

Gamma-hydroxybutyric acid (GHB)

Critical Review Report

Expert Committee on Drug Dependence
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Summary

γ -Hydroxybutyric acid (GHB), also known as 4-hydroxybutanoic acid and sodium oxybate, is a naturally-occurring substance found in the central nervous system, wine, beef, small citrus fruits, and almost all animals in small amounts. It is considered to act by binding to GHB-specific receptors and GABA_B receptors. At pharmacological doses it acts as a central nervous system depressant.

Since the 1960s GHB has undergone various preclinical and clinical trials and has been evaluated for a range of potential therapeutic uses in obstetrics, anaesthesia, alcohol/opiate withdrawal and treatment of narcolepsy and cataplexy. Furthermore, some reports have suggested antidepressant effects of GHB as well as sex enhancing effects in humans.

The international non-proprietary name of GHB is sodium oxybate. Pharmaceutically, it is presented as sodium gamma-hydroxybutyrate in liquid form. It was originally evaluated and is used as an anaesthetic, particularly in France and Germany as Gamma OH® and Somsanit®, respectively. It has also been assessed in the treatment of narcolepsy and associated disorders such as cataplexy, in addition to its use as an aid to opiate and alcohol withdrawal as Alcover® in Austria and Italy. In June 2005, the European Medicines Agency (EMA) recommended granting a marketing authorisation for the medicinal product Xyrem®, where the active substance is sodium oxybate (500 mg/ml), to treat adults who have narcolepsy with cataplexy (EMA, 2005).

Consequently, in October 2005 the European Commission granted a marketing authorisation for Xyrem® valid throughout the European Union.

Xyrem® can only be obtained with a special prescription; it is given at a dose of 4.5 to 9g per day in two equally divided doses (EMA, 2005). GHB is not authorised for veterinary use.

GHB is since 2001 placed in Schedule IV of the 1971 Convention by a decision of the United Nations Commission on Narcotic Drugs and therefore controlled by all Member Parties.

Tolerance and withdrawal has been observed at prolonged high dosage. Reports indicate that GHB is misused for various reasons and by various sections of society. These include, its sexual enhancing effects, growth hormone promoting effects and more recently its euphoric (“high”) effects. There have also been reports of GHB being used to facilitate sexual assault.

GHB can easily be manufactured in the home from inexpensive ingredients and recipes obtained from the Internet. The powder (usually GHB sodium salt) is invariably mixed with water prior to consumption. Many of the dangers associated with illicit GHB use are due to variances in the GHB concentrations of such solutions.

GHB has been reported to be mainly used and misused in USA, Australia and Europe and has resulted in numerous hospital admissions and related deaths. It appears that toxic effects can be produced directly from the compound and the presence of other substances and particularly alcohol may exacerbate such effects.

A range of factors such as low price, ease of availability and administration, lack of information, the need for sedation following heavy stimulant use, and careless media coverage, increase the probability of GHB diffusion and consequent harm. Other factors, such as antisocial effects, relatively short duration, and its low-status image, mitigate against widespread diffusion and so decrease the probability of harm.

The most recent substance misuse indicators demonstrate that misuse in the USA has stabilized and involves GHB of clandestine manufacture primarily and is not the result of diverted pharmaceutical products (e.g. Xyrem®).

With the introduction of national control measures, the numbers of countries able to report to INCB on manufacture of and trade in GHB has increased. However, the Board notes in its 2009 Report that more than half of all countries have not yet informed the Board of having extended the requirement for import authorizations to include *gamma*-hydroxybutyric acid (GHB), although the substance was added to Schedule IV of the 1971 Convention in 2001, more than eight years ago.

Concerns are increasing about the direct consumption of GHB's precursor chemicals, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). These are rapidly converted to GHB when ingested, yet are widely used in the chemical industry and are commercially available. They are used to bypass GHB restriction laws. Furthermore, GHB can be easily manufactured from GBL and 1,4-BD.

In view of concerns about the ongoing diversion of GHB from the domestic distribution channel and illicit trade of GBL and 1,4-BD, the Expert Committee suggested at its 34th Meeting a critical review of GHB and recommended that its possible rescheduling shall be considered at its next meeting.

1. Substance Identification

A. *International Non-proprietary Name (INN)*

Sodium oxybate (sodium salt)

B. *Chemical Abstract Service (CAS) Registry Number*

591-81-1 (free acid)

502-85-2 (sodium salt)

C. *Other chemical names*

γ -hydroxybutyrate, 4-hydroxybutyrate, GHB, sodium oxybate, 4-hydroxybutanoic acid, 4-hydroxybutyric acid, oxybutirate natrii, hydroxybutyrate sodium, sodium oxybutyrat.

D. *Trade names*

Alcover® (Austria, Italy), Gamma-OH® (France), Somsanit® (Germany), Xyrem® (Canada, EU, Switzerland, USA). (Also refer Annex 1)

E. *Street names*

A number of street names for GHB can be found in the literature, like “Blue Nitro”, “Blue Verve”, “Caps”, “Chemical X”, “Cherry Meth”, “Date Rape Drug”, “Drogue du Cambriolage Sexuel Parfait”, “Easy Lay”, “Ellie”, “Ever Clear”, “EZ Lay”, “Fantasy”, “G”, “Gamma-OH”, “Georgia Home Boy”, “Get-her-to-Bed”, “Goop”, “Great Hormones at Bedtime”, “Grievous Bodily Harm”, “G-Riffic”, “Jib”, “Liquid Dream”, “Liquid E”, “Liquid Ecstasy”, “Liquid G”, “Liquid X”, “Liquid-XTC”, “Natural Sleep 500”, “Organic Quaalude”, “Salty Water”, “Scoop”, “Scoop Her”, “Sleep”, “Soap”, “Somatomax”, “Somatomax PM”, “Vita-G”, “Water”.

One should be aware of the fact that street names are not always exclusive for just one substance.

F. *Physical properties*

GHB can form salts (e.g. sodium and potassium salts), which are soluble in water and alcohol. It is colourless and easily mixes in aqueous solutions; however, a salty taste may be noticeable [1].

G. *WHO Review History*

GHB was pre-reviewed by the 31st meeting of the ECDD which recommended critical review. It was then critically reviewed at the 32nd meeting in 2001, which recommended scheduling in Schedule IV of the 1971 Convention. In the same year it was put under international control by a decision of the United Nations Commission on Narcotic Drugs.

Some answers to the questionnaire for the 34th ECDD clearly showed that GHB is an authorized medicine in the EU, the United States of America and Canada and according to the Guidelines, in such a case the review shall be

subjected to a pre-review instead of a critical review. For this reason GHB was pre-reviewed by the 34th meeting of the ECDD, which recommended considering its possible rescheduling and therefore a critical review is proposed by the Secretariat for the Committee's 35th meeting.

2. Chemistry

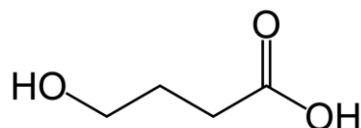
A. Chemical Name

IUPAC Name: γ -hydroxybutyric acid

CA Index Name: γ -hydroxybutyric acid

B. Chemical Structure

Free acid:



Molecular Formula: C₄H₈O₃ (free acid)

C₄H₇NaO₃ (sodium salt)

Molecular Weight: 104.11 g/mol (free acid)

126.09 g/mol (sodium salt)

Melting point: n/a (free acid)

145-146°C (sodium salt)

C. Stereoisomer

None.

D. Synthesis

Synthesis of the chemical GHB was first reported in 1874 by Alexander Zaytsev [2]. In the typical scenario, GHB has been synthesized from γ -butyrolactone (GBL) by adding sodium hydroxide (lye) in ethanol or water. As of late, GBL has become controlled in some countries and more circuitous routes have to be taken, such as those starting with tetrahydrofuran (THF).

GHB is reportedly synthesized in clandestine laboratories also using various methods. If pharmaceutical grade GHB cannot be obtained, users/producers usually exploit the conversion of GBL to GHB under certain conditions (e.g. alkaline pH >7). Notionally this requires the addition of sodium hydroxide (or potassium hydroxide) with water to GBL. There are various dangers associated with such a reaction, particularly as the reaction is exothermic and GBL is flammable. Furthermore, commercially available domestic or industrial products, which could be used for synthesis, are not meant for human

consumption and invariably contain other potentially toxic substances, including heavy metals and other organic solvents such as acetone or toluene. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. To aid the producer, “GHB Kits” are available which apparently contain the necessary “pure” ingredients in “accurately weighed” amounts. Various “recipes” have been presented both on the Internet and in books [1].

E. *Chemical description*

GHB is a naturally occurring short-chained fatty acid found in mammalian tissue. GHB is a hydroxycarboxylic acid, whose salts are also known as oxybates in pharmacy.

F. *Chemical properties*

GHB and GBL are subject to interconversion in aqueous media. GBL is converted to GHB via hydrolysis, whereas GHB is converted to GBL via intramolecular esterification, depending on solution pH and temperature [3]. The salts of GHB are odourless and partly hygroscopic. Sodium oxybate has a distinctive salty taste.

G. *Chemical identification*

The analytical profile of GHB has been described in numerous papers. Early data pertaining to GC-MS and GC-FID are described [4-7]; analysis usually requires conversion to γ -butyrolactone (GBL) or chemical derivation. However, newer analytical methods have become available, which have increased sensitivity and specificity [8-11], especially in forensic studies.

3. Convertibility into controlled substances

GHB is not readily converted into other controlled substances.

4. General Pharmacology

Described in this section are studies that have examined the pharmacological actions of GHB. GHB is generally believed to act through GABA_B receptor activation as well as a direct interaction with a GHB receptor. Earlier studies reported that the substance increased the levels of dopamine in the brain with relatively little effect on other neurotransmitter systems. It has also been reported to produce enhanced slow-wave/delta sleep without a decrease in oxygen consumption while the respiratory centre remains sensitive to carbon dioxide. Furthermore, there appeared to be some bradycardia but no effect on blood pressure and an increase in prolactin and growth hormone secretion has also been observed in humans.

4.1. Pharmacodynamics

Neuropharmacology

GHB (γ -hydroxybutyric acid) was first synthesized in 1960 by Laborit in an attempt to study the effects of butyric acid and GABA (γ -aminobutyric acid), producing a compound which would interfere with γ -oxidation and would cross the blood-brain barrier [12]. Bessman and Fishbein later discovered that GHB is an endogenous compound existing as a proposed metabolite of GABA [13]. During these studies GHB was isolated in the brain of both rats and humans. Some researchers also postulated that GHB was a putative neurotransmitter or neuromodulator [14-15].

There have been many studies detailing the effects of GHB on various neurotransmitter systems, particularly serotonin (5-HT), noradrenaline (NA, norepinephrine), dopamine (DA) and acetylcholine (ACh). Although these studies have produced variable results, the data suggest that GHB does have a significant effect on the dopaminergic system. There may also be an accompanied increase in the release of endogenous opioids e.g. dynorphin [16].

Giarman and Schmidt noted that at relatively high doses of GHB, ACh levels were increased in certain regions of the brain [17].

Early work by Gessa *et al.* studied the effect of GHB on 5-HT, NA and DA in the brains of rabbits and Long-Evans rats [18]. Rabbits were injected intravenously (i.v.) and rats were injected intraperitoneally (i.p.) with varying doses of GHB ranging from 250 mg/kg to 2000 mg/kg and sacrificed 0-4 hours post dose. The results of the various experiments indicated that there is a slight increase in 5-HT and NA levels in the brain; however, they observed a pronounced increase in brain DA levels (primarily in the caudate nucleus). The maximal increase in DA concentration occurred 1-2 hours after administration of 2000 mg/kg of GHB with a slow decline thereafter.

Further study of the effects of GHB on DA involved the administration of L-DOPA and a known monoamine oxidase inhibitor (MAOI), pargyline. It was found that although DOPA produced a higher initial increase in rat brain DA, GHB produced a more sustained increase and co-administration of the two compounds (DOPA 50 mg/kg i.v. and GHB 2000 mg/kg i.p.) produced a further increase. Furthermore, it appeared that DOPA-decarboxylase was not affected by GHB. Administration of pargyline (80 mg/kg i.p.) to rats produced complete monoamine oxidase (MAO) inhibition, whereas MAO activity was not inhibited following a 2000 mg/kg i.p. GHB dose. It was concluded that GHB does not appear to be a MAOI.

Other studies concerning GHB and brain DA levels confirmed that DA is altered in response to GHB [19-23]. It appears that there is an initial inhibition of DA release at the synapse but an increase in neuronal DA production. This is followed by either a time-dependent (DA increases with time) or dose-dependent stimulation of DA release (low doses inhibit, high doses stimulate). In the case of both theories, this will ultimately result in a pronounced increase in brain DA concentration. However, Feigenbaum and Howard have reported that GHB inhibits rather than stimulates DA release and that experiments showing DA stimulation were performed under anaesthesia or in the presence of high calcium concentrations; such conditions apparently have been found to spuriously enhance striatal DA release [24].

GHB was also found to have an affinity for two receptors in the brain, a GHB-specific receptor and GABA_B receptor. GHB appeared to have no affinity for the GABA_A receptor.

Evidence for a GHB-specific receptor came from experiments by Benavides *et al.* and Maitre *et al.* involving radiolabelled GHB ($[^3\text{H}]\text{GHB}$), which bound to the receptor even in the presence of GABA, and binding inhibition studies using a GHB antagonist NCS-382, which prevented GHB binding [25-26]. The highest concentrations of the GHB binding sites in rat brain were in the olfactory bulbs, hippocampus and cerebral cortex. Further work using rat brain membranes suggests that the receptor is linked to the G_i or G_o family of proteins [27].

Godbout *et al.* reported that there is an increase in spontaneous firing in prefrontal cortical neurons after administration of low doses of GHB [28]. As this is inhibited by NCS-382, it suggests that GHB binding to the GHB-specific receptor mediates this response. DA is known to inhibit prefrontal nerve cells, suggesting that GHB reduces the DA levels, thus preventing inhibition of prefrontal cortical neuronal firing. GHB inhibits DA release by binding to the GHB-specific receptor. However, administration of high doses of GHB produced inhibition of these neurons. It was postulated that this was due to an increase in DA levels resulting from GHB-induced stimulation of a second receptor, GABA_B [29-32]. GHB has been found to be only a weak agonist of this receptor, exhibiting a binding affinity of 1000 times less than GABA and 1000 times less than binding to the GHB-specific receptor [33].

Studies using a GABA_B antagonist, CGP 35348, indicated that GHB activation of the GABA_B receptor produces hyperpolarisation [32]. A Na^+ dependent GHB transporter has also been discovered which is thought to remove GHB from the synaptic cleft following neuronal release [24]. A review of the recent literature suggests that most of the physiological and pharmacological effects of exogenously administered GHB are mediated via the GABA_B receptor [35]. Later work [36, 37] has amplified this hypothesis and pointed to a possible specific GHB binding site. More recently, a GHB receptor from human brain has been identified, cloned and its functional characteristics described [38]. This opens further exploration of an endogenous system modulating physiological mechanisms underlying the actions of GHB.

Neuroendocrinology

Following an intravenous 2.5 g dose of GHB in six male human volunteers, a significant increase in both plasma prolactin and growth hormone (GH) was observed at 30, 45, 60 and 90 minutes post dose [39]. Five of the six patients fell asleep. These effects were not observed in the saline-controlled group. As DA is known to inhibit prolactin production, the results suggested there was a GHB-induced reduction in DA, however, as growth hormone secretion is known to be increased by dopaminergic stimulants it was concluded that the growth hormone increase in this case was not due to GHB-inhibition of DA release. Other work had indicated that 5-HT and a precursor (5-hydroxytryptophan) stimulated prolactin and growth hormone secretion in rats and man [40-41]. It was therefore speculated that GHB may induce prolactin and growth hormone release by modifying the release of 5-HT from the nerve terminals. Further postulation suggested that GHB acts directly on neurons in the hypothalamus and stimulate the release of GH-releasing hormone. The slow-wave and rapid-eye-movement (REM) sleep apparently induced by GHB (see Effects on Brain Function) is also thought to be the periods of sleep where GH production is at its greatest [42].

Cardiovascular and Respiratory Effects and Thermoregulatory Responses

Laborit observed a constant but short drop in blood pressure in rabbits after administration of GHB, but in dogs there was either no effect or a slight progressive increase in blood pressure (even under controlled ventilation conditions) [12]. In all animals, a constant bradycardia was observed. GHB also appeared to elevate the sensitivity threshold of the pressure receptors in the rabbit and dog, without having any obvious action on the chemoreceptors. Laborit and Leterrier also observed a strong hepatic and renal vasodilating action, particularly during haemorrhagic shock in animals, indicating that GHB has “antishock activity” [12]. In man, after a 2-4 g injection of GHB there appeared to be no effect on blood pressure, unless during surgery when, in the absence of adequate neuroplegic premedication, a progressive hypertensive episode occasionally occurred. In addition, there were no unfavourable effects observed in 50 human atherosclerotic patients under GHB anaesthesia. However, a frequent decrease in the amplitude of the *T*-wave was noted, but this appeared to be due to the hypokalaemia (reduction in serum potassium levels) associated with GHB [12]. This was reversed by the administration of potassium. A study in Poland of 100 patients also suggested that administration of GHB resulted in a constant drop in blood cholesterol levels [12].

Furthermore, Laborit observed in both animal and man that GHB-induced sleep is not accompanied by a decrease in oxygen consumption. At low hypnotic doses of GHB, a decrease in ventilatory rate was reported with an increase in amplitude. At high (sleep inducing) doses of GHB, a Cheyne-Stokes rhythm appeared (including periods of apnea, often observed in coma patients); however, the respiratory centre remained sensitive to an increase in carbon dioxide (pCO₂) [12].

Both Laborit and Gessa reported a slight drop in body temperature of animals given GHB. Gessa noted that this appeared particularly pronounced in rats who had received 2 g/kg GHB and has been kept at 18 °C compared to those kept in a room at 37 °C (room temperature) [17].

Effects on Brain Function

Many researchers have recorded the effects of GHB on brain function in animals and humans using an electroencephalogram (EEG) [12, 43-48]. The results have been contradictory to some extent, with GHB producing various EEG patterns in various animal and human models. Some animal studies report apparent epileptiform (epileptic/seizure-like) EEG changes which have not been observed in human volunteer studies following GHB administration. Random clonic movements of the face and extremities have been reported to be associated with GHB-induced anaesthesia without epileptiform EEG changes. In fact, Jouany *et al.* observed that GHB apparently controlled chemical-induced seizures (using ammonium chloride, strychnine, cardiazol and isoniazide) to some extent [12].

Based on behavioural and electroencephalographic criteria, GHB-induced sleep has been described as being indistinguishable from natural sleep, i.e. unlike coma, the natural stages of sleep 1-2-3-4-REM all occur in their normal sequence [46]. GHB has been noted to increase stages 3-4 (delta/slow-wave sleep) followed by REM sleep. The effect of GHB-enhanced sleep appears to wear off after 3-4 hours at “normal” doses, with no apparent side effects. The neurobiology and toxicology of GHB has recently been reviewed [49]. Since the medicine has been commercially available, large

information is available on its effects on various organ systems, toxicity, adverse side-effects, drug interactions, etc. [50].

4.2. Routes of administration and dosage

For narcolepsy with cataplexy

Xyrem® is required to be taken at bedtime while in bed and again 2.5 to 4 hours later. The dose of Xyrem® should be titrated to effect. The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose). One to two weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects. The effective dose range of Xyrem® is 6 to 9 g/night. The efficacy and safety of Xyrem® at doses higher than 9 g/night have not been investigated, and doses greater than 9 g/night ordinarily should not be administered.

Alcoholism

GHB is used in the treatment of alcoholism (50 to 100 milligrams per kilogram per day, in 3 or more divided doses), both for acute alcohol withdrawal and medium- to long-term detoxification.

Anesthesia

GHB has a decade's long track record of use as a general anesthetic. Administered intravenously, an anesthetic dose of GHB is in the range of 4-5 grams for a 150-pound person [51]. However, GHB can almost never be used in anesthesia without the additional administration of other medicines [51] because it does not produce complete surgical anesthesia except in children [52].

4.3 Pharmacokinetics

GHB can cross the blood-brain barrier and can be produced *in vivo* as a product of GABA metabolism and after administration of GBL or 1,4-BD. GHB is thought to be metabolized via the citric acid cycle producing carbon dioxide and water. It may also activate the pentose phosphate pathway. GHB is rapidly absorbed and metabolized, possessing a plasma half-life of approximately 20 minutes (following 12.5 mg/kg oral dose) and has a steep dose-response curve.

In 1969, Roth and Giarman demonstrated that [³H]GABA is converted to [³H]GHB via succinic semi-aldehyde (intermediate compound) in brain tissue [53]. This was later confirmed by Anderson *et al.* [54]. The conversion is catalysed by the enzymes GABA aminotransferase and succinic semi-aldehyde reductase (Figure 1).

Succinic semi-aldehyde reductase has been found to be different between species in human and pig brain the enzyme is dimeric (Mr between 82,000 and 110,000 Da), whereas it exists as a monomeric protein in rat and bovine brain tissue. The enzyme has also been isolated in mitochondria and as the substrate for succinic semi-aldehyde is synthesized in mitochondria, it has been postulated that the mitochondrion is the site of GHB synthesis, with subsequent transport to the cytosol. GHB can also be synthesized after administration of γ -butyrolactone (GBL). The hydrolysis of GBL to GHB is catalysed *in vivo* by a lactonase [55]. In rat whole blood, the half-life conversion of GBL was only 1 minute, with serum more active than plasma [92]. Rat liver was also

found to have substantial lactonase activity, however, human cerebrospinal fluid (CSF) did not. It was found that muscle tissue can sequester a large part of the initial GBL dose, thereby delaying conversion to GHB and prolonging the duration of action. It has also been reported that 1,4-BD is also rapidly metabolized to GHB *in vivo*, in a reaction catalysed by the enzyme alcohol dehydrogenase (ADH) [56-57]. GHB can be produced *in vivo* as a result of GABA metabolism or after the administration of GBL or 1,4-BD.

GHB is purported to be metabolized via succinic acid and the citric acid cycle (TCA cycle/Krebs cycle), ultimately producing carbon dioxide and water. GHB conversion to succinic semi-aldehyde can be catalysed by cytosolic GHB-dehydrogenase (accounts for majority of GHB metabolism in the young animal foetus) or mitochondrial GHB-etoacidtranshydrogenase (responsible for majority of GHB metabolism in adult animals) [58-59]. Although GHB has the potential to produce GABA, this was not observed after injecting mice with radiolabelled GHB [60]. Laborit also postulated that GHB “orientated” glucose-6-phosphate (G6P) into the pentose phosphate pathway (produces ribose for nucleic acid synthesis and NADPH) [12]. Under acidic conditions, GHB can be converted to the lactone, GBL, a process that has been exploited for gas chromatographic analysis of the compound [4]. No GBL has been detected in plasma or urine; therefore, it is assumed that this conversion does not occur *in vivo*.

In man, GHB is rapidly absorbed, with peak plasma concentrations (C_{max}) occurring within 20-60 minutes post oral dose ($t_{max} = 20-60$ min). With increasing doses, significant increases in t_{max} have been observed with little change in the peak plasma concentration (C_{max}) [61]. Following a 12.5 mg/kg dose, the half-life was 20 minutes [62]. Only 2-5% is eliminated as unchanged in urine [12, 63].

A later double-blind, randomized, crossover controlled oral dose-response study [64] measured both the pharmacokinetic and pharmacodynamic effects of GHB.

Physiological effects, psychomotor performance and subjective effects were measured. Mean peak GHB plasma concentrations were 79.1, 83.1, 113.5 and 130.1 mg/L after oral doses of 40, 50, 60 and 72 mg/kg respectively. GHB-mediated physiological and subjective effects were dose-dependent and related to plasma concentrations of GHB. Another controlled clinical pharmacology study of 1,4-BD (1,4-BD) (65) noted rapid conversion to GHB. The study reported pharmacokinetic data on both 1,4-BD and GHB. The data was similar to that reported above. Thus, after an oral dose of 25 mg/kg 1,4-BD, the maximum plasma concentration of GHB was 45.6 mg/L reached 39.4 min after 1,4-BD ingestion. GHB half-life averaged 32.3 min.

5. Toxicology

Animal and human studies indicate that GHB toxicity is dose-dependent and can result in coma, random clonic movements, decrease in body temperature, hypotonia, hallucinations, nausea, vomiting, bradycardia, respiratory depression and apnea. Other depressant or psychoactive compounds may exacerbate these toxic effects. In humans, there have been numerous reported nonfatal instances of GHB intoxication and related deaths, worldwide.

Toxicity in Animals

Laborit found sleep could be induced in the rat with 0.5 g/kg GHB (i.p.) and in rabbits and dogs using 1 g/kg (i.v.) [5]. In rats, the LD50 was 1.7 g/kg and the LD100 was 2 g/kg. The cause of death was reported to be respiratory depression; however, using artificial respiration, rabbits tolerated doses up to 7 g/kg. With respect to weight, bone marrow, liver and kidneys, there were no significant differences observed between controls and rats receiving 0.17 g/kg GHB daily for 70 days.

During the course of the various experiments involving the administration of GHB to animals at numerous doses, the following observations were made regarding the toxicity of GHB in animals. The toxicity of GHB appears to be dose-dependent and can induce various degrees of sleep, bradycardia, a decrease in body temperature and possible seizures/spasms, death has been reported to be due to respiratory depression in rats.

Toxicity in Humans

Short amnesia and hypotonia have been associated with an oral dose of 10 mg/kg GHB [42]. REM sleep can be induced in humans using an oral dose of between 20-30 mg/kg GHB [38-39]. 50-70 mg/kg GHB given intravenously produces hypnosis but has little analgesic effect [69]. This dose may also cause hypotonia, bradycardia, nausea, vomiting, random clonic movements of the face and extremities and Cheyne-Stokes respiration [12, 42]. Following a typical 65 mg/kg intravenous dose of GHB, sleepiness can occur within 5 minutes, followed by a comatose state lasting for 1-2 hours or more, after which there is a sudden awakening [66]. High oral doses of GHB (greater than 60 mg/kg) can also result in coma, usually lasting up to 4 hours [70]. The following table 1 shows a summary of resultant concentrations in humans following various GHB doses.

Table 1 Reported Concentration of GHB in Human Blood/Plasma and Urine

Dose	Effect(s)	GHB concentration	Reference
25mg/kg (oral)	Drowsiness	80mg/l (peak plasma)	Palatini et al (71)
75mg/kg	Sleep	90 mg/l (peak plasma) 2 hours 9 mg/l (plasma) 6 hours	Hoes et al (63)
50 mg/kg (i.v.)		170 mg/l (peak blood)	Helrich et al (72)
100 mg/kg (oral)		1100 mg/l (peak urine) in 4 hours	Hoes et al (63)

In 1964, Helrich *et al.* reported that blood GHB concentrations exceeding 260 mg/l were associated with deep sleep, 156-260 mg/l associated with moderate sleep, 52-156 mg/l associated with light sleep and levels less than 52 mg/l were associated with wakefulness [72].

There have been various published reports of GHB intoxication; however, the frequent presence of other substances may have complicated the clinical presentation. Typical presentation appears to be various degrees of consciousness, euphoria (“high”), aggressive behaviour, ataxia, amnesia, somnolence, bradycardia, confusion, hallucinations, respiratory depression and apnea, vomiting and random clonic movements (sometimes reported as being seizures) [73-76]. The adverse effects of GHB intoxication are exacerbated by the presence of other depressants such as opiates (e.g.

heroin or morphine) or alcohol (e.g. ethanol) and possibly other psychoactive compounds (e.g. metamfetamine or MDMA). In the USA, Chin *et al.* reported that of 86 presenting patients, 25 had an initial Glasgow Coma Scale (GCS) score of 3 (severe decrease in consciousness), other GCS scores were between 4 (decreased consciousness) and 15 (wakefulness) [73].

Various possible reversal/antagonizing agents have been tested against the clinical effects of GHB toxicity. Commonly used coma reversal agents such as naloxone (opiate/opioid antagonist) and flumazenil (GABA, benzodiazepine antagonist) had no effect [74-75, 77]. In addition, various anticonvulsant and other agents have been tested using animal models (e.g. ethosuximide, sodium valproate, clonazepam, diazepam, L-dopa, phenobarbital); however, although there were some EEG changes, the results appeared to be species-specific [74]. Due to the rapid gastrointestinal absorption of GHB, gastric lavage and administration of activated charcoal are of limited use. Treatment of GHB intoxication is therefore largely supportive and intubation with mechanical ventilation is sometimes used (particularly to protect the airway if the patient is vomiting) [76]. However, in the majority of cases, the patient awakes spontaneously within approximately 7 hours (presumed to be due to the short elimination half-life of GHB).

6. Adverse reactions in humans

Cases of GHB Intoxication in Humans

Non-fatal Cases

There have been many reported cases of apparent GHB intoxication; however, there also appears to be many more unconfirmed/anecdotal reports [78-79]. Global estimates of the number of GHB overdose cases by various agencies (e.g. FDA, DEA and CDC) and poison centers range from hundreds to thousands of cases [80-84]. There have been other reports of toxicity resulting from ingestion of GBL or 1,4-BD; the patients presented with identical symptoms to cases involving GHB ingestion [85-89]. This is consistent with the reported *in vivo* conversion of these compounds to GHB [90-91].

The majority of reported cases have occurred in the USA [7, 42, 73-75, 80-85, 92-96] and Europe (in particular; United Kingdom, Belgium, Denmark, Spain, Norway, Sweden and The Netherlands) after 1990 [97-104]. Misuse of GHB has also been reported in Australia [105]. A selection of reported cases is presented in Table 2. It appears that patients presented in various states ranging from initial confusion, dizziness or euphoria, leading to collapse, vomiting and loss of consciousness/coma. Administration of naloxone and flumazenil did not appear to have an effect and in the majority of cases, activated charcoal was administered and the patients were intubated. All patients eventually recovered and were either discharged or self-discharged. The reported “dose” of GHB varied, however the true amount/concentration of GHB ingested was unknown, as the exact composition of the GHB product was not ascertained/analysed. Furthermore, it was not known/confirmed if other substances were ingested which may have exacerbated the effects; however, the co-ingestion of alcohol (ethanol) was frequently mentioned.

As GHB is not usually detected during routine toxicological analysis [77, 98, 106], the evidence for GHB or related-product ingestion (e.g. GBL or 1,4-BD) is usually based on anecdotal or circumstantial evidence. In some cases, however, extensive drug screening has been performed and the presence of GHB has been confirmed and the concentration measured/estimated in biological fluid [7, 98-99, 107-110]. Elliott [111] analyzed urine and/or plasma from individuals admitted to hospital in the United Kingdom from May 1998 to May 2003 who had either ingested GHB (or a related product such as GBL) or presented with unexplained 'sedation'. GHB was detected in 27 cases of nonfatal intoxication and the majority occurred in 2002. Alcohol and other illicit substances were often present. GBL was also detected in the majority of the urine specimens analyzed but not in plasma. A selection of these cases is presented in Table 3. Additional recent [112] data from a Swiss retrospective study shows that overdosing of GHB and GBL frequently results in non-reactive coma reflecting the severity of the poisoning and that multiple substance use is common and significantly influences the clinical presentation as does the product data shown in reference [50].

There is arguably still a need for comprehensive clinical data to be obtained from patients who have only taken GHB before definite conclusions can be made as to the toxicity of this compound in humans. It is, however, not unexpected that patients present with varying degrees of sedation, as the clinical studies involving GHB alone clearly show it possesses hypnotic/sedative properties.

Table 2 Reported Hospital Admissions

Case No.	Patient Details	Reference + Country of Occurrence	Clinical Presentation	Comments
1	39 yr F	Chin et al [42] (USA)	Euphoria, drowsiness, confusion, twitching, hallucinations and difficulty breathing. Pulse, blood pressure (BP) and respiration normal.	4 "teaspoon" doses in 1 day. Hydrocodone and paracetamol (acetaminophen) also possibly ingested.
2	26 yr F	Chin et al [42] (USA)	Vomiting, drowsiness, headache, nausea, diarrhoea, confusion, euphoria and dizziness.	Bodybuilder. Unknown dose. Alcohol also ingested.
3	28 yr F	Chin et al [42] (USA)	Confusion, shaking followed by coma, vomiting and apnea. Intubated.	Ingested at nightclub. Unknown dose with ethanol (80 mg/dl in blood).
4	47 yr M	Chin et al [42] (USA)	Immobile, difficulty breathing, drowsiness, euphoria, shaking, dizziness followed by coma. Eventually became awake and alert.	1 "teaspoon" dose x 4 in 8 hours. Symptoms appeared approx half an hour after last dose.
5	23 yr M	Chin et al [42] (USA)	Vomiting, unresponsive except to pain, small pupils. BP 150/90, pulse 60 bpm. Asymptomatic 6 hours after admission.	1 "teaspoon" dose. Taken for growth hormone release.
6		Li et al [74] (USA)	Unconscious and apneic. GCS 3, BP 138/90, pulse 98 bpm. Intubated and received activated charcoal.	1 "single shot". Possibly co-ingested ethanol, cocaine and diphenhydramine.
7		Li et al [74] (USA)	Unconscious. GCS 3, pulse 118 bpm. Intubated and received activated charcoal.	1 "single shot". Possibly co-ingested ethanol and cocaine.

8		Li et al [74] (USA)	Brief euphoria then unconscious and severe respiratory depression. GCS 3, BP 88/64, pulse 80 bpm. Aborted intubation due to combativeness but received activated charcoal.	2 “shots”. Possibly co-ingested ethanol, cocaine and ibuprofen.
9		Li et al [74] (USA)	Unconscious and apneic. GCS 6, BP 138/90, pulse 81 bpm. Aborted intubated due to combativeness but received activated charcoal.	Unknown number of “shots”. Possibly co-ingested ethanol, cocaine and fluconazole.
10	32 yr M	Williams et al (UNK) [104]	Collapsed, unconscious, dilated pupils. GCS 8, BP 100/60, pulse 70 bpm. Discharged 2 hours after arrival.	Unknown dose. Reported to have also taken MDMA, cannabis, ethanol and amyl nitrate.
11	28 yr M	Williams et al (UNK) [104]	Collapsed, unconscious. GCS 3, BP 100/60, pulse 90 bpm. Naloxone given – no effect. Discharged 10 hours after arrival.	1 capsule of GHB at nightclub. Reported to have also taken MDMA.
12	29 yr F	Williams et al (UNK) [104]	Collapsed, unconscious, dilated pupils. BP 80/60, pulse 50 bpm. Discharged 1.5 hours after arrival.	Half a bottle of GHB at nightclub. No other substances or ethanol reportedly ingested.

Table 3 GHB Concentration Detected in Biological Fluid

Case No.	Patient Details	Reference	Drugs detected	GHB concentration	Comments
1	M	Couper and Logan [7]	GHB + opiates	Urine = 2200 mg/l Serum = 339 mg/l	Bodybuilder
2	61 yr M	Le Gatt et al. [107]	GHB	Serum = 410 mg/l	Drank GHB liquid by mistake
3	42 yr M	Stephens and Baselt [108]	GHB + cannabinoids	Urine = 1975 mg/l	Driver (asleep in traffic lane)
4	M	Paradha [109]	GHB + ethanol (90 mg/dL)	Blood = 94 mg/l	Road traffic accident
5	F	Louagie [99]	GHB + ethanol (134 mg/dL)	Serum = 125 mg/l	Party
6	F	Dyer et al. [110]	GHB	Urine = 141,000 mg/l Serum = 101 mg/l	Nightclub
7	33yr M	Elliott [111]	GHB, morphine, 6-MAM, codeine, benzodiazepines	Urine=3006 mg/l Plasma =216 mg/l	Possible or suspected overdose of heroin and GHB
8	32 yr M	Elliott [111]	GHB, MDMA, amphetamine, benzodiazepines	Urine=5581 mg/l Plasma=452 mg/l	Possible or suspected overdose of GHB GCS* 5
9	18 yr M	Elliott [111]	GHB, MDMA, amphetamine, cannabinoids	Urine=1089 mg/l Plasma=167 mg/l	Possible or suspected overdose of GHB and ‘ecstasy’
10	21yr F	Elliott [111]	GHB	Plasma=100 mg/l	Possible or suspected overdose of GHB 3 hours prior
11	44 yr M	Elliott [111]	GHB, MDMA, cocaine	Urine=135 mg/l Plasma=86 mg/l	?GHB and ‘ecstasy’ (cocaine powder and tablets seized)

12	24 yr M	Elliott [111]	GHB, MDMA, cocaine, cannabinoids	Urine=2033 mg/l Plasma=551 mg/l	Collapsed outside pub, ?alcohol and GHB ingested
13	17 yr M	Elliott [111]	GHB	Plasma=200 mg/l	Possible or suspected overdose of GHB
14	20 yr M	Elliott [111]	GHB, cannabinoids	Urine=5 mg/L Plasma=140 mg/m	Possible or suspected GHB ingested; respiratory arrest
15	M	Elliott [111]	GHB, morphine, cocaine, benzodiazepines	Urine=432 mg/l Plasma=133mg/l	No information
16	20 yr M	Elliott [111]	GHB	Urine=1689 mg/l Plasma=306 mg/l	GHB/GBL ingested
17	25 yr M	Elliott [111]	GHB, amphetamine	Urine=1898 mg/l Plasma=233 mg/l	Possible or suspected GHB ingested
18	F	Elliott [111]	GHB	Plasma=182 mg/l	? GHB and 'ecstasy' ingested; self discharged
19	25 yr M	Elliott [111]	GHB, morphine, benzodiazepines	Urine=763 mg/ml	Ingested GHB/GBL 2 hours prior; fitting
20	39 yr M	Elliott [111]	GHB	Urine=391 mg/ml	Ingested GHB in pub; comatose
21	30 yr M	Elliott [111]	GHB	Plasma=304 mg/l	Fitting, decreased consciousness
22	17 yr M	Elliott [111]	GHB, cannabinoids	Urine=333 mg/l Plasma=260 mg/l	GCS 3, unexplained sedation
23	22 yr M	Elliott [111]	GHB, MDMA, cocaine, ketamine, ephedrine	Urine=1825 mg/l	GCS 7 following respiratory arrest; awoke within 3 hours
24	22 yr M	Elliott [111]	GHB, amphetamine	Urine=1219 mg/l Plasma=434 mg/l	GCS 3, awoke within a few hours
25	M	Elliott [111]	GHB	Urine=4687 mg/l Plasma=180 mg/l	Possible or suspected overdose of GHB and 'ecstasy'
26	26 yr M	Elliott [111]	GHB, MDMA	Plasma=154 mg/l	Possible or suspected overdose of GHB
27	14 yr M	Elliott [111]	GHB	Urine=2608 mg/l	Found unconscious, given GHB by a friend
28	32 yr M	Elliott [111]	GHB	Urine=2388 mg/l	No information
29	12 yr M	Elliott [111]	GHB	Urine=979 mg/l	GHB administered by third party ?; GCS 3
30	21 yr M	Elliott [111]	GHB, MDMA, cocaine	Urine=1284mg/l Plasma=252 mg/l	Ingested GHB and alcohol
31	30 yr M	Elliott [111]	GHB, benzodiazepines	Urine=403 mg/l Plasma=239 mg/l	Possible or suspected overdose of GHB
32	38 yr M	Elliott [111]	GHB	Urine=1410 mg/l Plasma=303 mg/l	Possible or suspected overdose of GHB
33	32 yr M	Elliott [111]	GHB	Urine=4528 mg/l	Possible or suspected overdose of GHB; GCS 3

34	24 yr F	Strickland et al. 2005 [88]	Cannabinoids, 1,4-butanediol, GHB and methamphetamine	Final GHB blood level=1200 mg/l	Friends reported use of 4 mL GHB 5 hours prior to presentation; intubated and ventilated following respiratory arrest; remained sedated for 14 hours.
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*GCS=Glasgow Coma Score (3- no response to 15 - wakeful)

Table 4 Fatalities Involving GHB

Case No.	Patient Details	Reference	Drugs detected	Concentration(s)	Comments
1	42 yr M	Ferrara et al. [61]	GHB + morphine + 6-MAM [#]	Blood GHB = 12 mg/l Urine GHB = 258 mg/l Blood morphine = 770 µg/l Blood 6-MAM = 29 µg/l	Heroin user, used GHB (Alcover TM)
2	21 yr M	Davis [113]	GHB + ethanol	Blood GHB = 291 mg/l Blood ethanol = 100 mg/dl	Ingested GBL ("Blue Nitro")
3	26 yr F	Davis [113]	GHB + ethanol	Blood GHB = 721 mg/L Blood ethanol = 170 mg/dl	Ingested GBL ("Blue Nitro")
4 *	21 yr F	Hale [114, 99]	GHB + ethanol	Blood GHB = 356 mg/l Blood ethanol = 47 mg/dl	At a party ingested GHB product "Seventh Heaven"
5	18 yr M	Mozayani et al. [115]	GHB + cocaine + ethanol	Post-mortem (PM) Blood GHB = 309 mg/L Peri-mortem Blood GHB = 300 mg/l PM Blood ethanol = 160 mg/dl PM Blood cocaine = 40 µg/l	Admitted to hospital unresponsive and in respiratory failure.
6	26 yr M	Caldicott et al. [116]	GHB + fluoxetine + nortriptyline	Post-mortem: blood GHB , 10 mg/L, urine GHB , 90 mg/l Blood: carboxyhaemoglobin level, 21% saturation; Fluoxetine, 0.17 mg/l Nortriptyline, 0.28 mg/l	Found dead in the car with the hose attached to the exhaust
7	38 yr M	Caldicott et al. [116]	GHB	Postmortem: blood GHB, 77 mg/l	Found dead in apartment
8	22 yr M	Caldicott et al. [116]	GHB	Antemortem: blood GHB, 220mg/l; serum 250mg/l (both tests on admission to hospital 4-5 hrs after ingestion of 1,4-butanediol ±GHB)	Brain dead at arrival to hospital
9	31 yr F	Caldicott et al. [116]	GHB+ cannabis + cocaine	Postmortem: blood GHB, 50 mg/l; blood: cannabis; cocaine 0.28mg/l	Substances found at scene and tested
10	24 yr M	Caldicott et al. [116]	GHB + cannabis	Postmortem: blood GHB, 40 mg/l; urine: traces of cannabinoids	Fall from height; history of depression; containers of 1,4-butanediol found at scene
11	24 yr M	Caldicott et al. [116]	GHB + alcohol	Postmortem: blood GHB, 370 mg/l; blood alcohol level, 0.2 g/100ml	Consumed 'fantasy' at home

12	42 yr F	Caldicott et al. [116]	GHB + alcohol	Postmortem: blood GHB, 210 mg/l; blood alcohol level, 0.127 g/100ml	Cruise ship passenger; died after intercourse. History of asthma
13	35 yr M	Caldicott et al. [116]	GHB + cocaine + MDMA	Antemortem: blood GHB, 210 mg/L; urine GHB, 230 mg/l; urine cocaine metabolites and MDMA (3mg/l), none in blood	Ingested 30ml GHB. No pulse or respiration when ambulance arrived; regained pulse after CPR but life support terminated 2 days later
14	35 yr M	Caldicott et al. [116]	GHB+ MDMA+p hentermine	Postmortem: blood GHB, 230 mg/l; urine GHB 8.2g/l; Postmortem blood: MDMA (<1mg/l), phentermine 0.1mg/l:	Consumed alcohol and 'fantasy' .Collapsed outside hotel
15	21 yr M	Caldicott et al. [116]	GHB +methamp hetamine +amphetamines	Postmortem: blood GHB, 150 mg/l; urine GHB, 82 mg/l; antemortem blood: alcohol , methamphetamine 0.3 mg/l, amphetamines <0.1 mg/l	Ingested unspecified amount of "liquid E" at nightclub one hour before presenting to hospital

*** First reported death in the United Kingdom (08.09.95)**

6-MAM = 6-monoacetylmorphine (heroin metabolite)

From 1990 to 1997, approximately 60 deaths in the USA were linked to GHB [82]. In Europe, approximately eight GHB-related deaths have been reported since 1995 - United Kingdom (four deaths – September 1995, March 1996, November 1997 and January 1999), Sweden (two deaths – February 1996 and March 1997) and Finland (two deaths – 1998 and 1999) [78-79, 98-99]. Caldicott *et al.* [116] confirmed ten cases of GHB-associated deaths in Australasia, eight of which were directly attributable to GHB. Positive alcohol toxicology was present in only two cases causing the authors to conclude that “GHB overdose is associated with fatalities, and that fatal overdoses occur in the context of isolated use.” One death in New Zealand [117] and two in the United States [90] were linked to the use of 1,4-BD. There was no evidence of use of alcohol or any other substances except 1,4-BD. Table 4 shows reported cases involving GHB or GBL ingestion. Due to *in vivo* conversion of GBL to GHB, only GHB is detected in biological fluids analysed in such cases.

Four additional reported GHB-related deaths involved blood GHB concentrations ranging from 27 mg/l to 121 mg/l [109,115,]. Many other fatalities apparently involving/attributed to GHB have been reported in both the printed media and on the Internet, particularly in the USA [118]. The majority of cases have involved the “recreational” misuse of GHB for its apparent euphoric or “high” effects, primarily by young people. However, in certain cases there was a suggestion of alleged surreptitious administration of GHB via a “spiked drink”.

The total number of global GHB fatalities could be as high as one hundred or more. Without detailed analysis and assessment of each case, however, such numbers should be considered to be only estimates.

There are certain factors that should be noted in GHB cases:

1. The presence of other substances (particularly alcohol and opiates e.g. heroin, codeine, dihydrocodeine and morphine).
2. Some researchers describe the presence of GHB in postmortem blood specimens, in cases where there has been no evidence of GHB use.
3. The GHB concentration found is sometimes low.

The mode of misuse of GHB frequently involves the use of other substances whether it be alcohol or MDMA, therefore, deaths involving solely GHB are very rare. The presence of alcohol and other depressant or psychoactive substances is widely believed to exacerbate the toxic effects of GHB ingestion. Therefore, the presence of such substances in deaths involving GHB should be taken into consideration when assessing fatalities attributed to GHB intoxication. Ferrara *et al.* reported a death involving GHB and heroin (diacetylmorphine) [61]. A high concentration of morphine was detected in the blood (770 mg/l). In five other reported GHB deaths, ethanol has also been involved at significant concentrations [98, 113-114]. In these cases, the mechanism of death was reported to be respiratory depression.

Recently, several researchers have reported that GHB was present in significant concentrations in postmortem blood, even in cases where the decedents had died in circumstances apparently unrelated to GHB [119-121]. In 1998, Fieler, Coleman and Baselt detected GHB in 15 out of 20 postmortem blood specimens analysed [119]. The apparent concentrations ranged from 3.2–168 mg/l (average = 25 mg/l) using GC-MS analysis. Subsequent reanalysis using GC-FID confirmed these findings. No GHB was detected in the blood or urine of living patients, in addition, no GHB was detected in 8 postmortem urine specimens analysed. They suggested therefore, that in cases involving possible GHB ingestion, postmortem urine should be analysed and that GHB is a product of postmortem decomposition. Further work by Stephens, Coleman and Baselt published in 1999, indicated that certain storage conditions could elevate the concentration of GHB in postmortem blood samples; namely if the sample was stored in a nonfluoridated container above 4°C [121]. Again, they found concentrations within a range of 9 to 433 mg/l in postmortem blood (average = 57 mg/l) and only detected GHB in 3 out of 17 postmortem urine specimens. These data have profound implications for the interpretation of postmortem GHB concentrations; therefore, it is imperative that further work is performed to confirm these conclusions.

In the majority of GHB-related deaths, the concentration in postmortem blood has been found to be elevated; however in several cases, the concentration was found to be relatively low, e.g. less than 50 mg/l. Such concentrations are within the range of GHB concentrations apparently produced postmortem, as stated above. Furthermore, in living persons, similar concentrations have been detected in unconscious patients who awake a few hours later with no obvious side-effects. Due to the rapid absorption and metabolism of GHB, however, it is difficult to predict how much of the original dose such postmortem concentrations represent. Recent data indicates that lower levels might be used if only serum is collected or if the whole blood sample is frozen immediately after collection and the procedure well documented [122].

The WHO Uppsala Monitoring Centre (UMC) reported over a 2-year period of worldwide post-marketing surveillance (PMS)-data five cases of death (0.5 %) and no

cases of sudden death out of 988 reported adverse effects (unpublished, communication to WHO, 2005).

Finally, mention should be made of a recent international public health problem related to GHB. This involved a toy called 'Bindeez'. It consisted of plastic (magic) beads that when sprayed with water, stuck to surfaces, allowing the creation of colourful designs. Ingestion of these beads by children led to a comatose state. Thanks to rapid diagnosis and publications by Australian physicians and scientists, it was discovered that the toxic agent was 1,4-BD which is rapidly metabolized to GHB, and was responsible for the observed toxicity. Widespread reporting of the findings led to further reports and an international recall of the toy beads [123-124].

In conclusion, more research and thorough analysis of GHB in fatalities and poisonings are still required before the true involvement of GHB can be established and accurate mortality and morbidity figures produced.

7. Dependence potential

Animal Studies

In their review [125], Nicholson and Balster state that: "Primary physical dependence to GHB has not been examined in controlled animal studies." It had been reported that, in morphine-dependent rhesus monkey, GHB had partially substituted for morphine but not at higher doses [126]. Recently, however, Colombo *et al.* [127-128] reported a reproducible withdrawal syndrome for GHB and its precursors (1,4-BD and GBL) in alcohol-preferring rats. Finally, a series of papers from Goodwin *et al.* [129-131] examined the acute and chronic effects of GHB and GBL in the baboon. They clearly described 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.

Human Studies

There is evidence that GHB can produce tolerance and withdrawal as demonstrated as demonstrated by a withdrawal syndrome when the substance is abruptly discontinued following regular, chronic use. Although several cases of withdrawal from GHB and its precursors have been documented [132-136] the clinical features have not been fully characterized [137]. However 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 [138]. These symptoms can progress to severe delirium with autonomic instability in frequent, heavy users (every 1-3 hours 24 hours per day) [134]. One case of seizures related to GHB withdrawal [139] and one death due to complications of GHB withdrawal [134] have been reported. There is also some evidence that tolerance and withdrawal may occur in recreational users [140-141]. GHB withdrawal has recently been reviewed [137, 142-143].

8. Abuse potential

Animal Studies

In 2001, Nicholson and Balster published a review [125] on GHB, which summed up the preclinical abuse liability data available at that time. They concluded that: "Abuse potential assessment of GHB using standard animal models has not yielded a picture of a highly abusable substance, but little human testing has been done." For instance, rat drug discriminative stimulus studies "suggest that GHB administration produces unique discriminative effects with some characteristics most similar to those of ethanol and some GABA-mimetic drugs with different doses of GHB." A number of recent drug discrimination studies [144-147] have added little to the picture except to extend the mechanistic relationship between GHB and GABA systems and to demonstrate the precursors 1,4-BD and GBL are discriminated as GHB.

The early studies on the reinforcing effects of GHB were also not indicative of a profile of a highly abused substance. Thus, conditioned place preference (CPP) studies suggested a weaker effect compared to highly abused substances such as cocaine. Extensive self-administration studies in mice, rat and primates by both the oral and intravenous routes of administration were carried out. Again, overall results indicated that GHB is not as reinforcing as other highly abused substances. Little new has been published in this area. Leonard *et al.* have extended previous studies by Colombo *et al.* on GHB and ethanol interactions [148]. They reported that only a high sedative dose of GHB affected the intake of ethanol in rats. Winger [149] testing the hypothesis that "use of ethanol in combination with sedative and stimulant drugs is due to an ability of ethanol to enhance the reinforcing effects of these drugs," found that GHB and flunitrazepam did not do so.

Human Studies

The ability of a substance to produce reinforcing effects is the primary determinant of whether the substance will be misused. These effects may be positive reinforcers (e.g., producing pleasurable subjective effects) or negative reinforcers (e.g., alleviating negative states). For hypnotic substances, including GHB, some symptoms of withdrawal upon discontinuation (e.g., insomnia, anxiety), may potentiate 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. Griffiths and Johnson [150] used these factors to compare the relative abuse liability of several hypnotic substances. GHB's significant 'likelihood of abuse' was evident when it was ranked 6th out of 19 hypnotic substances (after pentobarbital, methaqualone, diazepam, flunitrazepam and lorazepam). These were compared taking into account animal and human abuse liability studies and observed rates of abuse. In addition, GHB was ranked 2nd only to pentobarbital with respect to toxicity taking into account withdrawal severity, cognitive impairment and, in particular, lethality in overdose.

A later more detailed well-controlled abuse liability study in man from the same laboratory was carried out [151]. They compared the psychomotor, subjective and cognitive effects of subtherapeutic doses of triazolam, pentobarbital and GHB. They concluded 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.”

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

GHB has been evaluated for various potential therapeutic uses including: obstetrics, anaesthesia, alcohol/opiate withdrawal and treatment of narcolepsy and cataplexy.

Use of GHB in obstetrics

Laborit observed that in women in labour, GHB had a “spectacular action on the dilation of the cervix”, an effect which was apparently independent of the anti-anxiety and reduced consciousness obtained [12]. Furthermore, in 1962, Barrier reported that GHB was beneficial in obstetric surgery due to the absence of respiratory depression in the infant and its antishock property against possible cardiac anoxia [12].

Anti-anxiety effects of GHB

Several researchers have observed an anti-anxiety effect of GHB, this was reported in a preliminary study by Danon-Boileau *et al.* in 1962, involving schizophrenic patients. A dose of 500 mg of GHB four times a day produced a temporary “disinhibiting effect” and relaxed the patients [12]. However, a large proportion of reports regarding GHB’s anti-anxiety effects appear to remain anecdotal.

Sexual Enhancing effects of GHB

In 1972, Laborit remarked on GHB’s “aphrodisiac” actions on man. There have been many anecdotal reports which suggest that GHB has four sexual enhancing effects: disinhibition (e.g. relaxation), heightened sense of touch, enhancement of male erectile capacity and increased power of orgasm [152]. Club drugs such as MDMA, GHB and ketamine are used for their ability to decrease social inhibitions and are popular among gay and bisexual men who attend circuit parties and other social gatherings. These substances also appear to promote high risk sexual behaviours that have been associated with increased HIV infection [153].

Antidepressant effects of GHB

The clinical evidence pertaining to GHB’s possible antidepressant effects are largely anecdotal. However, Laborit suggested that the increase of acetylcholine and dopamine levels in the brain and the apparent increase in cerebral protein synthesis, serotonin turnover and aspartic acid levels by GHB, may correct metabolic disturbances secondary to depressive states [12].

GHB as an anaesthetic agent

In the 1960s, early work involving GHB assessed its potential as an anaesthetic agent [12, 71, 64]. Anaesthetic doses within the range 60-70 mg/kg were given intravenously to a patient. GHB has been reported to be involved in over 6000 cases in general anaesthesia, Laborit noted various advantages compared to other general anaesthetics, including: nonhypotensive bradycardia, muscle relaxant properties, absence of respiratory depression while the response of the respiratory centre to CO₂ is maintained, antishock activity, allows easy induction and maintenance of hypothermia, no venous irritation and apparent low toxicity. However, various disadvantages have also been

noted including: lowers serum potassium levels, duration of action is too unpredictable, only produces complete general anaesthesia in children, poor pain control and the autonomic nervous system remains active – therefore other agents are required such as opioid analgesics or nitrous oxide. GHB was introduced in Europe in 1964 as an intravenous anaesthetic induction agent to be used especially in children. A high incidence of petit mal (absence) and grand mal seizures and vomiting limited its use [154, 155]. GHB is still approved for anaesthetic use in Italy and France although its use is declining [156].

Use of GHB in the treatment of narcolepsy and associated cataplexy

Various researchers have studied the use of GHB as a potential treatment for narcolepsy [69, 157-160] due to its sleep-inducing properties (see Section 3 - Effects on Brain Function). It was thought that in narcoleptic patients, GHB would act to “normalise” sleep patterns and reduce the problems associated with disorders such as cataplexy (sudden loss of muscle tone), sleep paralysis, daytime-drowsiness and hypnagogic events (hallucinations that occur at the onset of sleep). Mamelak obtained clinical data on 48 narcoleptic patients who had been treated with GHB for up to 9 years. As GHB-induced sleep wears off after about 3-4 hours post dose, patients took 2.25-3.0 g of GHB two or three times a night (i.e. upon waking) [69]. Within the first few weeks of treatment, many of the patients reportedly felt more alert during the day and there was a reduction in hallucinations, cataplexy and sleep paralysis (although this did intensify on the first or second night). A degree of weight loss was also reported in some obese patients. Daytime drowsiness continued to occur in many of the patients and some were prescribed stimulants such as Dexedrine as part of their treatment regimen, in order to achieve the optimal levels of sleep at night and wakefulness during the day. Symptoms appeared to intensify during periods of stress. Other studies noted the occurrence of intermittent episodes of sleepwalking in some GHB-treated patients and if sleep was resisted the patient became confused and emotionally labile [69, 158]. In 2002, Xyrem® (GHB) was approved by US FDA for the treatment of cataplexy in patients with narcolepsy. The Xyrem® International Study Group [161] reported that approval was largely based on the results of two efficacy trials [162-163] and one safety trial [164]. The results of a recent double-blind placebo-controlled study of 228 narcoleptic patients provide further evidence of the efficacy of sodium oxybate for the treatment of cataplexy. Sodium oxybate (4.5, 6, or 9 g) was found to significantly decrease the number of weekly cataplexy attacks. The improvements in cataplexy appear to depend on dose as well as duration of treatment [165]. A recent review [166] sums up the current therapeutic status of the medicine in the management of narcolepsy.

Use of GHB in alcohol and opiate withdrawal

The use of GHB in alcohol withdrawal has been investigated by various researchers. In 1989, Fadda *et al.* treated alcohol-dependent rats with GHB (at various doses), ethanol or a placebo, 8 hours after the last dose of alcohol [167]. The degree of withdrawal tremor was observed. It was found that GHB appeared to reduce the tremor over a 2-hour period. GHB has also been shown to inhibit voluntary ethanol consumption in ethanol-preferring rats [168]. Since there is cross-tolerance between GHB and alcohol, GHB has been investigated in the treatment of alcohol detoxification and to prevent relapse to alcohol dependence. The limited evidence supporting the efficacy of GHB in attenuating or preventing symptoms of alcohol withdrawal includes the results from one randomized, placebo-controlled double-blind study (GHB, n=11, placebo, n=12) [169] one randomized controlled single-blind study (GHB, n=60, diazepam, n=60) [170], one

report of two open label studies (n=22 and n=287) [171] and one double-blind, comparative study (GHB 50mg/kg n=33, GHB n=33 and clomethiazole n=32) [172]. With respect to reducing alcohol consumption and cravings, 3 months' treatment with GHB was found to be more effective than placebo in a randomized, double-blind study of 82 alcohol-dependent individuals [173]. In an open label study of 179 alcohol-dependent patients, 43 individuals were abstinent at 6 months and 30 individuals abstinent at 12 months following 6 months of GHB treatment, suggesting a role for GHB in relapse prevention [174]. Significantly, 10% of the subjects in this trial showed craving for GHB and increased their dosage 6 to 7 times the recommended levels. The clinical significance of the results of this group of studies has been questioned based on methodological concerns [175]. Overall, the utility of GHB as a substitution agent for alcohol is limited by its short half-life and its significant abuse potential.

The data supporting the use of GHB in opioid withdrawal is very limited. In a randomized double-blind placebo-controlled study, 22 male heroin users and 19 males maintained on methadone were admitted to hospital for opioid detoxification. An acute dose of GHB significantly decreased withdrawal symptoms (with the exception of insomnia and diarrhoea) in both the heroin and methadone groups compared to placebo measured out to 3 hours. Individuals randomized to receive GHB continued to receive GHB in an open study design for 8 days. No withdrawal symptoms were evident before or after a naloxone challenge [176]. In contrast, in another study, pre-treatment with GHB did not attenuate the severity of naloxone-precipitated withdrawal in 8 opioid-dependent patients [177].

The exact mechanism of GHB-enhanced alcohol and opiate withdrawal is not known. However, a profound inhibition of dopamine output in the nucleus accumbens and ventral caudate nucleus has been associated with alcohol and opiate withdrawal syndromes [178-180] and increased dopamine output is known to be involved in the rewarding effects of morphine and alcohol [181]. Therefore, it is possible that GHB suppresses these symptoms as it increases the dopamine levels in these regions of the brain and maintains the dopamine reward pathway.

10. Listing on the WHO Model List of Essential Medicines

Oxybate (GHB) is not listed.

11. Marketing authorizations (as a medicine)

Austria, Canada, Denmark, Germany, Great Britain, Finland, France, Ireland, Italy, Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland, United States of America.

12. Industrial use

GHB is used in the production of a wide variety of polymers. In addition, GBL and 1,4-BD are used as solvents in various industrial processes (e.g. production of polymers) and GBL as the starting material for other products (e.g. polyvinylpyrrolidone, methionin, piperidine).

13. Non-medical use, abuse and dependence

Common recreational doses of GHB are in the range of 1.8 to 2.7 grams, a large amount compared with most other sedative medicines, which can be active in amounts measured in milligrams. Doses required to induce complete sedation are even higher in most individuals.

At present, GHB appears to be mainly used and abused in the United States and Europe, where it was reported by the United Kingdom, Italy, The Netherlands, Belgium, Sweden, Finland, Ukraine, France, Spain, Switzerland, Czechia and Denmark). Australia reported minimal abuse. Due to the various effects of GHB and the various groups of people using the compound, it has a wide-ranging abuse potential.

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 627923 drug-related ED visits of which only 990 involved GHB. Later DAWN data [182] indicates a continued low incidence of GHB ED visits and a continued downward trend. Thus, in 2004 there was a total of 1253956 misuse/abuse ED visits. Of these, 2340 were attributed to GHB (0.19%). In 2005, the total ED visits was 1449154. Of these, 1861 were attributed to GHB (0.13%). Later DAWN reports indicated a continued trend towards lower attributions to the GHB. This was difficult to determine precisely because of its inclusion among "Club Drugs." Addiction Comprehensive Emergency Department reports from Spain, Sweden and U.S.A should be noted (see discussions below).

Additional United States trend data can be found in the NIDA Proceedings of the Community Epidemiology Work Group [183]. 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. Instances of GHB use has been reported in France, Denmark, Germany, Belgium, Finland, The Netherlands, Spain, Sweden, Norway and the United Kingdom [98-105, 184-185]. 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 from Belgium, the Czech Republic, Denmark, Estonia, France, the Netherlands, Sweden, Finland, the United Kingdom and Norway [101-105, 186, 188]. The latest report from this group [188] 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 helplines 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 [188]. In its last report the EMCDDA stated “recreational use of ketamine and GHB- both anesthetics, and widely used in human and veterinary medicine for 30 years has been reported in certain settings and among sub-groups of substance users in Europe. The illicit use of these substances has become a cause for concern for treatment services in a limited number of European countries [189].”

Initially abused by bodybuilders, it appears that GHB is now increasingly part of the dance music culture, which has involved the use of stimulant substance such as amphetamine and MDMA for many years. However, due to its many properties, GHB use is not solely associated with “ravers” and therefore has the potential for a global abuse problem. The US Drug Enforcement Administration (DEA) has amended its regulations to require additional recordkeeping and reporting requirements for products that contain GHB. The DEA made these changes under section 4 of the “Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act”. These changes were made to protect against diversion of GHB for illicit purposes [190]. Orphan Medical Inc., the pharmaceutical company that makes Xyrem® has taken precautions to minimize diversion and abuse of this product in the US by creating a proprietary drug distribution system called the Xyrem® Success ProgramSM. Some of the components of the system include a centralized distribution and dispensing system, patient and physician registries and a method for tracking prescription shipments [156]. There have been many reports in the media, highlighting various adverse effects of GHB (e.g. incidents of intoxication or death) which may lead to a negative perception of the substance by potential abusers. However, other sources, particularly the Internet and some books advocate the use of GHB, but most do state general precautions such as avoid concurrent alcohol and substance intake.

Out of a global database of 998 reported adverse effects, covering a 2-year period, the Uppsala Monitoring Center (UMC) reported, as far as it concerns dependency related adverse effects: 10 cases of withdrawal syndrome (1.0 %), 1 case of withdrawal convulsions (0.1 %), 1 case of withdrawal headache (0.1 %), 7 cases of substance abuse (0.7 %) and 1 case of substance dependence (0.1 %) (unpublished, communication to WHO, 2005).

In the 2005 WHO questionnaire, Sweden reported that GHB abuse is considered problematic. However, in other countries abuse was less severe: France reported widespread but isolated cases, Spain increasing use among young people and increasing number of intoxications, Finland some abuse by the younger generation. Poland reported that GHB was not very popular, although its use was increasing. Belgium reported 31 to 51 cases of use per year.

Several countries reported the prevalence of use:

Australia: 0.1% last month use, 0.5% lifetime use; 4% of users are dependent
Israel: 0.1% of age among 18-40 years old
Denmark: 1% lifetime use among 15 and 16 year olds
Czech republic: 0.9% last 30 days use, 2.1% last year, 6.7% lifetime

USA: last year use decreased from 2002 to 2005 and the average age of users was higher.

Similar data became available in 2005 and 2006 for college students and young adults (see Table 5).

Table 5 GHB use in students and young adults*

	2002	2003	2004	2005
8 th Grade	0.8	0.9	0.7	
10 th Grade	1.4	1.4	0.8	
12 th Grade	1.5	1.4	2.0	
College Students	0.6	0.3	0.7	
Young Adults	0.8	0.6	0.5	0.3

Again, incidence was lower and trended down over time [191,192].

*However, latest data from the U.S. national Institutes on Drug Abuse "Monitoring the Future National Results an Adolescent Drug Use" indicate that the annual prevalence of GHB use in 2008 was 1.1%, 0.5% and 1.2% in grades 8, 10 and 12, respectively [193].

Switzerland reported that out of 354 cases of hospitalization for reason of poisoning in the years 1997-2005, 71% (2.1%) were caused by abuse, 10% (6.4%) possible abuse, 9% (47%) accidental, 5% (0.01%) criminal, 0% (4.1%) other. For all medicines, these percentages were 2.1% for abuse, 6.4% for possible abuse, 47% for accidents, 0.01% for criminal use and 4.1% other. Multisubstance use was reported for 77 out of 250 cases, of which 33 were in combination with alcohol. Between 1996 and 2004, 36 GHB related deaths were reported in Sweden plus many cases of poisoning. The Netherlands reported that there were never fatal cases due to overdose reported. In Finland, there were 1 or 2 cases yearly. France registered several cases of dependency in 1999 and 2001. In the USA, GHB-related ED visits increased from 145 in 1995 to 4969 in 2000 and, after scheduling it under the Controlled Substances Act in 2000, then stabilized to the level of about 3330 cases in 2001 and 2002 (DAWN data).

A later WHO questionnaire in 2008 (see Annexe 1) added little to the extent of abuse. Of 51 countries responding, 14 reported on the use of GHB in a harmful way. Australia reported increasing misuse of GHB. From March 2001 to October 2005 there were 618 GHB related ambulance attendees in the city of Melbourne; 362 involving GHB and 256 involving the concurrent use of GHB and other substances. More recent reports from Spain, Sweden and USA should also be noted. A total of 505 patients with GHB poisoning or overdosing were admitted to the emergency department of the Hospital Clinic (Barcelona) during the period 2000 to 2007. Reduced consciousness was the most common manifestation [194]. In a report from Sweden, 23 deaths were identified as due to GHB overdose. 91% coingested other substances [195]. In a case series of 226 GHB associated deaths, 213 had cardio respiratory arrest and 13 had fatal accidents [196]. 35% had no cointoxicants. Postmortem blood GHB was 18 to 4400 mg/L (median, 347 mg/L) in deaths negative for cointoxicants. Sixteen deaths involved "supplements" and 1 involved pharmaceutical GHB (Xyrem®).

The most recent substance abuse indicators demonstrate that abuse in the USA has stabilized and involves GHB of clandestine manufacture primarily and is not the result

of diverted pharmaceutical product (Xyrem®). Post marketing data for Xyrem® have not revealed evidence of abuse of this product. From July 2002 to September 2004, 5869 patients were registered for Xyrem® use. There are five reports submitted to the HHS/FDA from the central pharmacy involving stolen Xyrem® bottles. Although GHB is currently controlled, it continues to be abused in the United States, fueled by illicit production in clandestine laboratories and illicit sales by trafficking organizations and internet pharmacies.

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

GHB is invariably obtained in the form of a powder (either loose or sometimes in a capsule) or a liquid formulation, therefore, the primary route of administration is oral. However, it does not preclude the possibility of the powder being "snorted" or "smoked" or the liquid being injected – although there are no *confirmed* reports of these routes of administration. GHB can easily be manufactured in the home from inexpensive ingredients and recipes obtained from the Internet [192]. The powder (usually GHB sodium salt) is invariably mixed with water prior to consumption. Many of the dangers associated with illicit GHB use are due to variances in the GHB concentrations of such solutions. Furthermore, the concentration of "pre-prepared" liquid solutions can also vary considerably. Many websites and books which advocate GHB use suggest that an individual "finds the dose they are comfortable with" and "take GHB on an empty stomach for a more rapid effect" [1]. This is due to the fact that GHB appears to "affect different people in different ways" i.e. a euphoric dose for one person could be a sedative dose for another [77]. The steep dose-response curve of GHB could also cause problems in terms of the user selecting the required dosage or taking subsequent doses in quick succession.

However, it is generally suggested that a 0.5 g dose be taken for relaxation and disinhibition, a 1g dose for euphoric effect and a 2-3 g dose for deep sleep [79-80, 1]. The average dose is reported to be between 1 to 5 g [192]. A dose of less than 1 g acts as a relaxant with loss of muscle tone and decreased inhibitions; 1 to 2 g causes increased relaxation with bradycardia, slowed respiration, and interference with blood circulation, motor control and balance; and doses of 2 to 4 g cause marked interference with motor and speech control and possibly a coma-like sleep which may require intubation to wake the user. GHB is frequently mixed with alcohol thereby enhancing its CNS depressant effects. This may lead to respiratory depression, loss of consciousness and coma [192].

A recent double-blind, placebo-controlled study of individual and combined effects of GHB and ethanol was carried out in human volunteers by Thai *et al.* [187]. They concluded that "modest doses of GHB do not affect haemodynamic function, but O₂sat was decreased. Gamma-hydroxybutyrate-plus-ethanol resulted in more adverse effects, including gastrointestinal disturbances, hypertension and decreased O₂sat but only minimal pharmacokinetic interactions were observed.

It appears that GHB or related products (e.g. GBL and 1,4-BD) are used by various groups of people, including; bodybuilders, insomniacs, narcoleptics, opiate misusers/alcohol abusers (as a withdrawal aid), people looking for a "high" and some

anti-ageing groups. The use and abuse of GHB appears to have increased since 1990 and may be linked to the increased presence of GHB related websites on the Internet. Bodybuilders exploit the possible growth hormone promoting properties of GHB in an attempt to increase muscle mass. GHB is therefore illicitly sold/distributed in gymnasiums or advertised on the Internet on related websites. Some people therefore erroneously refer to GHB as an anabolic steroid, which is not the case, as its chemical structure does not resemble a steroid. Conversely, other people sometimes use GHB as an apparent appetite suppressant or weight loss product, although there is very little definite scientific data to support these claims. Due to GHB's sleep-inducing effects, various people suffering sleep disorders such as insomnia or narcolepsy use GHB products to normalize their sleep patterns. Opiate misusers or alcohol abusers have used GHB illicitly or under clinical supervision (primarily in Europe) in order to alleviate withdrawal symptoms associated with cessation of opiate or alcohol usage. If taken unsupervised or abused there is the potential for coadministration of opiates or alcohol, resulting in serious toxicity and possibly death (as demonstrated by Fatal Case 1 – Table 4).

Some groups have actively promoted (usually via the Internet) the potential anti-ageing affects of GHB due to claimed indirect antioxidant properties of the compound by stimulating the glial cell pentose phosphate pathway producing NADPH for the reduction of oxidised glutathione [197]. GHB is also used as a sexual adjunct to enhance libido and sexual function, by both heterosexuals and homosexuals. Therefore, various GHB or related preparations are also sold in “sex shops”. However, by far the primary mode of abuse, worldwide, has been the use of GHB for its subjective hypnotic, euphoric and hallucinogenic properties. Although some users reportedly use GHB “to relax”, many users attempt to attain a desired “high”, similar to that sought from “Ecstasy” (e.g. MDMA). Hence, liquid GHB is sometimes referred to as “Liquid Ecstasy”, “Liquid X” or “Liquid E”, although the mode of action and chemical structure of MDMA and GHB are considerably different. GHB has therefore been found to be associated with social gatherings such as parties, nightclubs, dance events (e.g. “raves”), drinking establishments, etc. Some insight into the reasons underlying the use of GHB may be found in a study by Sumnall *et al.* [198]. They found that “GHB was more commonly used within the home (67%) compared to nightlife environments (26.1%).” “The most frequently reported primary GHB use functions were for recreation (but not in night clubs) (18.3%); to enhance sex (18.3%); to be sociable (13.1%); and to explore altered states of consciousness.” In such situations there is the danger of concomitant ingestion of other substances or alcohol, which will potentiate the effects of GHB. The majority of reported hospital admissions and deaths have been related to such instances of abuse.

Recently, there has been the suggestion that GHB has been allegedly used for illicit sexual activity or substance facilitated sexual assault (“date rape”), due to the potential incapacitating and sleep-inducing effects of GHB (and GBL or 1,4-BD) [199-203]. As GHB is colourless and easily dissolves/mixes in aqueous solutions (e.g. water and other liquids) it can be surreptitiously introduced into beverages. The required dosage to cause such effects, however, may require the introduction of possibly large noticeable quantities of GHB powder or liquid depending on the formulation and purity of the GHB used. Furthermore, if GHB sodium salt or solution is used, a slight salty taste may be noticeable, particularly if introduced into a previously tasteless liquid such as water [1]. Despite this, the use of GHB in such illicit activity is a contentious area of GHB

abuse, as unfortunately, it is usually difficult to prove, given the rapidity of GHB metabolism and elimination.

Thus, combined with the information presented in Section 12, the overall data indicates that the abuse of and dependence on GHB continues to be a public health problem. However, the magnitude of the problem has decreased over the past several years.

15. Licit production, consumption and international trade

GHB and related products have been produced and advertised by various companies based in Europe (and in the USA, until 1990) and sold/distributed by health food shops, “sex shops” or via the Internet, usually depending on the control status of the particular country the product is to be sent to.

As GHB was put under international control in 2001 only, very limited data were furnished by Governments to INCB for the year 2001. Currently, 30 countries have reported (annexe 1) that GHB is controlled under substance abuse legislation. With the introduction of national control measures, the number of countries able to report to INCB on manufacture of and trade in GHB has increased. In 2004, Germany (5 tons) and Latvia (4.4 tons) were the main manufacturers of GHB accounting together for 62 per cent of global manufacture. The other main manufacturers were the United States (3.9 tons) and Ukraine (1.5 tons). The main exporters in 2004 were Germany and Latvia, both with 4.6 tons, and the main importer was Italy, with 4.4 tons. During the last three years, 22 countries reported, at least once, the import of more than 1 kg of GHB. Latest data (See Annexe 1) indicate that 14 countries authorized GHB as a medical or veterinary product. Twelve countries indicated that they imported the substance.

More recent information from US shows that the legitimate use in 2012 was 47 tons (Annex 2).

16. Illicit manufacture and traffic and related information

Reports of Illicit Activity and Seizures

Data collected in 2008 (Annexe 1 Report on WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD) show that in total, 13 countries have tracked illicit activities involving the substance. Clandestine manufacturing is reported 8 times, smuggling 7 times and diversion 5 times. Other illicit activities are reported 4 times.

Eight countries reported on the quantity of seizures, the Czech Republic, Denmark, Germany, Lithuania, Norway, the Republic of Korea, Poland and the USA. Most seizures are reported in Norway and in the USA. Norway reported 8.5L/57 seizures in 2005, 18.2L/65 seizures in 2006 and 361L/163 seizures in 2007. In the USA there was a total of 146 substance exhibits reported from 2004-2007. Seizures of upto 47g of powder and a total of 166126 ml of liquid until June 30, 2008 were made. There were a total of 835 GHB exhibits from 2004 - June 30, 2008.

B. GHB Seized Material

Seized GHB material appears to consist of either powder or liquid preparations. Seizures of GBL and 1,4-BD are predominantly in liquid form. Below is a list of some common (mostly previously available) GHB-related products usually sold as “nutritional or dietary supplements” [204]:

“Blue Nitro”	contains	GBL, Vitamin B12 and Potassium
“RenewTrient”	contains	GHB
“Midnight Blue”	contains	GBL
“SomatoPro”	contains	1,4-BD
“Serenity”	contains	1,4-BD
“Enliven”	contains	1,4-BD

GHB and related products are generally perceived to be cheap to purchase compared to other illicit substances, in respect of the cost per effective dose.

In the Annual Reports Questionnaire (ARQ) for 2003 submitted by Governments to UNODC, four Governments reported the seizures of GHB: Australia, Canada, Hong Kong, SAR of China and Lithuania. The largest seizures were reported by Canada (1.7 kg) and Australia (1.3 kg).

In the Annual Reports Questionnaire (ARQ) for 2004 submitted by Governments to UNODC, six Governments reported the seizures of GHB: Canada, Hong Kong SAR of China, France, the Netherlands, Norway and Spain. The largest seizures were reported by Norway (30 kg, including GBL) and the Netherlands (23 kg).

17. Current international controls and their impact

As GHB has been under international control since 2001, it may be assumed that all parties to the Convention on Psychotropic Substances (1971) made GHB a controlled substance. Impact needs to be addressed.

18. Current and past national controls

Data from the 2008 WHO Questionnaire for Review of Psychoactive Substances (Annexe 1) show that 30 countries have controls under legislation

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

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: Evaluation of gamma-hydroxybutyric acid (GHB)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for gamma-hydroxybutyric acid (GHB) by 51 countries.

LEGITIMATE USE

14 countries authorized GHB as a medical or veterinary product. Of the countries that responded to the questionnaire France was the first country to grant market admission in 1961. The most recent distributions on the market were done by Spain and Norway in 2006. The most common registered indication is anaesthetic. It is used in general anaesthesia for small operation procedures, for initial and basic anaesthesia in surgery, gynaecology and obstetrics, especially for patients with hypoxic conditions. Other registered indications are depression, glaucoma, insomnia, narcolepsy with cataplexy, alcohol and opiate withdrawal, psychosis and sedation in neurotraumatology. It is also used for treatment of narcolepsia. Off-label GHB is used as a dietary supplement and as protection against cerebral ischemia for patients with head injuries.

The most common dosage use is 500 mg/ml in an oral solution. A dosage of 250 mg/ml, 200 mg/ml also exist. The reported dosage for injections is 5 ml and 10 ml.

4 countries legitimated GHB for technical use (Forensic analysis, clinical trials and for the laboratory as a standard reference) and 2 countries authorized GHB for other legitimate use (production of medical product - sol. Natrii oxybutyrati- for export and it is currently being studied in a Phase III registration program for the treatment of fibromyalgia syndrome).

12 countries indicated that they import the substance. In Australia and the USA GHB is manufactured as well as imported in the country. The latter indicated that a negligible amount of GHB was imported.

ABUSE

Of the 51 countries responding, 14 countries reported on the use of GHB in a harmful way and 8 countries reported on the extent of the harmful use. When abused, GHB is administered orally (powdered liquid, capsule or crystalline powder form) or injected.

In Australia 0,1% of the general population used GHB at least once in their lifetime. In China the extent of harmful use is mild. In the Czech Republic there is a very marginal use, only several cases were reported. Denmark indicated that in 2006 less than 2% of the youth population between the ages of 16-20 said that they have tried "other drugs", presumably GHB being among them. Since 2000 the GHB seizures made by the police have been registered systematically. From 2000 to 2007 quite a few seizures were made - between 6 and 14 seizures annually. In the Netherlands the extent of the use is sparse; there are small subcultures which use it regularly. In the USA a national high school survey was done among eighth, tenth and twelfth grade students from 2004 to 2007. Data indicates that GHB abuse among this population has slightly decreased from 2006 to 2007.

5 countries reported on the extent of public health or social problems associated with the harmful use of GHB, while 4 countries reported not having information or data related to public health or social problems associated with the harmful use of GHB. Australia reported to have evidence of increasing abuse of GHB. From March 2001 to October 2005 there were 618 GHB related ambulance attendees in the city of Melbourne; 362 involving GHB and 256

involving the concurrent use of GHB and other substances. Most patients were younger than 25 years, that attended public spaces, and had a Glasgow Coma Score < 10.¹ Around 90% of patients were admitted to hospital. In the Czech Republic no case of overdose caused by GHB has been notified till 2007. In Denmark there has been no systematic reporting of either deaths or poisonings caused by GHB, nor has GHB been a contributing factor to deaths or poisonings. Sporadic information on poisonings caused by GHB does exist, but has not been verified.

Germany reported that the main health risk associated with the use of GHB appears to be the high risk of loss of consciousness, especially when the substance is combined with alcohol or other sedative substances. GHB use can also result in other problems including coma, decrease in body temperature, hypotonia, hallucinations, nausea, vomiting, bradycardia and respiratory depression. Dependence to GHB has been observed following prolonged use. Additional health risks may be posed due to possible presence of solvents or heavy metal contaminants. Further Germany indicated that consumers of GHB had to be medicated by an emergency doctor in 15 cases in 2007. In 2006 consumers had been under medical treatment of an emergency doctor in 7 cases. Further GHB was at least one of the causes for the death of a person with polysubstance use.

CONTROL

30 countries reported that GHB is controlled under legislation that is intended to regulate availability of substances of abuse.

In total, 13 countries have tracked illicit activities involving the substance. Clandestine manufacturing is reported 8 times. Smuggling is reported 7 times and diversion is reported 5 times. Other illicit activities are reported 4 times.

8 countries reported on the quantity of the seizures, the Czech Republic, Denmark, Germany, Lithuania, Norway, the Republic of Korea, Poland and the USA. Most seizures are reported in Norway and in the USA. In Norway the following seizures are reported in 2005 8.5L/57 seizures, in 2006 18.2L/65 seizures, in 2007 36L/163 seizures. In the USA there were a total of 146 substance exhibits reported from 2004-2007. Seizures of upto 47 g of powder and a total of 166126 ml of liquid until June 30, 2008 were made. There were a total of 835 GHB exhibits from 2004 - June 30, 2008

IMPACT OF SCHEDULING

2 countries (Armenia and Tuvalu) reported that if GHB is placed under more strict international control, the availability for medical use will be affected.

5 countries reported how a transfer will impact the medical availability.

Armenia reported that the process of medicine prescribing to the patients and getting them from the appropriate place will be difficult and that as a result the access to medicines will be complicated.

Australia indicated that the import and export of GHB to and from Australia is subject to control under Australian Customs legislation, requiring that prospective importers or exporters possess both a license and permit to import or export for each shipment. China reported that GHB is controlled as strict as those in schedule I and II. The Republic of Korea mentioned that GHB is not used for medical purposes, so even if it is included in the international control, it will not be affected a lot. Tuvalu finally reported that restrictions and control mechanisms will make it harder to access proposed quantities because of controls.

¹ The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. A Coma Score of 13 or higher correlates with a mild brain injury, 9 to 12 is a moderate injury and 8 or less a severe brain injury (Teasdale G., Jennett B., LANCET (ii) 81-83, 1974).

Gamma-hydroxybutyric acid (GHB)

Brand Name

- Xyrem
- Natrium Oxybutyras
- Gamma-OH
- Sodium oxibutirate
- Sodium Oxy butyras
- Somsanit

Form

- Liquid
- Powder
- Capsule
- Orally
- Injected
- Solid form (similar to hardened vegetable fat).

Technical Use

- Forensic analysis
- For lab standard reference
- Clinical trials

Other legitimate use

Production of medicinal product- sol.Natrii oxybutyrati 20% amp. 10ml N10 - for export

Off-label

- Protection against cerebral ischemia in patients with head injures
- Dietary supplement

Annex 2: Abuse of GHB in the United States

In 2000, Monitoring the Future (MTF), a U.S. secondary school survey, sponsored by the National Institute on Drug Abuse added a question regarding the abuse of GHB by students in the U.S. The following table summarizes the annual prevalence of GHB use among eighth, tenth and twelfth grade students from 2007 to 2011. Since 2010, the annual prevalence rates in these age groups have remained steady.

GHB Annual Prevalence Use Reported by MTF (Percent of Students)

	2007	2008	2009	2010	2011
8 th Grade	0.7	1.1	0.7	0.6	0.6
10 th Grade	0.6	0.5	1.0	0.6	0.5
12 th Grade	0.9	1.2	1.1	1.4	1.4

The Drug Abuse Warning Network (DAWN) emergency department (ED) visits which involved GHB from 2007 – 2009 are listed in the table below.

DAWN Emergency Department (ED) Data (2007 – 2009)

Year	ED Visits- GHB	ED Visits – Total Illicit Drugs	% GHB
2007	2,207	1,301,085	0.17%
2008	1,441	1,335,206	0.11%
2009	1,758	1,340,301	0.13%

Note: Data after 2009 are not currently available

DAWN data indicate that the primary users of GHB are white, males and between 25 and 29 years of age.

Data from poison centers across the U.S. indicate that the intentional abuse of GHB and its analogues/precursors has increased slightly since 2008 and many of those exposed individuals were treated at a health facility. The table below provides information on GHB exposures as reported in American Association of Poison Control Centers' National Poison Data System (NPDS), formerly known as the Toxic Exposure Surveillance System (TESS); this database is composed of information from 57 poison centers throughout the U.S.

GHB Exposures Reported by NPDS (National Poison Data System)

	2008	2009	2010
Total Exposures	448	541	546
Intentional Exposures	154	191	201
Treated at a Health Facility	232	276	272
Serious Outcome*	37	46	48
Death	0	1	0

Note: GHB exposures include analogs or precursors

* Exposures resulted in life-threatening or continued long-term medical conditions

Seized Clandestine Laboratories involving GHB from 2004-2007 (no update after 2007)

	2004	2005	2006	2007
GHB	11	5	6	2

Source: Form D data (submitted to INCB)

Total quantity of seizures

According to the System to Retrieve Information from Drug Evidence (STRIDE), a DEA database that systematically collects drug analysis results from DEA and other federal laboratories, GHB has been seized in large quantities primarily in the liquid form and to a smaller extent in the powder form. There were a total of 120 drug exhibits reported in the STRIDE from 2008-2011. The table below provides additional data on selected federal GHB cases reported to STRIDE (2008-2011). These cases are provided to demonstrate that some GHB cases involve significant amounts of seized GHB. These data also indicate that illicit activities with GHB continue to be a serious problem in the U.S despite the various regulatory controls and enhanced penalties that have been placed on both the substance and the product.

STRIDE Data for GHB (2008 – 2011)

Year	Number of exhibits	Powder (grams)	Liquid (mls)	Tablets	Capsules
2008	36	0.5	31,272	--	--
2009	54	334	75,040	--	246
2010	16	16	9,945	--	--
2011	14	--	25,558	--	--
TOTAL	120	350.5	141,815	--	246

STRIDE database queried 03-27-2012

Note: Number of Exhibits includes all drugs analyzed – primary, secondary, etc.

Quantities (g, ml, etc.) are only available for primary drugs analyzed.

According to the National Forensic Laboratory Information System (NFLIS), a DEA sponsored program to systematically collect drug analyses results from state and local forensic laboratories, there were a total of 682 GHB exhibits from 2008 – 2011.

NFLIS Data for GHB (2008 – 2011)

Year	Number of Exhibits
2008	165
2009	230
2010	161
2011	126

NFLIS database queried 03-27-2012

Legitimate use of GHB in the United States

The Aggregate Production Quotas (maximum amounts that can be legitimately manufactured in the U.S. annually) for GHB for 2008-2012 are as follows:

2008: 21,940 kg

2009: 24,200 kg

2010: 52,156 kg
 2011: 5,772 kg
 2012: 47,000 kg

U.S. Exports (rounded to the nearest gram) for GHB (2009-2011)

Declared U.S. Exports of GHB (grams)			
Foreign Country	2009	2010	2011
CANADA	597,600.00	298,800.00	889,389.21
FRANCE	0.00	41,044.84	0.00
UNITED KINGDOM	7,594,749.00	1,399,056.00	4,265,825.37
Total Exports	8,192,349.00	1,738,900.84	5,155,214.58