

Gamma-butyrolactone (GBL)

Critical Review Report

Agenda item 4.3

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014



Acknowledgements

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

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Summary

Gamma-Butyrolactone (GBL) has widespread industrial use. It is a common solvent found in paint strippers, nail polish removers, stain removers and circuit board cleaners. It is also a common intermediate in industrial chemistry including the manufacture of pyrrolidones and in some pharmaceuticals. International production and trade of GBL is at least of the order of hundreds of thousands of metric tons. Single consignments can be up to 500 tons alone.

Since the end of the 1990s, certain individuals have ingested GBL for the purpose of intoxication. GBL is chemically similar to gamma-hydroxybutyrate (GHB), a compound in Schedule II of the 1971 Convention. GHB is easily synthesized from GBL by changing the pH with addition of an alkali (e.g. sodium hydroxide), and recipes and "kits" have been provided on the Internet identifying or providing the ingredients to do so. Synthetic conversion of GBL to make GHB is unnecessary, however, because it is rapidly metabolized to GHB following its ingestion, and its clinical effects are identical to GHB. This makes the epidemiology of GBL's and GHB's use and abuse intrinsically (and forensically) linked. Because the onset of action of GBL is faster than GHB, its potency greater, and its duration of activity longer, its abuse potential may actually be greater than GHB itself.

There is a steep dose-effect curve between doses producing desired and excessive effects, and there have been numerous published reports of adverse reactions to GBL including fatalities. Signs and symptoms can include: euphoria, relaxation, reduced inhibition and sedation progressing to vomiting, urinary and fecal incontinence, agitation, convulsions, bradycardia, respiratory depression, coma and death.

GBL is sold as a liquid, often presented in illicit sale as GHB. Prices of GBL vary between 9 cents to 2 euros for a recreational dose (1 ml). GBL is often used with other drugs, particularly cannabis, alcohol and ecstasy. Accurate estimates of the prevalence of the use of GBL for its intoxicating effects are not available, in part because of its rapid conversion to GHB, but also because it is not routinely tested during forensic examination. Best estimate of the prevalence of its use, while giving consideration that reports of GHB use may actually be attributable to the ingestion of GBL, is low in Europe and the United States, but possibly significantly higher in other pockets of the world such as Australasia.

In view of concerns about the illicit trade and use of GBL, some Member States have chosen to control it under drug control or equivalent legislation. Several member states treat the illicit use and sale of GBL as involving a direct analog of GHB and can prosecute as such. Furthermore, the European Community and the Member States have taken additional voluntary measures to prevent its diversion.

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

1. Substance identification

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

None.

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

96-48-0

C. *Other Names*

1,2-butanolide, 2,3-dihydro furanone, 2(3H)-furanone dihydro, 3-hydroxybutyric acid lactone, 4-butanolide, 4-butyrolactone, 4-hydroxybutanoic acid lactone, butyrolactone, butyrolactone gamma, dihydro-2(3H)-furanone, gamma butyrolactone, gamma hydroxybutyric acid lactone, tetrahydro-2-furanone, oxolan-2-one, 4-hydroxybutyric acid lactone, 1,4-lactone, 4-hydroxybutyric acid lactone, 4-hydroxybutyric acid, γ -lactone, butyl lactone, butyric acid lactone, hydroxybutanoic acid lactone

D. *Trade Names*

No approved medical use.

Industrial trade names: ISP AGSOLEX BLO®

Industrial trade products containing GBL: Dapro NA 1621; Dynasolve 699; Dynasolve CU-5; Dynasolve CU-6; Foam Flush Urelthan Remover; ShipShape Resin Cleaner

E. *Street names*

GBL has been associated (not necessarily exclusively) with street names including:

"GBL", "Blue Nitro", "Blue Nitro Vitality", "Firewater", "G3", "Gamma G", "G.H. Revitalizer", "Insom-X", "Invigorate", "Paint Stripper", "Remforce", "Renewtrient", "Revivarant", "Serenity 2", "Thunder", "Verve", "Weigth Belt Cleaner", "revivarant", "revivarant G", "blue moon", "BLO", "GH-gold (GHG)", "genx" (genex), "verve" (verv), "liquid gold", "N-force", "pure raine", "reactive", "rejoov", "rejuv+nite", "regenerize", "remedy GH", "thunder", "X-12"

F. *Physical properties*

GBL is a colorless oily liquid. GBL has been characterized as having an intense bitter taste¹ with faint to pleasant odor².

G. *WHO Review History*

During the discussion of gamma-hydroxybutyric acid (GHB) at the 34th Meeting of the WHO Expert Committee on Drug Dependence (ECDD), the Committee "noted information relating to the abuse of GBL itself (convertible to GHB in the body) and suggested this substance for pre-review."³ Based on the evidence presented in the pre-review of GBL during the 35th Meeting of the WHO ECDD, given its close association with GHB, and the recommendation made by the Expert Committee to reschedule GHB from Schedule IV to Schedule II of the 1971 Convention, the Committee recommended that a critical review of GBL be undertaken⁴.

2. Chemistry

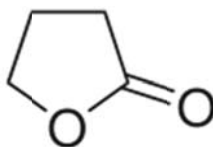
A. Chemical Name

IUPAC Name: oxolan-2-one
CA Index Name: butyrolactone

B. Chemical Structure

Free Base:

Molecular formula: C₄H₆O₂
Molecular weight: 86.09 g/mol
Boiling point: 204-205°C
Melting point: - 45°C
Density: 1.12 g/ml (15°C)
Refractive index (nd): 1.4355 – 1.4375
Acidity (pK_a): 4.5
Viscosity: 1.7 cp (25°C)



C. Stereoisomers

n/a

D. Synthesis

GBL can be synthesized from *gamma*-hydroxybutyric acid (GHB) by removal of water or by distillation from such a mixture. It may also be obtained via oxidation of tetrahydrofuran (THF). One such process, which affords GBL in yields of up to 80%, utilizes bromine generated *in situ* from an aqueous solution of sodium bromate and potassium hydrogen sulfate ⁵.

Despite efforts to curb GHB and GBL abuse, clandestine chemists are finding ways to obtain the desired substance. Since THF is a common solvent in most chemical laboratories and 1,4-butanediol (1,4-BD) is readily available, the above oxidation and dehydration reactions offer a high potential for synthesizing GBL for either direct ingestion or subsequent conversion into GHB ⁶.

E. Chemical description

GBL is a lactone. It is hydrolyzed under basic conditions, for example in a sodium hydroxide solution into sodium *gamma*-hydroxybutyrate, the sodium salt of *gamma*-hydroxybutyric acid. Under acidic conditions it forms an equilibrium mixture of both compounds. These compounds then may go on to form a polymer.

F. Chemical properties

GBL is an oily, colorless liquid, soluble in methanol, ethanol, acetone, ether and benzene and is miscible in water ².

G. Chemical identification

GC-MS methods with good sensitivity and selectivity are available for its analysis ^{7, 8, 9} including quantitative determination in whole blood and urine by protein precipitation and LC-MS-MS analysis ¹⁰.

3. Ease of convertibility into controlled substance

GBL is readily converted both chemically and in the body to gamma-hydroxybutyrate (GHB) ^{11, 12}. Chemically, GBL can be converted into GHB in plain tap water without additional adjustments ^{13, 14}. GHB was rescheduled from Schedule IV of the 1971 Convention to Schedule II in March of 2013 ¹⁵.

4. General pharmacology

Early in the investigation of GBL, it became evident that most of its pharmacological and toxicological effects were mediated through a metabolite, GHB ^{16, 17}. Further research activity was sporadic until concern arose in the late 1990s about the widespread abuse of GHB, especially in young people. National and international controls of GHB prompted substitution of GBL for GHB among the young abusers. This popular trend paralleled the rise in the use of the Internet for the exchange of information. Thus, at the request of the WHO, the College on Problems of Drug Dependence (CPDD) initiated comprehensive studies on GBL, which, in turn, aroused interest by other investigators. These are detailed below.

At the 2002, CPDD Meeting, Aceto *et al.* ¹⁸ reported that the compound was inactive as an analgesic in a variety of mouse models and neither substituted for morphine nor exacerbated withdrawal in the morphine-dependent rhesus monkey. At the same meeting, other preliminary results were presented. These were later published in full papers. For instance, McMahon *et al.* ¹⁹ reported that in monkey self-administration studies, GBL was not self-administered. In drug discrimination studies GBL did not fully substitute for pentobarbital, midazolam or flumazenil.

4.1. Pharmacodynamics

Animal studies

As would be expected from its rapid conversion to GHB, GBL produces mixed depressant and stimulatory effects in a wide variety of tests in rodents ^{20, 21, 22, 23, 24, 25, 26}. A mechanistic relationship to the GABA_B receptor system has been described ^{20, 22, 25}. Of particular interest was a report that GBL given directly to the brain of rats (ICV)

lacked the typical behavioral response seen with GHB. These data suggest that GBL is not metabolically converted to GHB in the brain and that enhanced brain penetration cannot account for potency differences between the compounds ²¹. Similarly, infusing GBL directly into the thalami or hippocampi of rhesus monkeys were without effect on EEG activity reinforcing the belief that the biological activity of GBL is principally attributable to its conversion to GHB ²⁷.

Human studies

Apparently there have been no reported double-blind placebo controlled human clinical studies of GBL. In one study in which GBL was intentionally administered to human subjects under experimental conditions, Schrock and colleagues ²⁸ administered a single dose of 1.5 ml of GBL spiked to a soft drink to each of two volunteers. The dose of GBL was estimated to be equivalent to 2.1 g of GHB (27 mg/kg body weight and 28 mg/kg body weight for the two subjects, respectively). Two blood samples were taken every 20 min within 5 h of GBL consumption and urine samples were collected during 24 h. After approximately 15 min weak CNS effects were observed including dizziness, slight dilation of pupils and delayed reaction to light. These effects disappeared half an hour later. At 20 min, maximum concentrations of GHB in serum for subjects 1 and 2 were 95 and 106 µg/ml, respectively, and maximum concentrations of GHB in whole blood were 58 and 83 µg/ml, respectively. After 4-5 h GHB concentrations in serum and whole blood decreased to below analytical limits. Maximum GHB concentrations in urine for the two subjects were 140 and 120 µg/ml. GHB levels were immeasurable in urine 8 and 10 h after GBL ingestion for Subjects 1 and 2, respectively.

Other, experimental studies involving the intentional administration to humans appear lacking. Additional information regarding the pharmacodynamics of GBL in humans, however, can be inferred from non-controlled observations. The clinical hallmark of GBL (and 1,4 BD) intoxication in humans is CNS depression with relatively short duration of action, and which is clinically indistinguishable from that of GHB intoxication ²⁹. CNS depression induced by GBL may be accompanied by confusion, agitation, and a labile consciousness, as well as coma ²⁹. There appears to be a general dose-response relationship relating degree of CNS effect to dose, with very high doses producing significant respiratory depression with apnea. Major motor seizures have been inconsistently associated with GBL intoxication. Isolated case reports describing generalized seizures induced by GBL are often not properly documented with confirming blood or urine measurements and "should be interpreted with care" ²⁹. Mild hypothermia has been frequently reported in hospitalized cases of GBL (and 1,4 BD) intoxication ^{30, 31}. GBL intoxication can often induce nausea and vomiting especially when co-abused with alcohol ³². The effects of GBL on cardiovascular function are variable, and there does not appear to be strong evidence for direct myocardial depression ²⁹.

4.2. Routes of administration and dosage

When abused, GBL is administered orally in a liquid form. A milliliter of pure GBL metabolizes to roughly 1.6 g of GHB, so doses are measured in the single milliliter range, either taken all at once or sipped over the course of a night. GBL has a distinctive taste and odor described as stale water or burnt plastic.

4.3. Pharmacokinetics

GBL is rapidly converted into GHB by lactonase enzymes found in the blood. GBL is more lipophilic (fat soluble) than GHB, and so it is absorbed faster and has higher bioavailability; the paradox is that this can mean that GBL has a faster onset of effects than GHB itself, even though it is a prodrug³³. The levels of lactonase enzyme can vary between individuals, and GBL is not active in its own right, so people who have never tried GBL before may have delayed or fewer effects than expected; however, once someone has taken GBL a few times, the production of lactonase enzymes is increased and he/she will feel the effects as normal³⁴. It has been suggested that muscle tissue may sequester a large part of the initial GBL dose, thereby delaying conversion to GHB and prolonging the duration of action³⁵.

Likely because of these pharmacokinetic features, GBL tends to be more potent, faster-acting and of a longer duration of activity than GHB³³.

5. Toxicology

GBL has a relatively low acute toxicity in that the oral LD₅₀ of gamma-butyrolactone is in the range of 1540-1800 mg/kg in rat, 800-1720 mg/kg in mouse, and 500-1690 mg/kg in guinea pig² with few other clinical signs than central nervous system depression. In a teratogenicity study, rats given either vehicle or GBL up to 500 mg/kg/day i.g. on gestation days 6 through 15 did not show significant differences as regards corpora lutea and total implantation sites, alive and dead fetuses, resorptions, preimplantation and postimplantation losses, or male/female ratios nor were embryotic effects observed³⁶. In early carcinogenicity studies little or no positive results were observed with GBL^{37,38}. In the late 1980s the U.S. National Toxicology Program initiated a "Toxicology and Carcinogenic Study of gamma-butyrolactone"³⁹. This was based on the rationale that GBL had "the potential for widespread exposure" due to its use as a chemical intermediate in the manufacture of a variety of products including polymers and herbicides. Sixteen-day and 13-week toxicity studies were carried out in mice and rats. GBL was administered in corn oil by gavage. Again, lethal potency was relatively low. In the 13-week study, no lesions related to the administration of GBL occurred in mice of either sex. Based on these studies, 2-year carcinogenic studies were initiated in male and female rats and mice. Body weights and survival time in the GBL rats differed little from those of controls. Greater effects were seen in mice. For instance, survival in high-dose males was significantly lower than that of the controls. This was attributed to bite wounds and fighting in high-dose males recovering from the sedative effects of GBL. It was concluded that, under the conditions of these studies, there was no evidence of carcinogenic activity in male or female rats. There was no evidence of carcinogenic activity in the female mice. There was equivocal evidence of carcinogenic activity in male mice. However, "the sensitivity of the study in male mice to detect a carcinogenic effect was reduced by the low survival of the high-dose group associated with fighting."

6. Adverse reactions in humans

For a number of reasons, one is unable to obtain precise data on the incidence of adverse effects in humans. This is primarily due to the fact most of the adverse effects reported are due to the rapid conversion of GBL to GHB. Secondly, it has rarely been determined precisely what an individual has ingested (GBL, 1,4-BD or GHB). In addition, recent

survey data treat the three compounds as a single agent (for instance, see the European Monitoring Centre's use of the term "GHB/GBL" ³⁵). Despite this, there are numerous published reports of adverse reactions to GBL including fatalities ^{29, 31, 40, 41, 42, 43, 44}. The general symptoms reported include: vomiting, urinary and fecal incontinence, agitation, convulsions, bradycardia, loss of consciousness, respiratory depression, coma progressing to death.

7. Dependence potential

Animal Studies

In the morphine-dependent rhesus monkey, GBL neither substituted for nor exacerbated withdrawal ¹⁸. In one study in Sprague-Dawley rats, withdrawal from six-day regimens of GBL couldn't be assessed because of lethality when dosage regimens were given at equi-molar doses to GHB and 1,4 BD ⁴⁵. Finally, in a series of papers, Goodwin and colleagues ^{46, 47, 48} examined the acute and chronic effect of GHB and GBL in the baboon. They clearly observed a spontaneous and precipitated withdrawal syndrome after chronic administration of both GHB and GBL, and presented evidence that the (GABA)_B receptor system may be involved ⁴⁸.

Human Studies

There have now been several reports that GBL can produce physical dependence as demonstrated by a withdrawal syndrome when the substance is abruptly discontinued following regular chronic use ^{49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61}. Withdrawal from GBL appears similar to withdrawal from other sedative-hypnotic drugs such as ethanol and benzodiazepines. In a review of the English literature pertaining to withdrawal from GHB, 1,4-BD and GBL, 32% of which directly involved GBL, the most common patient symptoms included tremor (67%), hallucinations (63%), tachycardia (63%), insomnia (58%), seizures (7%) and rhabdomyolysis (7%) ⁶⁰. In one of the earliest case studies involving GBL withdrawal, signs and symptoms of withdrawal resolved in a range from 24 h to 11 days ⁵¹. This range in the duration for the signs and symptoms of GBL withdrawal to resolve is similar to that reported in other case studies most of which included treatment with benzodiazepines or pentobarbital ^{55, 56, 57, 58, 59, 60, 61, 62}. It is difficult to accurately identify the level of exposure necessary to induce dependence upon GBL from available data. In one report involving five case studies of GBL dependence, patients reported a range from 2-9 months of use involving dosage regimens from once to eight times per day prior to their withdrawal episode ⁵⁹.

8. Abuse potential

Animal Studies

Since it is generally thought that GBL owes its central nervous system activity to conversion to GHB (e.g., ^{16, 17}), and conversion appears essential because it is behaviorally inactive when delivered directly into the CNS ²¹, the abuse potential of the substance should essentially mimic that of GHB. Animal studies that contribute to our determination of abuse potential revolve around a compound's pharmacological resemblance to substances with known abuse liability and the substance's reinforcing or rewarding actions. The procedures used to provide this evidence most often include

general pharmacology, drug discrimination studies, and self-administration studies. As indicated above, the general pharmacology of GBL most closely resembles that of GHB, and there are no true pathognomonic signs or symptoms to separate GBL (or 1,4-BD) intoxication from poisoning due to GHB²⁹. Drug discrimination studies indicate that GBL does not fully generalize to the benzodiazepines or pentobarbital in rats, pigeons or rhesus monkeys^{63, 19, 64, 65} or to phencyclidine or heroin in rats⁶⁶. Studies on the reinforcing effects of GHB do not indicate it to be a robust reinforcer in that it is not self-administered by rhesus monkeys under conditions in which most drugs of abuse are^{19, 63, 66}, although it is self-administered by baboons when given extended access⁶⁷ and by mice⁶⁸. Similar to GHB, GBL was reported to be not self-administration by rhesus monkeys¹⁹ although it was self-administered by baboons under extended access conditions⁶⁹.

Human Studies

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

Controlled, laboratory-based evaluations of the pharmacological properties of GBL predictive of abuse potential have not been conducted. Such studies have been carried out with GHB, however⁷⁰, in which the authors concluded that the profile of effects of GHB in subjects with drug abuse histories: "... partially overlaps with that of triazolam and pentobarbital. Although the likelihood of GHB to be abused is intermediate to triazolam and pentobarbital, the possibility of accidental overdose (greater sedation than intended) with GHB appears to be greater." In another laboratory-based examination of GHB's pharmacological effects the researchers concluded that in subjects without a sedative-abuse history, "... GHB produced dose-related increases in self-reported sedative-like and dissociative-like effects, and ratings of drug liking and high..."⁶². No such studies exist for GBL. Considering how rapidly GBL is converted to GHB⁷¹, these pharmacological predictors should apply to GBL. Considering that numerous case reports observe that GBL can induce physical dependence (*vide supra*), along with the observation that GBL is a precursor and/or analog to GHB that is itself a Schedule II compound in the 1971 Convention, GBL likely has an abuse potential overlapping with GHB. Considering its onset of action is shorter, potency is greater, and its duration of activity longer than GHB, its overall abuse potential actually may be somewhat greater than GHB itself (e.g.,^{33, 71}).

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

While GBL was sold in health food stores and athletic venues as a dietary supplement and purported to induce sleep, release growth hormone, enhance sexual activity and athletic performance, there is no recognized therapeutic indication for the substance.

10. Listing on the WHO Model List of Essential Medicines

GBL is not listed.

11. Marketing authorizations (as a medicine)

GBL itself is not authorized as a medicine.

12. Industrial use

GBL has widespread industrial uses (e.g., ^{72, 73}). One significant use of GBL is as an intermediate in the manufacture of pyrrolidones, which are widely used industrial chemicals. A second significant use of GBL, because of its strong solvency properties, is in cleaning products such as circuit board cleaners in electronics, in paint strippers and as a component of nail polish removers. It is used as a solvent for polyacrylonitrile, cellulose acetate, methylacrylate polymers, and polystyrene. Other applications include the production of herbicides and pharmaceuticals, and is used as an intermediate in the synthesis of DL-methionine, piperidine, phenylbutyric acid and thiobutyric acid. United States production alone is on the order of 185,000 metric tons of GBL ⁷⁴.

13. Non-medical use, abuse and dependence

GBL is abused as a liquid often falsely presented as GHB during illicit sale. One ml of high-purity GBL is about equivalent to 2.5 g GHB ⁴⁹. There are online chemical suppliers that sell GBL marketing GBL as a cleaning solvent, multi-purpose remover or chrome polish, and as a wheel cleaner. A total of 15 chemical suppliers that sell 99.9 % pure GBL were identified located in the UK, Germany, the Netherlands and Poland ³⁵. All except three suppliers provided health warnings ³⁵. GBL has been sold over-the-counter and on the Internet in kit form with instructions for the home synthesis of GHB. These kits typically have packaged GBL with sodium hydroxide, and when mixed, the lactone is saponified by the hydroxide anion to yield GHB ²⁹. However, kit-form packaging of GBL appears to now be rare ³⁵. Prices of GBL vary between 9 cents to 2 euros for a recreational dose (1ml) ³⁵. The number of confirmed cases of GBL (and 1,4-BD) intoxication is relatively low compared to GHB. This is likely attributable to a several factors including the longer period of GHB availability, inaccurate or unknown identity of the substance ingested by intoxicated persons, similarity of symptoms, and perhaps most importantly, metabolic conversion of GBL to GHB ²⁹. This latter factor is compounded by the fact that there is currently no readily available toxicological test to differentiate between the presence of GHB, GBL or 1,4BD in patients presenting with self-reported ingestion of one of these drugs ⁷². One estimate of the relative proportion of GBL to GHB usage was provided in a retrospective review of cases of self-reported recreational GHB, GBL and 1,4-BD users in 2006 that were found in a toxicological database of a large inner city emergency department (ED) in London. There were a total of 158 ED presentations, of which 150 (94.9%) and 8 (5.1%) were GHB and GBL self-reported ingestions, respectively. Of the 418 samples seized, 225 (53.8%) were in liquid form; 85 (37.8%) contained GHB and 140 (62.2%) contained GBL. None of the seized samples contained 1,4-BD and there were no self-reported 1,4BD ingestions ⁷².

The epidemiology of the use and abuse of GBL is intrinsically linked to that of GHB. It is rapidly metabolized to and reported forensically as GHB. Indeed, forensic samples of blood and other tissues are not analyzed for its precursors and not routinely even for GHB. Indicative of this regarding survey data, the European Monitoring Centre for Drugs and Drug Addiction stipulates, "Hence, when referring to prevalence and patterns of use, the term GHB/GBL may include known or unknown use of GBL or 1,4-BD, particularly in surveys conducted after GHB was placed under drug control and when it began to be substituted by GBL." ³⁵. Compounding the difficulties of discriminating abuse of GBL from that of GHB or 1,4-BD there are no true pathognomonic signs or symptoms to separate GBL or 1,4-BD intoxication from poisoning due to GHB ²⁹. Overall, accurate estimates of GBL's specific use are impossible to currently derive.

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related emergency department (ED) visits for the United States. In 2004 there was a total of 1,253,956 misuse/abuse ED visits. Of these, 2,340 were attributed to GHB (0.19%) ³⁴. In 2005, the total number of ED visits was 1449154. Of these, 1861 were attributed to GHB (0.13%) ³⁴. The most recent data are from 2011 in which total ED visits involving GHB was 2,406, which was 0.2% of all ED visits ⁷⁵. Thus, in the United States the use of GHB leading to ED visits, and by inference, its precursors, was low and steady over a seven year span between the years of 2004 and 2011.

Additional United States trend data can be found in the National Institute of Drug Abuse Proceedings of the Community Epidemiology Work Group (CEWG) ⁷⁶. In its most recent review in January of 2013, GHB was identified among drug reports from forensic laboratories in 13 CEWG areas of the 25 reporting National Forensic Laboratory Information System data in the first half of 2012, including Chicago, Denver, Colorado, Los Angeles, Miami, Michigan, Minneapolis/St. Paul, New York City, San Diego, San Francisco, Seattle, Texas, and Washington, DC. Numbers were very low, and in no case did the percentage reach higher than 0.1 percent of total reports ⁷⁶. Seizures of illicitly marketed GBL in United States data can also be used to infer incidence and prevalence of its illicit use. Seizures of GBL intended for illicit use in the United States increased from 117 to 151 from 2011 to 2012, although gross amount declined from 28.6 to 5.5 kg ⁷⁴.

The European Monitoring Centre for Drugs and Drug Addiction's (EMCDDA) 2008 report on GHB and its precursor GBL concluded, "Use of GHB/GBL is, generally, low in the EU..." (*sic*), but also observed that there was, "... evidence of some sub-populations, settings and geographical areas where it is commonly used, such as in gay nightclubs." ³⁵ For instance, among respondents sampled in 'gay' Amsterdam bars prevalence estimates for GHB/GBL use rise to 17.5% compared to less than 5% among respondents in the more mainstream or student pubs. Lifetime incidence was between 0.5% and 1.4% among 15-16 year old students in 12 EU countries. This estimate increases to between 3% and 19% of lifetime incidence when survey data are collected in dance music settings. It should be noted that these estimates are based on GHB or GBL as well as GHB's other precursors, and not specifically for GBL. The EMCDDA expressed concern that, "The ease with which GBL can be acquired allows potentially much easier and cheaper access than that usually found in illicit drug markets in the EU.", and further commented, "Since the sale of GHB was controlled under drug laws in all Member States, information suggests that there has been an increase in use of the precursor chemical GBL.", however specific reference to the data supporting this "information" was not provided. At the time of the EMCDDA's report, no EU member

state had reported any incidence of large-scale production, trafficking or distribution of GHB, and the proportion of reported seizures of GHB/GBL in the EU was referred to as "very small" compared to seizures of other synthetic illicit compounds ³⁵.

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

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

It is extremely difficult to accurately assess the magnitude of public health problems related to the abuse and dependence upon GBL considering the near absence of data explicitly related to GBL. Most data are confounded by the inclusion of GHB and 1,4-BD. Seizures, of GHB and of its precursors, GBL and 1,4-BD, have been reported in Belgium, the Czech Republic, Denmark, Estonia, France, the Netherlands, Sweden, Finland, the United Kingdom and Norway ⁷⁷, and in Greece, Bulgaria, Italy, Hungary, Spain, and Austria ⁷⁸. Belgium reported that there are regular seizures of GHB/GBL, with GBL being more commonly found than GHB ⁷⁹. The European Parliament reported that GBL had been seized in 24 cases in 2005, 6 cases in 2006, 126 cases in 2007 and 148 cases in 2008. GBL use or seizures were mentioned in the National Reports of two countries in 2005, by three countries in 2006, by seven countries in 2007 and by nine countries in 2008 and 2009 ⁸⁰. In Australia, overdose on GBL or GHB is perceived to be a relatively common presentation to hospital by some ^{81, 82}. Caldicott and colleagues concluded, "Because of the restrictions in obtaining GHB, it is probable that most of the "GHB" being consumed in Australia is now in the form of GBL or 1,4-BD.", and implied that many of the deaths associated with GHB are likely attributable to its precursors ⁴¹.

The frequency of abuse and associated health problems of GBL, relative to many other drugs of abuse, is likely low in the EU ³⁵ and in the United States (e.g., ⁷⁶), higher in some other countries such as Australia ⁴¹. Trends of GHB use, and by implication, GBL, were decreasing in the United States ⁸³ while in New South Wales lifetime use increased from 0.5% to 0.8% during the years 2005 to 2010, although "recent use" held constant at 0.1% ⁸⁴.

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

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

15. Licit production, consumption and international trade

No country out of the 58 countries reported authorized GBL as a medical or veterinary

product for the 35th ECDD ³⁴. As reported in Section #12 above, GBL is a major industrial chemical used and traded in large volumes by the chemical industry as a precursor for the synthesis of plastics and also as a major industrial solvent. Standard volumes of GBL trade are 20 tons but can be up to 500 tons per consignment ⁸⁰. The US DEA estimates that current United States production is on the order of 185,000 metric tons of GBL ⁷⁴. Detailed international statistics showing the amounts of GBL in circulation in the world are unavailable.

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

16. Illicit manufacture and traffic and related information

See the report of the WHO questionnaire for review of psychoactive substances (Annex 1).

17. Current international controls and their impact

GBL is not currently under international control.

18. Current and past national controls

European Union: GBL is a non-scheduled drug precursor and in accordance with the EU legislation on control and monitoring of trade in drug precursors (Regulation (EC) No 273/2004(4) and Regulation (EC) No. 111/2005(5)), GBL is covered by the EU voluntary monitoring scheme for drug precursors ⁸⁰.

Australia: GBL is a border controlled substance and is illegal to import into Australia without a permit. The importation of a commercial quantity of a border controlled drug (over 1 kg of GBL) is punishable by up to life imprisonment and/or an \$825,000 fine ⁸⁵.

Austria: GHB was included in the list of substances controlled by the Austrian Narcotic Substances Act in 2003. In November 2008 amendments to the Decree on Narcotic Drugs were sent out for examination. They include the synthetic substances BZP and GBL as well as the opiate Oripavin ⁷⁸.

Bulgaria: From April 2010 both GHB precursors (GBL and 1,4-BD) are enlisted in Schedule III - "Dangerous substances" ⁷⁸.

Canada: GBL is a Controlled Substance under Schedule VI of the "Controlled Drugs and Substances Act" in Canada. Schedule VI of the "Controlled Drugs and Substances Act" requires vendors to collect information regarding purchases of GBL. The Act also prohibits the import and export of GBL into or out of Canada classifying it as either an indictable offense punishable with up to 10 years in prison or an offense punishable on summary conviction liable to imprisonment for up to eighteen months ⁸⁶. It is not illegal for an individual to possess GBL in Canada.

Germany: GBL is not listed in the narcotics law, but its distribution is controlled. Possession is not illegal, but may be punished according to the Medicines Act, when intended to be sold for human consumption or synthesis of GHB. In recent years, an increase of GBL consumption has been observed due to the prohibition of GHB.

Hong Kong SAR: GBL is a dangerous drug controlled under Schedule 1 of the Dangerous Drugs Ordinance, Cap.134 (with exemption clause at Paragraph 16D). Any person who is found to have in his possession of it not in accordance with this Ordinance can be liable, on conviction upon indictment, a fine of HK\$1,000,000 and to imprisonment for 7 years.

Israel: GBL has been classified as a proscribed substance since 2007.

The Netherlands: September 2011, based on the CAM advice, the Minister of Health has recently decided to promote GHB from class 2 to class 2 of the Opium law. It is now in the class of hard drugs. It is advocated to place GBL and 1,4 BD in the highest class of the Wvmc (European trade treaty; 273/2004)⁷⁸.

Poland: GBL is not classified as a drug and can be purchased in chemistry shops as a solvent.

Romania: GBL is controlled by Governmental decision that entered in force on 15 February 2010⁷⁸.

Sweden: February 1st, 2000 GHB was scheduled in Sweden. Since 1 September 2005 GBL and 1,4-butandiole are also under control⁷⁸.

United Kingdom: GBL has been classified as a Class C drug since 23 December 2009, with a prison term of up to two years for possession and 14 years for dealing⁸⁷.

Norway: 1,4-butandiol and GBL were added to the Norwegian National Drug List with effect from 24 March 2010⁷⁸.

Italy: GBL is controlled under a 1999 law on drugs and addiction. The rationale is said to have been GBL's role as a starting substance in the production of GHB. A permit issued by the Health Ministry is now required for the production of GBL, and the import and export of the substance are regulated by means of licenses issued by the same ministry.

Enforcement is the responsibility of the customs authorities.

United States: GBL is placed as a List I chemical of the Controlled Substances Act (CSA) that imposes regulations including criminal, civil, and administrative penalties, sanctions and regulatory controls on the manufacture, distribution, possession, importation, and exportation of GBL. The U.S. Drug Enforcement Administration (DEA) issued an "Exempt chemical mixtures containing gammabutyrolactone Final Rule" in 2010 [Fed. Reg. (124) 37301-07]. This regulation made GBL chemical mixtures, in concentrations greater than 70%, subject to List I chemical regulatory requirements of the CSA, except if exempted through an existing categorical exemption. DEA took this action because there was perceived a serious threat to the public safety associated with the ease by which GBL is chemically converted to the Schedule I controlled substance GHB. Under the Controlled Substances Act Analogue Provisions

GBL can also be treated as a controlled substance analogue of GHB for purposes of prosecution ⁷⁴. A prerequisite is that the substance must be intended for human use, which may be difficult to prove.

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

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

Prudent consideration should be given to whether the GBL should be scheduled under the Psychotropic Convention or controlled under the Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances given its extensive use as an industrial chemical. Scheduled control of GBL would likely be ineffective considering its metric tonnage of trade, and would disrupt industry dependent upon it.

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Annex 1

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of GBL

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

A total of 66 Member States answered the questionnaire for Gamma-butyrolactone (GBL). Of these, only 30 respondents (AMR 6, EUR 19, SEAR 1, WPR 4) had information on this substance.

LEGITIMATE USE

None reported that GBL was currently authorized or in the process of being authorized/registered as a medical product in their country. Ten respondents stated that this substance was used in medical and scientific research. There was no use stated for GBL in animal/veterinary care. On any other legitimate uses, 21 stated that its main use is in the chemical industry as a solvent. 16 reported that this was imported, 3 manufactured in country and one manufactured in country and imported for legitimate use. The approximate amount needed for legitimate use varied greatly, from grams to over 100,000 tons

HARMFUL USE

Sixteen respondents confirmed that there was recreational/harmful use of GBL; 15 stated that the common route of administration was oral. For such use, the substance was obtained only via trafficking in five responses and in 7 via diversion and trafficking. Liquid was stated as the common formulation in 15 responses and powder and liquid forms by one. When asked if GBL was used by any special populations 3 respondents stated that it was used by the general population and in clubs, 1 only in the general population and 3 only in clubs. For 2012, four deaths due to GBL were reported by 1 respondent and 37 total emergency room visits by three respondents. Enrolment into addiction programme was reported as 231 for GBL/GHB by one respondent. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by GBL. These are same as that caused by GHB.

Additional information provided suggest that a proportion of people dependent on GHB, in fact use GBL. 'Between years 2006-2010 GHB was identified in 21 autopsy cases, of which 11 according to information obtained on the case the substance ingested was actually GBL (52 %). Age median for those 11 was 27 y and all were between 19-33 y. During the same time period there was 14 GHB induced lethal poisonings and of these GBL was responsible of 10 (71 %). This is in line with the assumption that GBL might actually be more toxic than GHB. The intoxications were 2008: 1, 2009: 6, 2010: 2; identification for GHB.'

CONTROL

Of those with information on this substance, 20 reported that GBL was controlled under legislation that was intended to regulate its availability - 12 under "controlled substance act", 4 under "medicines law", 1 under "analogue legislation" and 2 as "other" types. Only four respondents stated that there were challenges with the implementation of this legislation; this included its legitimate use as a solvent. On illicit activities involving GBL, two respondents reported clandestine manufacture and none the synthesis of the product itself. Two

respondents reported processing into the consumer product, 11 reported trafficking, seven reported diversion and 10 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	577 (13)	763 (14)
Total quantity seized (kg)	157.40 (4)	415.97 (5)
Total quantity seized (l)	1663.04 (8)	1451.58 (9)
Total quantity seized (other)	24 samples	111 samples

IMPACT OF SCHEDULING

Twenty-five respondents reported that if GBL was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use.