

## Pre-review of gamma-hydroxybutyric acid (GHB)

### 1. Substance Identification

**A. International Nonproprietary Name (INN):**

None

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

591-81-1 (free acid) 502-85-2 (sodium salt)

**C. Other Names:**

$\gamma$ -hydroxybutyrate, 4-hydroxybutyrate, GHB, sodium oxybate, 4-hydroxybutanoic acid, 4-hydroxybutyric acid, oxybutirate natrii, hydroxybutyrat de sodium, sodium oxybutyrat, "Liquid Ecstasy", "Liquid E", "GBH", "Easy Lay", "Scoop", "Liquid X", "Fantasy", "Cherry Meth".

**D. Trade Names:**

Alcover (Italy), Gamma OH (France), Somsanit (Germany), Xyrem (USA, EU, Canada)

**E. Identification Characteristics:**

GHB sodium salt is a white solid, soluble in water and methanol. The analytical profile of GHB has been described in numerous papers. Data pertaining to GC-MS and GC-FID are described [1-4]; analysis usually requires conversion to  $\gamma$ -butyrolactone (GBL) or chemical derivatization.

**F. WHO Review History:**

GHB was pre-reviewed by the 31<sup>st</sup> meeting of the ECDD which recommended critical review. It was critically reviewed then in its 32<sup>nd</sup> meeting, which recommended scheduling in Schedule IV of the 1971 convention.

In its letter to WHO of 29 august 2005, Ref INCB-PSY 166/05, the INCB mentioned not only the diversion of GHB from the domestic distribution channel in several countries, but also the illicit trade of its precursor (gamma-butyrolactate (GBL)).

As a consequence, according to point 15 of the Guidelines, the WHO Secretariat decided to perform a critical review. As such the critical review of GHB was announced on the first draft-agenda of the ECDD (October 2005). However, some answers to the questionnaire clearly showed that GHB is an authorized medicine in the EU, the United States of America and Canada. According to the same point 15, in such a case the review should be a pre-review. For this reason GHB is on the agenda now under point 5, Pre-review

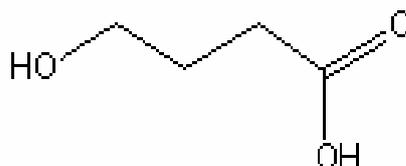
## 2. Chemistry

### A. Chemical Name:

**IUPAC Name:**  $\gamma$ -hydroxybutyric acid

**CA Index Name:**  $\gamma$ -hydroxybutyric acid

### B. Chemical Structure:



**Molecular Formula:** C<sub>4</sub>H<sub>8</sub>O<sub>3</sub>

**Molecular Weight:** 104.11

### C. Stereoisomers:

None.

## 3. General Pharmacology

*Described in this section are studies that have examined the pharmacological actions of GHB. GHB is generally believed to ultimately increase 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.*

### Neuropharmacology

GHB ( $\gamma$ -hydroxybutyric acid) was first synthesized in 1960 by Laborit in an attempt to study the effects of butyric acid and GABA ( $\gamma$ -aminobutyric acid), producing a compound which would interfere with  $\beta$ -oxidation and would cross the blood-brain barrier [5]. Bessman and Fishbein later discovered that **GHB is an endogenous compound** existing as a proposed metabolite of GABA [6]. During these studies GHB was isolated in the brain of both rats and humans. Some researchers also postulated that GHB was also a putative neurotransmitter or neuromodulator [7-8].

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 [9].

Giarman and Schmidt noted that at relatively high doses of GHB, **ACh levels were increased in certain regions of the brain** [10].

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 [11]. 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 an initial higher 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 also 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 [12-16]. 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 [17].

**GHB was also found to have an affinity for two receptors in the brain, a GHB-specific receptor and GABA<sub>B</sub> receptor**. GHB appeared to have no affinity for the GABA<sub>A</sub> receptor. Evidence for a GHB-specific receptor came from experiments by Benavides et al. and Maitre et al. involving radiolabelled GHB (<sup>3</sup>H]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 [18-19]. 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 suggest that the receptor is linked to the G<sub>i</sub> or G<sub>o</sub> family of proteins [20]. Godbout et al. reported that there is an increase in spontaneous firing in prefrontal cortical neurones after administration of low doses of GHB [21]. 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 neurones. It was postulated that this was due to an increase in DA levels resulting from GHB-induced stimulation of a second receptor, GABA<sub>B</sub> [22-25]. 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 [26]. Studies using a GABA<sub>B</sub> antagonist, CGP 35348, indicated that **GHB activation of the GABA<sub>B</sub> receptor produces hyperpolarisation** [25]. A Na<sup>+</sup> dependent GHB transport has also been discovered which is thought to remove GHB from the synaptic cleft following neuronal release [27]. A review of the recent literature suggests that most of the

physiological and pharmacological effects of exogenously administered GHB are mediated via the GABA<sub>B</sub> receptor [156].

### Neuroendocrinology

Following an intravenous 2.5 g dose of GHB in 6 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 [28]. 5 of the 6 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 [29-30]. 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 or block the release of GH-releasing or GH-release inhibiting and prolactin-release inhibiting hormone. The slow-wave and 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 [31].

### 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) [5]. 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” [5]. 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 neuroleptic 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 hypokaliemia (reduction in serum potassium levels) associated with GHB [5]. 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 [5].

Laborit also 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 (pCO<sub>2</sub>)** [5].

Both Laborit and Gessa reported a slight drop in body temperature of animals given GHB. Gessa noted that this appeared particularly pronounced in rats receiving 2 g/kg GHB kept at 18°C compared to those kept at 37°C (room temperature) [10].

### Effects on Brain Function

Many researchers have recorded the effects of GHB on brain function in animals and humans using an electroencephalogram (EEG) [5,32-37]. 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 [5].

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 (rapid eye movement) all occur in their normal sequence [35]. **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 [158].

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 [5]. 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 [5].

#### 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. 500 mg of GHB four times a day produced a temporary “disinhibiting effect” and relaxed the patients [5]. 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 [99]. 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 drugs also appear to promote high risk sexual behaviours that have been associated with increased HIV infection [123].

#### 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 [5].

### GHB as an Anaesthetic Agent

In the 1960s, early work involving GHB assessed its potential as an anaesthetic agent [5,40,98]. 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; non-hypotensive bradycardia, muscle relaxant properties, absence of respiratory depression while the response of the respiratory centre to CO<sub>2</sub> 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[124,125]. GHB is still approved for anaesthetic use in Italy and France although its use is declining [126].

### 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 [38,101-104], 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 the disorder 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) [38]. 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 is resisted the patient may become confused and emotionally labile [38,102]. In 2002, Xyrem® (GHB) was approved by US FDA for the treatment of cataplexy in patients with narcolepsy. The Xyrem® International Study Group [130] reported that approval was largely based on the results of two efficacy trials [127, 128] and one safety trial [129]. 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 9g) 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 [130].

### 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 either GHB (at various doses), ethanol or a placebo, 8 hours after the last dose of alcohol [105]. 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 [132]. 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) [106] one randomized controlled single blind study (GHB, n=60, diazepam, n=60) [133], one report of two open label studies (n=22 and n=287) [134] and one double blind, comparative study (GHB 50mg/kg n=33, GHB n=33 and clomethiazole n=32) [135]. 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 [136]. 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 [137]. 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 [138]. 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 randomised 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 diarrhea) in both the heroin and methadone groups compared to placebo measured out to 3 hours. Individuals randomised 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 [107]. In contrast, in another study, pre-treatment with GHB did not attenuate the severity of naloxone-precipitated withdrawal in 8 opioid dependent patients [139].

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 [108-110] and increased dopamine output is known to be involved in the rewarding effects of morphine and alcohol [111]. 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.

#### **4. Toxicology - Including Adverse Reactions in Man**

*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 the toxic effects. In humans, there have been numerous reported non-fatal 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 LD<sub>50</sub> was 1.7 g/kg and the LD<sub>100</sub> was 2 g/kg. The cause of death was reported to be respiratory depression; however, using artificial respiration rabbits tolerated doses up to 7 mg/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 have been 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 [31]. 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 [40]. This dose may also cause hypotonia, bradycardia, nausea, vomiting, random clonic movements of the face and extremities and Cheyne-Stokes respiration [5,31]. 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 [41]. High oral doses of GHB (greater than 60 mg/kg) can also result in coma, usually lasting up to 4 hours [42]. The following table shows a summary of resultant concentrations following various GHB doses.

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

Dose	Effect(s)	GHB concentration	Reference
25 mg/kg (oral)	Drowsiness	80 mg/L (peak plasma)	Palatini et al [43]
75 mg/kg (oral)	Sleep	90 mg/L (peak plasma) 2 hours 9 mg/L (plasma) 6 hours	Hoes et al [44]
50 mg/kg (i.v.)		170 mg/L (peak blood)	Helrich et al [45]
100 mg/kg (oral)		1100 mg/L (peak urine) in 4 hours	Hoes et al [44]

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 [45].

There have been various published reports of GHB intoxication, however, the frequent presence of other drugs 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) [46-49]. 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. methamphetamine or MDMA). In the USA, Chin et al. reported that of 86 presenting patients, 25 had an initial GCS score (Glasgow Coma Scale) of 3 (severe decrease in consciousness), other GCS scores were between 4 (decreased consciousness) and 15 (wakeful) [46].

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 [47-48,50]. In addition, various anticonvulsant and other agents have been tested using animal models (e.g. ethosuximide, sodium valproate, clonazepam, diazepam, L-dopa, phenobarbitone); however, although there were some EEG changes, the results appeared to be species specific [47]. Due to the rapid gastro-intestinal 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) [49]. 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).

### 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 [51-52]. Global estimates of the number of GHB overdose cases by various agencies (e.g. FDA, DEA and CDC) and poison centres range from hundreds to thousands of cases [53-57]. There have been other reports of toxicity resulting from ingestion of GBL or 1,4-butanediol; the patients presented with identical symptoms to cases involving GHB ingestion [58-60,157, 160]. This is consistent with the reported *in vivo* conversion of these compounds to GHB [61-62].

The majority of reported cases have occurred in the USA [4,31,46-48,53-58,63-67] and Europe (in particular; United Kingdom, Belgium, Denmark, Spain, Norway, Sweden and The Netherlands) after 1990 [68-75]. Abuse of GHB has also been reported in Australia [76]. A selection of reported cases is presented in **Table 2** (page 9). It appears that patients present 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 patient was 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 drugs 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 [50,69,77], the evidence for GHB or related product ingestion (e.g. GBL or 1,4-butanediol) 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 [4,69,70,78-81]. Elliott [120] analysed 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 analysed but not in plasma. A selection of these cases is presented in **Table 3**.

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 [31] (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 [31] (USA)	Vomiting, drowsiness, headache, nausea, diarrhoea, confusion, euphoria and dizziness.	Bodybuilder. Unknown dose. Alcohol also ingested.
3	28 yr F	Chin et al [31] (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 [31] (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 [31] (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 [47] (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 [47] (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 [47] (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 [47] (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) [75]	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) [75]	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) [75]	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 drugs 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 [4]	GHB + opiates	Urine = 2200 mg/L Serum = 339 mg/L	Bodybuilder
2	61 yr M	Le Gatt et al. [78]	GHB	Serum = 410 mg/L	Drank GHB liquid by mistake
3	42 yr M	Stephens and Baselt [79]	GHB + cannabinoids	Urine = 1975 mg/L	Driver (asleep in traffic lane)
4	M	Paradha [80]	GHB + ethanol (90 mg/dL)	Blood = 94 mg/L	Road traffic accident
5	F	Louagie [70]	GHB + ethanol (134 mg/dL)	Serum = 125 mg/L	Party
6	F	Dyer et al. [81]	GHB	Urine = 141,000 mg/L Serum = 101 mg/L	Nightclub
7	33yr M	Elliott [120]	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 [120]	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 [120]	GHB, MDMA, amphetamine, cannabinoids	Urine=1089 mg/L Plasma=167 mg/L	Possible or suspected overdose of GHB and 'ecstasy'
10	21yr F	Elliott [120]	GHB	Plasma=100 mg/L	Possible or suspected overdose of GHB 3 hours prior
11	44 yr M	Elliott [120]	GHB, MDMA, cocaine	Urine=135 mg/L Plasma=86 mg/L	?GHB and 'ecstasy' (cocaine powder and tablets seized)
12	24 yr M	Elliott [120]	GHB, MDMA, cocaine, cannabinoids	Urine=2033 mg/L Plasma=551 mg/L	Collapsed outside pub, ?alcohol and GHB ingested
13	17 yr M	Elliott [120]	GHB	Plasma=200 mg/L	Possible or suspected overdose of GHB
14	20 yr M	Elliott [120]	GHB, cannabinoids	Urine=5 mg/L Plasma=140 mg/mL	Possible or suspected GHB ingested; respiratory arrest
15	M	Elliott [120]	GHB, morphine, cocaine, benzodiazepines	Urine=432 mg/L Plasma=133mg/L	No information
16	20 yr M	Elliott [120]	GHB	Urine=1689 mg/L Plasma=306 mg/L	GHB/GBL ingested
17	25 yr M	Elliott [120]	GHB, amphetamine	Urine=1898 mg/L Plasma=233 mg/L	Possible or suspected GHB ingested
18	F	Elliott [120]	GHB	Plasma=182 mg/L	? GHB and 'ecstasy' ingested; self discharged
19	25 yr M	Elliott [120]	GHB, morphine, benzodiazepines	Urine=763 mg/mL	Ingested GHB/GBL 2 hours prior; fitting
20	39 yr M	Elliott [120]	GHB	Urine=391 mg/mL	Ingested GHB in pub; comatose

21	30 yr M	Elliott [120]	GHB	Plasma=304 mg/L	Fitting, decreased consciousness
22	17 yr M	Elliott [120]	GHB, cannabinoids	Urine=333 mg/L Plasma=260 mg/L	GCS 3, unexplained sedation
23	22 yr M	Elliott [120]	GHB, MDMA, cocaine, ketamine, ephedrine	Urine=1825 mg/L	GCS 7 following respiratory arrest; awoke within 3 hours
24	22 yr M	Elliott [120]	GHB, amphetamine	Urine=1219 mg/L Plasma=434 mg/L	GCS 3, awoke within a few hours
25	M	Elliott [120]	GHB	Urine=4687 mg/L Plasma=180 mg/L	Possible or suspected overdose of GHB and 'ecstasy'
26	26 yr M	Elliott [120]	GHB, MDMA	Plasma=154 mg/L	Possible or suspected overdose of GHB
27	14 yr M	Elliott [120]	GHB	Urine=2608 mg/L	Found unconscious, given GHB by a friend
28	32 yr M	Elliott [120]	GHB	Urine=2388 mg/L	No information
29	12 yr M	Elliott [120]	GHB	Urine=979 mg/L	GHB administered by third party ?; GCS 3
30	21 yr M	Elliott [120]	GHB, MDMA, cocaine	Urine=1284mg/L Plasma=252 mg/L	Ingested GHB and alcohol
31	30 yr M	Elliott [120]	GHB, benzodiazepines	Urine=403 mg/L Plasma=239 mg/L	Possible or suspected overdose of GHB
32	38 yr M	Elliott [120]	GHB	Urine=1410 mg/L Plasma=303 mg/L	Possible or suspected overdose of GHB
33	32 yr M	Elliott [120]	GHB	Urine=4528 mg/L	Possible or suspected overdose of GHB; GCS 3
34	24 yr F	Strickland et al. 2005 [157]	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.

\*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. [82]	GHB + morphine + 6-MAM <sup>1</sup>	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™)
2	21 yr M	Davis [83]	GHB + ethanol	Blood GHB = 291 mg/L Blood ethanol = 100 mg/dL	Ingested GBL ("Blue Nitro")
3	26 yr F	Davis [83]	GHB + ethanol	Blood GHB = 721 mg/L Blood ethanol = 170 mg/dL	Ingested GBL ("Blue Nitro")
4 *	21 yr F	Hale [84, 69]	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. [85]	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. [121]	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. [121]	GHB	Postmortem: blood GHB, 77 mg/L	Found dead in apartment
8	22 yr M	Caldicott et al. [121]	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. [121]	GHB+ cannabis + cocaine	Postmortem: blood GHB, 50 mg/L; blood: cannabis; cocaine 0.28mg/L	Drugs found at scene and tested
10	24 yr M	Caldicott et al. [121]	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. [121]	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. [121]	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. [121]	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. [121]	GHB+ MDMA+phentermine	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. [121]	GHB +methamphetamine +amphetamines	Postmortem: blood GHB, 150 mg/L; urine GHB, 82 mg/L; antemortem blood: alcohol , methamphetamine 0.3 mg/L, amphetamines <0.1mg/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)

<sup>1</sup> 6-MAM = 6-monoacetylmorphine (heroin metabolite)

### Fatal Cases

GHB has been implicated in various deaths, although no official data have been published, therefore exact numbers are unknown. However, all reported fatalities have occurred after 1990.

Approximately 60 deaths in the USA have been linked to GHB since 1990 [55]. In Europe, approximately 8 GHB-related deaths have been reported since 1995. **United Kingdom** (4 deaths – September 1995, March 1996, November 1997 and January 1999), **Sweden** (2 deaths – February 1996 and March 1997) and **Finland** (2 deaths – 1998 and 1999) [51-52,68-69]. Caldicott et al. [121] confirmed 10 cases of GHB-associated deaths in Australasia, 8 of which were directly attributable to GHB. Positive alcohol toxicology was present in only 2 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 [159] and two in the United States [160] were linked to the use of 1,4-butanediol. There was no evidence of use of alcohol or any other drugs except 1,4-butanediol. **Table 4** shows reported cases involving GHB or GBL ingestion. Due to *in vivo* conversion of GBL to GHB, only GHB is detectable in biological fluids analysed in such cases.

4 additional reported GHB related deaths involved blood GHB concentrations ranging from 27 mg/L to 121 mg/L (Fraser et al., Mozayani et al. and Woodward and Todd) [80]. Many other fatalities apparently involving/attributed to GHB have been reported in both the printed media and on the Internet, particularly in the USA [86]. The majority of cases have involved the "recreational" abuse of GHB for its apparent euphoric or "high" effects, primarily by young people. However, in certain cases there has been 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 drugs (particularly alcohol and opiates e.g. heroin, codeine, dihydrocodeine and morphine).
2. Some researchers describe the presence of GHB in post mortem blood specimens, in cases where there has been no evidence of GHB usage.
3. The GHB concentration found is sometimes low.

The mode of abuse of GHB frequently involves the use of other drugs whether it be alcohol or MDMA, therefore, deaths involving solely GHB are very rare. The presence of alcohol and other depressant or psychoactive drugs is widely believed to exacerbate the toxic effects of GHB ingestion. Therefore, the presence of such drugs 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) [82]. A high concentration of morphine was detected in the blood (770 µg/L). In five other reported GHB deaths, ethanol has also been involved at significant concentrations [68,83-84]. In these cases the mechanism of death was stated to be respiratory depression.

Recently, several researchers have reported that GHB was present in significant concentrations in post mortem blood, even in cases where the decedents had died in circumstances apparently unrelated to GHB [87-89]. In 1998, Fieler, Coleman and Baselt detected GHB in 15 out of the 20 post mortem blood specimens analysed [87]. 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 post mortem urine specimens analysed. They suggested therefore, that in cases involving possible GHB ingestion, post mortem urine should be analysed and that GHB is a product of post mortem decomposition. Further work by Stephens, Coleman

and Baselt was published in 1999 indicating that certain storage conditions could elevate the concentration of GHB in post mortem blood samples; namely if the sample was stored in a non-fluoridated container above 4°C [89]. Again, they found concentrations within the range (9-433 mg/L) in post mortem blood (average = 57 mg/L) and only detected GHB in 3 out of 17 post mortem urine specimens. These data have profound implications for the interpretation of post mortem 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 post mortem blood has been found to be “high”, 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 post mortem, 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 post mortem concentrations represent.

The WHO Uppsala Monitoring Centre (UMC) reported over a 2 year period of world wide PMS-data 5 cases of death (0.5 %) and no cases of sudden death out of 988 reported adverse effects (unpublished, communication to WHO, 2005).

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.

## 5. 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-butanediol. GHB is thought to be metabolised via the citric acid cycle producing carbon dioxide and water. It may also activate the pentose phosphate pathway. GHB is rapidly absorbed and metabolised, 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 [<sup>3</sup>H]GABA is converted to [<sup>3</sup>H]GHB via succinic semialdehyde (intermediate compound) in brain tissue [90]. This was later confirmed by Anderson et al. [91]. The conversion is catalysed by the enzymes; GABA aminotransferase and succinic semialdehyde reductase (Figure 1.).

Succinic semialdehyde reductase has been found to be different between species; in human and pig brain the enzyme is dimeric (M<sub>R</sub> 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 the mitochondria and as the substrate for succinic semialdehyde is synthesised 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 synthesised after administration of  $\gamma$ -butyrolactone (GBL). The hydrolysis of GBL to GHB is catalysed *in vivo* by a lactonase [92]. 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-butanediol is also rapidly metabolised to GHB *in vivo*, in a reaction catalysed by the enzyme alcohol dehydrogenase (ADH) [93-94]. **GHB can be produced *in vivo* as a result of GABA metabolism or after the administration of GBL or 1,4-butanediol.**

**GHB is purported to be metabolised via succinic acid and the citric acid cycle (TCA cycle/Krebs cycle), ultimately producing carbon dioxide and water.** GHB conversion to succinic semialdehyde can be catalysed by cytosolic GHB-dehydrogenase (accounts for majority of GHB metabolism in the young animal foetus) or mitochondrial GHB-ketoacidtranshydrogenase (responsible for majority of GHB metabolism in adult animals) [95-96]. Although GHB has the potential to produce GABA, this was not been observed after injecting mice with radiolabelled GHB [97]. Laborit also postulated that GHB “orientated” glucose-6-phosphate (G6P) into the **pentose phosphate pathway** (produces ribose for nucleic acid synthesis and NADPH) [5]. Under acidic conditions, GHB can be converted to the lactone, GBL, a process that has been exploited for gas chromatographic analysis of the compound [1]. 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 ( $C_{max}$ ) [82]. Following a 12.5 mg/kg dose, the **half-life** was **20 minutes** [98]. Only 2-5% is eliminated as unchanged drug in urine [5,44].

## 6. Dependence and Abuse

*Physical dependence has been observed at prolonged high dosage. Reports indicate that GHB is abused for various reasons and by various sections of society. These include, its sexual enhancing effects, growth hormone promoting effects (e.g. apparently increasing muscle bulk) and more recently its euphoric (“high”) effects. There have also been reports of GHB being used to facilitate sexual assault.*

### A. Preclinical Studies

#### Reinforcing Properties

The ability of a drug to produce reinforcing effects is the primary determinant of whether the drug will be abused. These effects may be positive reinforcers (e.g., producing pleasurable subjective effects) or negative reinforcers (e.g., alleviating negative states). For hypnotic drugs, including GHB, some symptoms of withdrawal upon discontinuation (e.g., insomnia, anxiety), may potentiate the reinforcing effects of the drug. Also of importance is the adverse event (toxicity) profile of the drug. Both of these factors are used to determine relative abuse liability. Griffiths and Johnson [140] used these factors to compare the relative abuse liability of several hypnotic drugs. GHB's significant 'likelihood of abuse' was evident with its 6th-place ranking out of 19 hypnotic drugs compared (after pentobarbital, methaqualone, diazepam, flunitrazepam and lorazepam) 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.

There is evidence that GHB can produce physical dependence as evidenced by a withdrawal syndrome when the drug is abruptly discontinued following regular, chronic use. Although several cases of withdrawal from GHB and its precursors have been documented [141;142;143;144;145] the clinical features have not been fully characterized [146]. 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 two weeks [100]. These symptoms can progress to severe delirium with autonomic instability in

frequent, heavy users (every 1-3 hours 24 hours per day) [143]. One case of seizures related to GHB withdrawal ([147] ) and one death due to complications of GHB withdrawal [143] have been reported. There is also some evidence that physical dependence may occur in recreational users [148;149]. GHB withdrawal has recently been reviewed [146;150;151].

## B. Clinical Studies

### Use and Abuse of GHB (including Subjective Effects in Man)

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 [119]. 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" [112]. This is due to the fact that GHB appears to "effect different people in different ways" i.e. a euphoric dose for one person could be a sedative dose for another [49]. 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 0.5g dose be taken for relaxation and disinhibition, a 1g dose for euphoric effect and a 2-3g dose for deep sleep [51-52,112]. The average dose is reported to be between 1 to 5 grams. [119]. A dose of less than one gram acts as a relaxant with loss of muscle tone and decreased inhibitions; 1 to 2 grams causes increased relaxation with bradycardia, slowed respiration, and interference with blood circulation, motor control and balance; and doses of 2 to 4 grams 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 [119].

It appears that GHB or related products (e.g. GBL and 1,4-butanediol) are used by various groups of people, including; bodybuilders, insomniacs, narcoleptics, opiate addicts/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 normalise their sleep patterns. Opiate addicts 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 co-administration 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 in-direct antioxidant properties of the compound by stimulating the glial cell pentose phosphate pathway producing NADPH for the reduction of oxidised glutathione [113]. 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. In such situations there is the danger of concomitant ingestion of other drugs 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 drug facilitated sexual assault (“date rape”), due to the potential incapacitating and sleep inducing effects of GHB (and GBL or 1,4-butanediol) [114,115,152-154]. 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 [112]. 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.

## 7. Epidemiology of Drug Use and Abuse with an Estimate of the Abuse Potential

*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 (ER) visits for United States. For Q3-Q4, 2003 DAWN reports a total of 627,923 drug-related ER visits of which only 990 involved GHB. Comparison to previous DAWN data is not possible because the methodology for data collection has been changed [122].

Reports to various drug 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. [68-75,116-117]. 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 drugs 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 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 [131].

Initially abused by bodybuilders, it appears that GHB is now increasingly part of the dance music culture, which has involved the use of stimulant drugs 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 drug 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 [155]. 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 Program<sup>SM</sup>. 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 [126]. 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 drug 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 drug intake.

Out of a global database of 998 reported adverse effects, covering a 2 year period, the 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 drug abuse (0.7 %) and 1 case of drug dependence (0.1 %) (unpublished, communication to WHO, 2005).

#### *Data from WHO Questionnaire*

In the 2005 WHO questionnaire Sweden reported that the 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 is not very popular, although its use is 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 2000 to 2005 and the average age of users was higher (see table)

GHB Abuse in the USA; Reported by MTF:

	<u>2000</u>	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>
8th Grade	<b>1.2</b>	1.1	0.8	0.9	0.7	0.5
10th Grade	1.1	1.0	<b>1.4</b>	<b>1.4</b>	0.8	0.8
12th Grade	1.9	1.6	1.5	1.4	<b>2.0</b>	1.1

Data are expressed as percent of students reporting use during the past year. Peak use year appears in bold print

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. Multidrug 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 Emergency Department visits increased from 145 in 1995 to 4969 in 2000 and, after scheduling of the drug under the Controlled Substances Act in 2000, then stabilized on the level of about 3330 cases in 2001 and 2002 (DAWN data).

The most recent drug 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, 5,869 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.

## 8. Nature and Magnitude of Public Health Problems

As described in Section 6 and 7, at present GHB has been reported to be mainly used and abused 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 drugs and particularly alcohol may exacerbate such effects.

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. (In between brackets figures for all medicines). Multidrug use was reported for 77 out of 250 cases, of which 33 were in combination with alcohol.

Between 1996 and 2004 36 GHB related death 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.

France reported over the years 2004-2005 6 cases of criminal use of the substance (rape, burglary and 'not specified'). Due to the method of reporting there could be under-reporting.

## 9. National Control

As GHB is under international control since 2001. Hence, in a general way, it may be assumed that all parties to the Convention on Psychotropic Substances (1971) made GHB a controlled substance.

Data as from 2002 Critical Review:

<u>Austria:</u>	Scheduled (listed as 4-hydroxy-butanoic).
<u>Australia:</u>	Monitored by Medicines Act.
<u>Canada:</u>	Schedule III substance since April 1998 (GBL is a Category 1 chemical).
<u>Denmark:</u>	Controlled under Euphorians Act (since December 1999).
<u>Finland:</u>	Listed as a medicine; illegal to buy or sell without supporting documentation.
<u>France:</u>	Controlled (since April 1999).
<u>Ireland:</u>	Controlled under Misuse of Drugs Act (since May 1999).
<u>Netherlands:</u>	Controlled under the Opium Act.
<u>Norway:</u>	Control as a narcotic drug will be effective shortly.
<u>Sweden:</u>	Controlled under Narcotics Act (since January 2000).
<u>UK:</u>	Controlled.
<u>USA:</u>	Schedule I of CSA since March 2000 (GBL List I Chemical but a scheduled substance in some US states).

In 2005 Japan also reported that the GHB is a controlled substance. Sweden reported that it brought also gammabutyrolactone (GBL) and 1,4-butanediol (BD) under control. France is considering also the control of GBL by prohibiting sales to the public, but not for industrial use.

## 10. Therapeutic and Industrial Use

In France, GHB is registered as Gamma OH<sup>TM</sup> as an adjuvant anaesthetic in surgery and obstetrics and for sedation in neurotraumatology. In several countries it is available as a generic medicine for anaesthesia (e.g. Germany - Somsanit<sup>TM</sup>, Austria, Lithuania). In the USA, Xyrem<sup>TM</sup> is licensed for the treatment of narcolepsy since 2002, and in the European Union (since 2005) and Canada (expected 2006), for the treatment of cataplexy associated with narcolepsy. Xyrem has the status

of an orphan drug in the EU and the USA. GHB has been used as an aid to alcohol withdrawal in Italy and Sweden (Alcover<sup>TM</sup>). In Israel it is used for myoclonus-dystonia. There are no known reported industrial uses of GHB, however, GBL and 1,4-butanediol are used as solvents in various industrial processes (e.g. production of polymers) and GBL as starting material for other substances (e.g. polyvinylpyrrolidone, methionin, piperidine)

## **11. 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. 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.

## **12. Illicit Manufacture, Illicit Traffic and Related Information**

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

Australia: considerable illicit activity and seizures

Belgium: usually this substance is discovered

Czech republic: one seizure of 0,5 litre in 2005 only; no in 2003 and 2004

Denmark: 6 - 11 seizures a year (2000-2004)

Finland: seizures and illicit production (in 2003, case of 243 litres)

France: 2-5 seizure yearly, between 5 grams and 1,4 litres per year; originating from the Netherlands

Israel: no manufacture, no smuggle, no diversion, very few seizures

Jordan: no illicit activities noted

Lithuania: in 2005 2.5 kgs of pure solid substance was seized

Mauritius: attempts for illicit importation

Poland: clandestine lab found, 2 litres seized

Spain: illicit trade is source

Sweden: manufactured in Sweden, but also smuggling from other countries. Diversion from medicine market negligible.

United States: from 1990 until 1999 the number of dismantled clandestine laboratories increased from 1 to 51, and after scheduling in 2000 it stabilized between 4 and 12

laboratories per year. Seized quantities are after a peak of 43 cases totalling up to 1,15 tons in 2000, around 35 to 150 kgs per year (11 - 40 cases per year).

### **B. GHB Seized Material**

Seized GHB material appears to consist of either powder or liquid preparations. Seizures of GBL and 1,4-butanediol 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” [118]:

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

GHB and related products are generally perceived to be cheap to purchase compared to other illicit drugs, 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).

### C. Method of Synthesis

Illicit GHB is reportedly synthesised 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 [112].

### 13. International controls and their impact.

GHB is included in Schedule IV of the 1971 Convention.

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