of the reinforcing and discriminative stimulus effects of 1,4-butanediol and gamma-butyrolactone in rhesus monkeys. *European Journal of Pharmacology*, 2003, **466**: 113-120.
31. Baker LE, Van Tilburg TJ, Brandt AE, Poling A. Discriminative stimulus effects of gamma-hydroxybutyrate (GHB) and its metabolic precursor, gamma-butyrolactone (GBL) in rats. *Psychopharmacology (Berl)*, 2005, **181**: 458-466.
32. Koek W, Chen WB, Mercer SL, Coop A, France CP. Discriminative stimulus effects of gamma-hydroxybutyrate: Role of training dose. *Journal of Pharmacology and Experimental Therapeutics*, 2006, **317**: 409-417.
33. Beardsley PM, Balster RL, Harris LS. Evaluation of the discriminative stimulus and reinforcing effects of gammahydroxybutyrate (GHB). *Psychopharmacology*, 1996, **127**: 315-322.
34. Aceto M, Bowman ER, Harris LS, Hughes LD, Kipps BR, May EL. Dependence studies of new compounds in the rhesus monkey, rat and mouse (2002). In: Dewey WL, Harris LS (eds). **Problems of Drug Dependence 2002: Proceedings of the 64th Annual Scientific Meeting. The College on Problems of Drug Dependence, Inc.**, vol. 183. National Institute on Drug Abuse: Bethesda, MD, 2002, pp 191-227.
35. Gomes C, Flygt C, Henning M, Norin L, Svensson TH, Trolin G. Gammahydroxy butyric acid: cardiovascular effects in the rat. *J Neural Transm*, 1976, **38**: 123-129.
36. Boyd AJ, Sherman IA, Saibil FG. The cardiovascular effects of gamma-hydroxybutyrate following hemorrhage. *Circ Shock*, 1992, **38**: 115-121.

37. Blumenfeld M, Suntay RG, Harmel MH. Sodium gamma- hydroxybutyric acid: a new anesthetic adjuvant. *Anesth Analg*, 1962, **41**: 721-726.
38. Hicks AR, Kapusta DR, Varner KJ. Mechanisms underlying the sympathomimetic cardiovascular responses elicited by gamma-hydroxybutyrate. *J Cardiovasc Pharmacol*, 2004, **44**: 631-638.
39. Vree TB, van Dalen R, vander Kleijn E, Gimbrere J. Pharmacokinetics of 1,4-butanediol and 4-hydroxybutyric acid in man, rhesus monkey and dog. *Anaesthesiologie und intensivmedizin*, 1978, **110**: 66-73.
40. Fung HL, Tsou PS, Bulitta JB, Tran DC, Page NA, Soda D, *et al.* Pharmacokinetics of 1,4-butanediol in rats: bioactivation to gamma-hydroxybutyric acid, interaction with ethanol, and oral bioavailability. *Aaps J*, 2008, **10**: 56-69.
41. GAF Corporation. Summary of toxicity information for 1,4-butanediol. Pamphlet No. 201-628-3000.
42. Jedrychowski R, Stetkiewicz J, Andstetkiewicz I. I. Acute toxicity of 1,4-butanediol in laboratory animals. *Pol J Occup Med*, 1990, **3**: 415-420.
43. Materials Safety Data Sheet. 1,4-Butanediol. Schenectady, N. Y.: Genium Publishing Corporation; 1985.
44. Taberner PV, Pearce MJ. Hypothermic and toxic actions of 2-butyne-1,4-diol and other related diols in the rat. *J Pharm Pharmacol*, 1974, **26**: 597-604.
45. Kinney LA, Burgess BA, Stula EF. Acute and subchronic inhalation toxicity of 1,4-butanediol in the rat. *Toxicologist*, 1985, **5**.
46. Price CJ, Marr MC, Myers CB, Heindel JJ, Schwetz BA. Developmental toxicity evaluation of 1,4-butanediol (BUTE) in Swiss mice. *Teratology*, 1993, **47**: 433 (Abstr.).
47. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen*, 1992, **19 Suppl 21**: 2-141.
48. Japan Ministry of Health and Welfare. *Toxicity testing reports of environmental chemicals*; 1997.
49. Irwin RD. A review of evidence leading to the prediction that 1,4-butanediol is not a carcinogen. *J Appl Toxicol*, 2006, **26**: 72-80.
50. Palmer RB. Gamma-butyrolactone and 1,4-butanediol: abused analogues of gamma-hydroxybutyrate. *Toxicol Rev*, 2004, **23**: 21-31.
51. World Health Organization. *Gamma-hydroxybutyric acid (GHB): Critical Review Report, Expert Committee on Drug Dependence Thirty-fifth Meeting*. Geneva: World Health Organization; 2012. Report No.: 35th ECDD (2012) Agenda item 4.1.
52. Ingels M, Rangan C, Bellezzo J, Clark RF. Coma and respiratory depression following the ingestion of GHB and its precursors: three cases. *J Emerg Med*, 2000, **19**: 47-50.
53. Pillkington E, Pallister D. Global scare after ecstasy-like chemical found in toy. New York: The Guardian News and Media Ltd.; 8 Nov 2007.
54. ABC News. Bindeez banned over GHB fears. ABC News, New South Wales; 6 Nov 2007.
55. McDonald K. How Bindeez was busted. Australian Life Scientist. 2008:17-18.
56. Suchard J, Nizkorodov S, Wilkinson S. 1,4-Butanediol content of aqua dots children's craft toy beads. *J Med Toxicol*, 2009, **5**: 120-124.
57. Gunja N, Doyle E, Carpenter K, Chan OT, Gilmore S, Browne G, *et al.* Gamma-hydroxybutyrate poisoning from toy beads. *Med J Aust*, 2008, **188**: 54-55.
58. Griffiths J. Scientific sleuthing: how GC/MS uncovered toy danger. *Anal Chem*, 2008, **80**: 6.

59. Colombo G, Agabio R, Diaz G, Fa M, Lobina C, Reali R, *et al.* Gamma-hydroxybutyric acid intake in ethanol-preferring sP and -nonpreferring sNP rats. *Physiol Behav*, 1998, **64**: 197-202.
60. Colombo G, Agabio R, Lobina C, Loche A, Reali R, Gessa GL. High sensitivity to gamma-hydroxybutyric acid in ethanol-preferring sP rats. *Alcohol Alcohol*, 1998, **33**: 121-125.
61. Carai MA, Quang LS, Atzeri S, Lobina C, Maccioni P, Orru A, *et al.* Withdrawal syndrome from gamma-hydroxybutyric acid (GHB) and 1,4-butanediol (1,4-BD) in Sardinian alcohol-preferring rats. *Brain Res Brain Res Protoc*, 2005, **15**: 75-78.
62. Quang LS, Colombo G, Lobina C, Maccioni P, Orru A, Gessa GL, *et al.* Evaluation for the withdrawal syndrome from gamma-hydroxybutyric acid (GHB), gamma-butyrolactone (GBL), and 1,4-butanediol (1,4-BD) in different rat lines. *Ann N Y Acad Sci*, 2006, **1074**: 545-558.
63. Goodwin AK, Gibson KM, Weerts EM. Physical dependence on gamma-hydroxybutyrate (GHB) prodrug 1,4-butanediol (1,4-BD): Time course and severity of withdrawal in baboons. *Drug and Alcohol Dependence*, 2013, **132**: 427-433.
64. Mycyk MB, Wilemon C, Aks SE. Two cases of withdrawal from 1,4-butanediol use. *Annals of Emergency Medicine*, 2001, **38**: 345-346.
65. Wojtowicz JM, Yarema MC, Wax PM. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *Canadian Journal of Emergency Medicine*, 2008, **10**: 69-74.
66. Carter LP, Unzeitig AW, Wu H, Chen W, Coop A, Koek W, *et al.* The Discriminative stimulus effects of gamma-hydroxybutyrate and related compounds in rats discriminating baclofen or diazepam: The role of GABA(B) and GABA(A) receptors. *J Pharmacol Exp Ther*, 2004, **309**: 540-547.
67. Goodwin AK, Kaminski BJ, Weerts EM. Self-administration of gamma-hydroxybutyric acid (GHB) precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) in baboons. *Psychopharmacology*, 2013, **225**: 637-646.
68. Goodwin AK, Kaminski BJ, Griffiths RR, Ator NA, Weerts EM. Intravenous self-administration of gamma-hydroxybutyrate (GHB) in baboons. *Drug Alcohol Depend*, 2011, **114**: 217-224.
69. Martellotta MC, Cossu G, Fattore L, Gessa GL, Fratta W. Intravenous self-administration of gamma-hydroxybutyric acid in drug-naïve mice. *Eur Neuropsychopharmacol*, 1998, **8**: 293-296.
70. Carter LP, Richards BD, Mintzer MZ, Griffiths RR. Relative abuse liability of GHB in humans: A comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. *Neuropsychopharmacology*, 2006, **31**: 2537-2551.
71. Oliveto A, Gentry WB, Pruzinsky R, Gonsai K, Kosten TR, Martell B, *et al.* Behavioral effects of gamma-hydroxybutyrate in humans. *Behav Pharmacol*, 2010, **21**: 332-342.
72. PubMed Health. Busulfan (by mouth). National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM); 2014.
73. Bishop JB, Wasson JS. Toxicological review of busulfan (Myleran). *Mutat Res*, 1986, **168**: 15-45.
74. World Health Organization. *1,4-Butanediol (1,4-BD) Pre-Review Report: Expert Committee on Drug Dependence Thirty-fifth Meeting*. Geneva: World Health Organization; 2012. Report No.: 35th ECDD (2012) Agenda item 5.5.
75. Wood DM, Warren-Gash C, Ashraf T, Greene SL, Shather Z, Trivedy C, *et al.* Medical and legal confusion surrounding gamma-hydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD). *Qjm-an International Journal of Medicine*, 2008, **101**: 23-29.
76. Hillebrand J, Olszewski D, Sedefov R. *EMCDDA Thematic Papers — GHB and its Precursor GBL: An Emerging Trend Case Study*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction; 2008.

77. World Health Organization. *Gamma-butyrolactone (GBL) Pre-Review Report: Expert Committee on Drug Dependence Thirty-fifth Meeting*. Geneva: World Health Organization; 2012. Report No.: 35th ECDD (2012) Agenda item 5.4.
78. Substance Abuse and Mental Health Services Administration. *Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
79. National Institute on Drug Abuse CEWG. *Epidemiologic Trends in Drug Abuse: Proceedings of the Community Epidemiology Work Group*. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health; 2013 January 2013.
80. DEA, Sannerud CA. *DEA Response to WHO Questionnaire for Review of Dependence-Producing Psychoactive Substances for the Thirty-sixth Expert Committee on Drug Dependence*: Drug Enforcement Agency, USA; 2014.
81. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Annual Report 2005: The State of the Drugs Problem in Europe*. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2005.
82. EMCDDA. *GHB (GBL), unpublished report*: European Monitoring Centre for Drugs and Drug Addiction; 2014.
83. Mason PE, Kerns WP, II. Gamma hydroxybutyric acid (GHB) intoxication. *Acad Emerg Med*, 2002, **9**: 730-739.
84. Roberts DM, Smith MW, Gopalakrishnan M, Whittaker G, Day RO. Extreme gamma-butyrolactone overdose with severe metabolic acidosis requiring hemodialysis. *Ann Emerg Med*, 2011, **58**: 83-85.
85. Caldicott DG, Chow FY, Burns BJ, Felgate PD, Byard RW. Fatalities associated with the use of gamma-hydroxybutyrate and its analogues in Australasia. *Med J Aust*, 2004, **181**: 310-313.
86. Anderson IB, Kim SY, Dyer JE, Burkhardt CB, Iknoian JC, Walsh MJ, *et al*. Trends in gamma-hydroxybutyrate (GHB) and related drug intoxication: 1999 to 2003. *Annals of Emergency Medicine*, 2006, **47**: 177-183.
87. Whittaker E, Scott L, Burns L. *NSW Trends in Ecstasy and Related Drug Markets 2012. Findings from the Ecstasy and Related Drugs Reporting System (EDRS)*. Sydney: National Drug and Alcohol Research Centre, University of New South Wales; 2013.
88. Knyshova SP. [Specific features of biologic action and the hygienic significance of 1,4-butyndiol and 1,4-butanediol]. *Gig Sanit*, 1968, **33**: 37-41.
89. ProQuest. *1,4-Butanediol Market, By Application & Geography, Trends & Forecasts to 2017*. **PR Newswire**. New York; 2013.
90. EMCDDA Action on new drugs 2011. *Early warning system on new synthetic drugs: Summary on GHB based on the EWS Final Reports 2011*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA); 2011.
91. European Monitoring Centre for Drugs and Drug Addiction. *Report on the Risk Assessment of GHB in the Framework of the Joint Action on New Synthetic Drugs*. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2002.

**Annex 1:
Report On WHO Questionnaire For Review Of Psychoactive Substances for
the 36th ECDD 1,4-Butanediol**

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 65 Member States answered the questionnaire for **1,4-butanediol**. Of these only 24 respondents (AMR 4, EUR 16, SEAR 1, WPR 3) had and so provided information on this substance.

LEGITIMATE USE

None reported 1,4-butanediol as currently authorized or in the process of being authorized/registered as a medical product in their country. Seven respondents stated that this substance was used in medical and scientific research and for reference standards. There was no use stated for animal/veterinary care. Thirteen respondents stated that it could be used as a solvent in the chemical industry with quantities ranging from 1,000 kg to 935 million pounds per year. Nine respondents stated they imported 1,4-butanediol, two that it was manufactured in their country and another 2 stated it was both imported and manufactured in their country.

HARMFUL USE

Eight respondents confirmed recreational/harmful use; the common route of administration was stated as oral by seven with one stating this was by injection. The substance for such use was obtained via diversion and trafficking by three and only via trafficking by four. All eight respondents reported that 1,4-butanediol was available in liquid form. In addition in one country this substance was also available in powder form. It has also been formulated into illicit dietary supplements and sold as a libido enhancer, sleep inducer and muscle builder. Three respondents replied that it was used by the general population and in clubs, and one each only in clubs and the general population. Two respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by 1,4-butanediol. These include vomiting, hypotonia, tremors, sedation, seizures, coma, respiratory depression, decreased body temperature, decreased heart rate, euphoria and disinhibition. Alcohol was reported to act synergistically as a depressant on the central nervous system and respiration. Concurrent ingestion of alcohol also increases the duration of action of 1,4-butanediol. It is also reported as associated with sexual assault.

CONTROL

Of those with information on this substance, 12 reported that 1,4-butanediol was controlled under legislation that was intended to regulate its availability; nine under “controlled substance act”, and one each under the “medicines law”, “hazardous substance act” and “analogue legislation”. One respondent stated that there are problems with implementation since this is a chemical solvent. No respondents reported clandestine manufacture, synthesis of the product itself or processing into the consumer product. Three respondents reported trafficking, diversion and an internet market.

Details on seizures are presented below.

	Numbers reported 2011 (number of respondents)	Numbers reported 2012 (number of respondents)
Total number of seizures	199 (2)	163 (3)
Total quantity seized (kg)	14.00 (1)	5.1 (2)
Total quantity seized (L)	22.03 (2)	27.47 (2)

IMPACT OF SCHEDULING

Twenty respondents reported that if 1,4-butanediol was placed under international control, they would have the laboratory capacity to identify the substance. This substance has no reported medical use.