E.M.C.D.D.A.

European Monitoring Centre for Drugs and Drug Addiction

Report on the risk assessment of GHB in the framework of the joint action on new synthetic drugs

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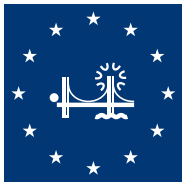

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Cataloguing data can be found at the end of this publication.

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Contents

Foreword

It gives me particular pleasure to present with this publication the results of the risk assessment undertaken by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the substance gamma-hydroxybutyric acid (GHB). The risk assessment was carried out under the terms of a joint action adopted on 16 June 1997 by the Council of the European Union ([1]) and is the fourth such exercise undertaken to date by the EMCDDA ([2]).

GHB has been used experimentally in human medicine for 30 years, but since the mid-1990s has been surfacing as a recreational drug. Some EU countries have reported concern over GHB's surreptitious use in sexual assaults.

Information on the patterns of use and implications for illegal drugs-trafficking networks were collected through the EMCDDA's early warning system via the European network of national focal points and Europol's national units. On the basis of the findings, the Horizontal working party on drugs of the European Council requested a risk-assessment procedure to be carried out which reviewed the pharmacotoxicological data on GHB and assessed the public health risks and the available sociological and criminological evidence. The resulting 'Report on the risk assessment of GHB' was presented to the Council in March 2001. On the basis of the report, the Council requested the EMCDDA and Europol to 'actively' monitor GHB until the end of 2001 — its consumption, trafficking and the public health-related problems linked to it as well as its clinical effects, prevalence and patterns of use, seizures, the role of organised crime in production, diversion and trafficking and the role of the Internet in marketing the drug for non-medical use.

([1]) Joint action concerning the 'information exchange, risk assessment and the control of new synthetic drugs' (OJ L 167, 25.6.1997). A joint action is a decision adopted unanimously by the EU Member States within the framework of the third pillar of the Treaty on European Union (cooperation in the field of justice and home affairs). Synthetic drugs are psychoactive substances produced in laboratories and not derived from natural products. They include MDMA (ecstasy), other amphetamines and LSD.

([2]) The three previous risk-assessment exercises concerned the substances N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), 4-methylthioamphetamine (4-MTA) and ketamine.

I would like to thank all of those who participated in the risk-assessment process for the high-quality work carried out. I trust that the results presented here will make a significant contribution to the knowledge pool on GHB and that they prove to be a valuable resource to politicians responsible for the final decision on control and prevention measures.

Georges Estievenart
Executive Director, EMCDDA

Abbreviations

ACh	acetylcholine
BP	blood pressure
bpm	beats per minute
CAS	chemical abstracts registration
DA	dopamine
EEG	electroencephalogram
GABA	gamma-aminobutyric acid
GBL	gamma-butyrolactone
GC-FID	gas chromatography with flame ionisation
GC-MS	gas chromatography with mass spectrometry
GHB	gamma-hydroxybutyric acid or gamma-hydroxybutyrate
GCS	Glasgow coma score
KGHB	GHB potassium salt
i.p.	intraperitoneal
i.m.	intramuscular
i.v.	intravenous
MAO	monoamine oxidase
MDMA	3,4-Methylenedioxy-*N*-methylamphetamine
NA	noradrenaline (norepinephrine)
NaGHB	GHB sodium salt
SSRI	selective serotonin reuptake inhibitor
5-HT	5-hydroxytryptamine (serotonin)

Introduction

A risk assessment of any chemical is a unique scientific event in which a range of evidence is evaluated and discussed in depth. Risk assessments of new synthetic drugs under the aegis of the joint action of July 1997 are even more unique because not only the pharmacotoxicological effects on health must be considered but also the social effects and the possible consequences of prohibition. The risk assessments performed in September 2000 on ketamine ([3]) and GHB were respectively the third and fourth such risk assessments performed by the extended Scientific Committee at the EMCDDA. The unique feature of both these substances is that they are both licensed medicines of value in human or veterinary medicine. The task faced by the risk-assessment committee therefore involved not just an assessment of the scientific evidence but also an assessment of how best to safeguard public health while simultaneously ensuring that valuable medicines could still be available to practitioners and their human (and animal) patients. These assessments involved detailed and robust discussions among the multidisciplinary committee, drawn from each of the Member States. The ability of scientists from a range of laboratory and non-laboratory sciences to debate the issues surrounding new synthetic drugs is a key strength of the joint action process and my colleagues on the Committee are to be commended on their detailed and learned contributions to our overall understanding of these two substances. Their individual contributions allied to those of the two experts, Dr Leon van Aerts (ketamine) and Mr Simon Elliott (GHB) plus the invaluable inputs from the staff of the Monitoring Centre provided the basis for the final recommendations made to Council about the two drugs. These recommendations relate not only to the question of control of ketamine and GHB but also highlight the need for the Member States to consider other elements such as the need for research on the neurotoxicity of ketamine and on the role of GHB (and other drugs) in cases of drug-assisted sexual assault. Given that these subsidiary recommendations come from a Committee composed of the leading experts on new synthetic drugs in the EU, their importance should not be underestimated by the Commission, the Council or the Member States.

([3]) The 'Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs' is also available.

As ever in these risk assessments an enormous debt of gratitude is due to my colleagues on the steering committee for risk assessment who worked incredibly hard before, during and after the meetings to finalise the reports. The work of Salme Ahlström (Finland), Aldo Perissino (Belgium), Wolfgang Werdenich (Austria), Jean-Pol Tassin (France) and Christina Poethko-Müller (Germany) was more than matched by the efforts of the staff of the Centre including Alain Wallon, Lena Westberg and Deborah Olszewski.

My admiration of all of them has grown with each risk assessment because of their acumen, commitment and enthusiasm for a unique European activity.

Dr Desmond Corrigan
Chairperson, Scientific Committee of the EMCDDA

Report on the risk assessment of GHB in the framework of the joint action on new synthetic drugs

On 17 April 2000, the Portuguese Presidency of the European Council formally notified gamma-hydroxybutyric acid (GHB) for risk assessment under Article 4 of the joint action on new synthetic drugs of 16 June 1997.

A meeting of the Scientific Committee of the EMCDDA, extended with experts nominated by the Member States and representatives of the European Commission, Europol and the European Agency for the Evaluation of Medicinal Products (EMEA), to assess the health and social risks — as well as the possible consequences of prohibition — of GHB was held on 25 and 26 September 2000.

The meeting considered the following documents:

- 'Review of the pharmacotoxicological data on gamma-hydroxybutyric acid (GHB)', report to the EMCDDA;
- 'Public health risks of GHB: epidemiological evidence', EMCDDA;
- 'Sociological and criminological evidence on the risks of GHB', EMCDDA;
- Europol's contribution to the risk assessment of GHB; and
- EMEA's contribution to the risk assessment of GHB.

These documents, in conjunction with further information and comments from the expert participants, formed the basis of the risk assessment reported below.

1. Chemical description

Gamma-hydroxybutyric acid refers to the protonated form whereas gamma-hydroxybutyrate refers to the deprotonated form of the carboxylic acid moiety. The abbreviation GHB refers to both of these chemical names. Other chemical names include oxybate, 4-hydroxybutanoic acid, and 4-hydroxy-

butyric acid. GHB can also form various salts (for example, sodium and potassium salts) which are soluble in water and methanol.

GHB was initially developed as an anaesthetic agent but was later found to be a naturally occurring compound in mammalian brain and tissue, existing as a by-product of GABA metabolism and putative neurotransmitter. Major chemical and metabolic precursors include gamma-butyrolactone (GBL) and 1,4-butanediol which are both rapidly converted to GHB in the body.

Registered names for GHB are: Alcover, Somsanit, Gamma-OH.

GHB has various street names including 'liquid ecstasy', 'liquid E', 'GBH', 'easy lay', 'scoop', 'liquid X', 'fantasy' and 'cherry meth'.

2. Pharmaceutical description

Pharmaceutically, GHB is available as sodium gamma-hydroxybutyrate in liquid form. Recreationally, GHB is available as either a liquid formulation or as a powder (either loose or in tablets or sometimes in a capsule).

GHB is used therapeutically in anaesthesia, in the treatment of alcohol withdrawal and in long-term sedation, and is being investigated for the treatment of narcolepsy-associated cataplexy. It is a licensed medicine for human use in only four Member States. GHB is not authorised for veterinary use. There are no known reported industrial uses of GHB, however, GBL and 1,4-butanediol have many uses in various industrial processes.

3. Health risks

3.1. Individual health risks

(a) Acute effects: Evidence relating to the activity of GHB on neurotransmitter systems is largely contradictory. However, it is believed that GHB binds to GABA B and GHB-specific receptors. It blocks dopamine release at the synapse and produces an increase in intracellular (neuronal) dopamine. This is followed by a time-dependent or dose-dependent non-functional leakage of dopamine from the neurone. In addition, GHB does not appear to be a monoamine oxidase (MAO) inhibitor.

GHB has been reported to lengthen slow-wave/delta sleep without a decrease in oxygen consumption while the respiratory centre remains sensi-

tive to carbon dioxide. It also induces anaesthesia but does not provide pain relief. An increase in growth hormone and prolactin release has been reported in one study of six human subjects.

GHB can cross the blood-brain barrier and is rapidly absorbed and metabolised, possessing a plasma half-life of approximately 20 minutes. It also has a steep dose-response curve, where a small increase in the dose can cause sedation as opposed to just nausea. Following an oral dose, effects usually occur after 15 minutes and can last up to 7 hours, depending on the dose.

At present there are no animal or human data concerning reproductive toxicity, neurotoxicity or the mutagenicity and carcinogenic potential of GHB. However, animal and human studies indicate that GHB toxicity is dose-dependent and can result in nausea, vomiting, hypotonia, bradycardia, hypothermia, random clonic movements, coma, respiratory depression and apnoea.

Other depressant or sedative drugs (e.g. opiates, benzodiazepines, alcohol and barbiturates) and possibly other psychoactive compounds (e.g. amphetamine) can exacerbate the toxic effects of GHB ingestion.

Reported subjective effects of GHB use include: euphoria, hallucinations, relaxation and disinhibition.

(b) Clinical effects: GHB has been associated with 11 deaths in the EU between September 1995 and January 2000: four in the United Kingdom, four in Sweden, two in Finland and one in Denmark. Two deaths have been reported in Norway. Deaths involving solely GHB appear to be rare. The majority of these cases have involved the 'recreational' abuse of GHB for its subjective euphoric ('high') effects, primarily by young adults. The mode of GHB abuse frequently involves the use of other drugs such as alcohol or MDMA.

Non-fatal hospital admissions associated with GHB are difficult to assess as GHB analysis is not routinely performed by hospital toxicology laboratories. However, there have been at least 200 reported GHB overdose cases in Europe (in particular in Sweden, the United Kingdom, the Netherlands, Denmark, Belgium, Finland, Spain and Norway). Clinical management of such patients can be quite difficult, posing risks to both patients and staff.

(c) Dependence: There have been few studies regarding the dependence potential of GHB. However, during studies involving administration of GHB to patients at varying concentrations, no dependence has been observed at

low doses of GHB. At prolonged high doses, however, physical dependence as evidenced by a withdrawal syndrome has been noted in some cases and included symptoms of insomnia, muscular cramping, tremor and anxiety.

(d) Psychological effects: There is limited published data concerning specific psychological effects of GHB either acutely or chronically, therefore the exact effect of GHB on cognition, mood and psychomotor ability is unclear. However, the effects of GHB on the central nervous system have implications for the ability to drive and to operate machinery.

3.2. Public health risks

(a) Availability and quality: Preparations containing GHB have marketing authorisation ([4]) in four countries: in Austria and Italy for alcoholic craving and in France and Germany as an anaesthetic. Growing concern about non-medical use of GHB in Europe as well as in the United States and in Australia has prompted a number of these countries to introduce new and more stringent controls on GHB. The disruption of overt supply has lead to distribution patterns similar to illicit drug networks.

More discreet methods have therefore been adopted by suppliers of GHB alongside the appearance of substitutes for GHB in name or content as well as the development of a home-made 'kitchen-sink' GHB industry due to the fact that it is easily manufactured and no special equipment is required for this process. However, there have been some reports of burns to mouths due to high caustic soda content in home-made preparations.

In dance settings, GHB is frequently sold in liquid form in small 3 ml plastic bottles containing approximately 3 g of GHB, where it is used socially for relaxation, mild euphoria or post-party for sleep. Pharmaceutical-grade GHB is also available through the Internet, catalogue sales and specialist shops in some countries. This market has recently been curtailed by legislation and bad publicity.

On the basis of the available information, it is generally suggested that a 0.5 g dose be taken for relaxation and disinhibition, a 1g dose for euphoric effect, and a 2–3 g dose for deep sleep.

([4]) Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992, and Article 12 of Directive 75/319/EEC of 20 May 1975 regulates through the Committee for Proprietary Medicinal Products (CPMP) the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with Pharmacovigilance.

(b) Knowledge and perception of GHB among users: Although media reporting of GHB is limited, information is available to the populations who use recreational drugs, smart drugs or body-building drugs, via associated social networks. A vast number of Internet sites and newsgroups promote the use of GHB for a wide rage of purposes which include: inducing sleep, mood enhancement, treatment of drug and alcohol withdrawal, sexual enhancement, body-building and anti-ageing.

(c) Prevalence and patterns of use: There are no data specifically on prevalence or patterns of the use of GHB and at present there is little evidence that GHB is used on a wide scale in any Member State.

Anecdotal and Internet reports suggest that use of GHB may not be confined to recreational party drug settings. Some sub-populations appear to use GHB for desired specific effects. Internet postings and outreach workers suggest that GHB can also be used as a substitute for alcohol or drugs to achieve inebriation whilst avoiding detection tests in treatment, the workplace, and for driving. Some police sources and media cover have expressed concern about the ease with which GHB may be used to facilitate sexual assault, but the extent of this is unclear. In this regard, it should be noted that GHB dissolves easily and is colourless, odourless and may be difficult to taste. It can therefore be taken unobtrusively in social settings where drinks are served.

(d) Characteristics and behaviour of users: There is limited information available concerning the characteristics and behaviour of users. Within recreational drug settings, anecdotal reports from youth media and drug workers suggest that the negative effects of GHB may lead to a negative image for the drug. However, it should be noted that the comparatively low price of GHB provides a cheap alternative to alcohol and when used for illicit purposes the effects of GHB are much closer to those produced by alcohol, cannabis and benzodiazepines, than they are to MDMA and other stimulant drugs. The physical incapacity and unconsciousness resulting from a relatively small increase in GHB doses demonstrates that health risks in relation to road traffic or operating machinery are high.

(e) Indicators of health consequences: There is no information on the health consequences for the general population. GHB has been associated with 11 deaths in the EU between September 1995 and January 2000: four in the United Kingdom, four in Sweden, two in Finland, and one in Denmark. In addition, two deaths have been reported in Norway.

Non-fatal hospital admissions associated with GHB are difficult to assess as GHB analysis is not routinely performed by hospital toxicology laboratories.

However, there have been at least 200 reported GHB overdose cases in Europe (in particular in Sweden, the United Kingdom, the Netherlands, Denmark, Belgium, Finland, Spain and Norway).

(f) Context of use: An important factor with regard to context of use is the lack of reliable indications of dose accompanying sales of GHB at 'street level'. However, the steep dose response curve of GHB makes it risky for recreational use even where dose is both accurately measured and known. The combination of GHB with other drugs, particularly alcohol and other sedative drugs, also substantially increases the risks related to taking GHB.

4. Social risks: sociological/criminological aspects

4.1. Sociological aspects

(a) Social consequences: The social consequences for the user are mainly related to the steep dose-response curve and unpredictable dose resulting in loss of physical control and consciousness, and to the ingestion of caustic soda.

(b) Consequences for the social behaviour of the user: There is anecdotal evidence of clumsy behaviour, vomiting and loss of consciousness in dance settings which is regarded unfavourably by music promoters, club owners and youth media journalists.

(c) Other social consequences: The ease with which GHB can be acquired or manufactured allows more consumer power than that usually found in illicit drug markets in the EU. The use of GHB to induce relaxation and sleep promotes the concept of illicit drug use for self-medication purposes rather than hedonism.

The similarity to alcohol regarding effects and route of administration may facilitate diffusion, i.e. in the absence of major value conflicts about use. In view of the pharmacological effects and known health risks, there are implications for a number of social institutions: the media, drug outreach workers, research institutes, hospital emergency departments, community drug and rape services, and the police.

A range of factors such as low price, ease of availability and administration, lack of information, the need for sedation following heavy stimulant use, and careless media coverage, increase the probability of GHB diffusion and consequent harm. Other factors, such as antisocial effects, relatively short dura-

tion, and its low-status image, mitigate against widespread diffusion and so decrease the probability of harm.

4.2. Criminological aspects

No Member State has information on large-scale production, trafficking and distribution of GHB. Seizures of GHB in the EU are very small when compared to seizures of 'regular' types of synthetic drugs such as amphetamine, MDMA and MDA.

Three Member States — France, the Netherlands and the United Kingdom — have information on illicit production of GHB in their country. Production in France seems to be incidental and limited to one 'kitchen'-type facility.

Two Member States — the Netherlands and the United Kingdom — report on the role of organised crime in the production, trafficking and distribution of GHB. In both countries producers of GHB are thought to also be involved in the production of controlled drugs, with dealers possibly having links to ecstasy producers. They are individuals with a criminal background or members of small groups, rather than criminal networks.

A particular consequence that has been linked with GHB by some media and police reports is the potential for GHB to be used surreptitiously for sexual purposes, possibly including rape.

5. Possible consequences of prohibition

5.1. Legal status

An analysis of the legal status of GHB in the 15 Member States shows that the drug is controlled under the misuse of drugs legislation in six of them: Belgium, Denmark, France, Ireland, Italy and Sweden. It is similarly controlled in Norway. GHB is controlled by the Medicines Act in Austria, Finland, Germany and the Netherlands. In the United Kingdom where its manufacture and supply fall within the scope of the Medicines Act, consideration is being given to controlling GHB under the misuse of drugs legislation. In Greece and in the Netherlands, it is subject to monitoring.

The precursor GBL (gamma-butyrolactone) is currently on the voluntary monitoring list of the Drug Precursors Committee of the European Commission. The other precursor of GHB — 1,4-butanediol — is not on this list. The list is circulated to the chemical industry, members of which are

asked to notify any suspicious enquiries and transactions in the chemicals to the competent authorities. There are no formal controls on the chemical.

5.2. Possible consequences of prohibition

The possible consequences of prohibition were discussed at the meeting and included the points listed below.

- The EMEA drew attention to the existence on the market of authorised medicines containing GHB in four Member States and the possibility of an application for Orphan Drug Designation for GHB being submitted in light of the submission to the US-FDA (US-Food and Federal Administration). The EMEA also highlighted the fact that changes in the conditions of marketing authorisations for GHB containing medicinal products proposed by the meeting should be dealt with at national level.
- The meeting was informed of the results of a critical review of GHB by the 32nd WHO Expert Committee on Drug Dependence which recommended to the Commission on Narcotic Drugs (CND) that GHB be listed in Schedule IV of the 1971 United Nations Convention on Psychotropic Substances. It was pointed out that it was for the CND to decide whether or not to accept this recommendation.
- It was reported by a number of participants that Member States who had subjected GHB to control had noted a reduction in intoxications involving GHB. It was pointed out that following a decision not to control GHB in one Member State, a reduction in non-fatal emergencies was also observed. Systematic data, however, was unavailable in both instances.
- Concern was expressed about the possible impact of prohibition on the licit production of GBL and 1,4-butanediol because of the high level of production and the wide range of industrial applications for both compounds.
- Concern was also expressed about the negative effects of prohibition on black market conditions.
- Considerable debate took place about the possible methods of control. One opinion was that medicines legislation [5] was sufficient because it

[5] That is to say EU Regulation based upon Council Directive 65/65/EEC of 26 January 1965, as amended by Directives 83/570/EEC, 87/21/EEC, 89/341/EEC and 93/39/EEC, as well as Decisions of the Court of Justice of the European Communities, especially Case C-112/89.

could permit seizure of products and prevent both advertising and sale of such products. Other participants were of the view that medicines legislation was insufficient and that stronger measures of control were necessary. It was pointed out that such strong measures of control did not mean that the consumer should be punished. Doubt was expressed as to whether medicines legislation would be effective where no marketing authorisations were in place and it was recommended that this point should be further investigated.

6. Conclusions

The Scientific Committee of the EMCDDA, extended with experts from the Member States, and representatives of the Commission, Europol and the EMEA, have considered the health and social risks as well as the possible consequences of prohibition of GHB and in accordance with Article 4 of the joint action, submit the following conclusions:

6.1. GHB is not a new synthetic drug. It has therapeutic potential and preparations containing it are registered medicines in four Member States. It is also used in recreational settings.

6.2. GHB has anaesthetic and sedative properties. In recreational use, the dose margin between the desired and the serious adverse effects is narrow. Because of the effects of the drug, the levels of fatal and non-fatal emergencies and reports of dependency, GHB is considered to pose significant risks to health. The possible involvement of GHB in drug-assisted sexual assaults was of concern even though the extent of this involvement is unclear.

6.3. An opinion which received significant support at the meeting was that this substance should be subjected to more stringent control measures than the medicines legislation.

6.4. Another opinion was that control through medicines legislation is sufficient.

6.5. The meeting noted that the precursor GBL was rapidly converted to GHB both within and outside the body whereas the precursor 1,4-butanediol was rapidly converted within the body. Noting that GBL is included in the monitoring programme under the Precursor Regulations, the meeting recommended that the Drug Precursors Committee set up under

Article 10 of Regulation 3677/90/EEC and Directive 92/109/EEC should strongly consider the inclusion of 1,4-butanediol within the monitoring system.

6.6. The Committee recommended that Member States should consider convening an expert group to consider the role of GHB and other drugs in cases of sexual assault.

6.7. The meeting noted that biological samples could contain levels of GHB in circumstances where there was no evidence of GHB consumption and recommended that this phenomenon should be the subject of further study with a view to establishing guidance for best practice in the handling and analysis of biological samples containing GHB.

6.8. The meeting highlighted the need to target objective information on GHB to existing and potential users as well as to key professional groups.

Lisbon, 26 September 2000

Europol–EMCDDA progress report on GHB in accordance with Article 3 of the joint action of 16 June 1997 concerning the information exchange, risk assessment and the control of new synthetic drugs

Introduction

The Horizontal Working Party on Drugs, at its meeting of 22 September 1999, requested the EMCDDA and Europol to provide preliminary information on the substance GHB under Article 3 of the joint action. Europol national units and Reitox national focal points were subsequently requested to provide information on GHB. The EMCDDA and Europol also conducted enquiries. No reporting took place using the 'Europol–EMCDDA reporting form on new synthetic drugs'.

Six Member States have decided to put GHB under permanent control: Belgium (Royal Decree 22.1.1998); Denmark (Euphorians Act, 16.12.1999); France (Decree 28.4.1999); Ireland (Misuse of Drugs Act, May 1999); Italy (Decree 266, 11.11.1999); and Sweden (Narcotics Act, 13.1.2000).

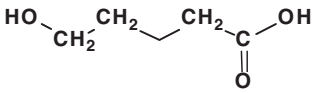
In Austria, Finland and Germany, GHB is controlled by the Medicines Act. In Greece, it is subject to monitoring. In the United Kingdom, the Advisory Council of the Misuse of Drugs recommended monitoring of GHB misuse; its manufacture and supply fall within the scope of the Medicines Act 1968. In the Netherlands, GHB has been controlled by the Medicines Act since 1996. In October 1999, the Dutch Coordination Centre for Assessment and Monitoring of New Drugs of Misuse (CAM) concluded its risk assessment on GHB and recommended continued monitoring and a further risk assessment in case of new evidence.

Available information on GHB

Chemical and physical description, including the name under which GHB is known

The full chemical name for GHB is gamma-hydroxybutyrate.

Figure 1: Structural formula of GHB



GHB is known by a variety of street names: 'liquid ecstasy', 'gamma-OH', 'oxybate', 'somatomax', 'GBH', 'happiness drops', 'liquid loving' and others. It is usually available as a clear, odourless, colourless and sometimes tasteless liquid. The substance is most frequently sold in plastic bottles or in capsules. It is also available in the form of white powder tablets.

GHB was originally developed as an anaesthetic drug and is used as a licensed medicine in some Member States. It acts as a central nervous system depressant and hypnotic and is chemically related to the brain neurotransmitter gamma-aminobutyric acid (GABA). In some Member States, GHB is offered for retail sale through shops, the Internet and magazine advertisements. The typical dose is around 10 ml equivalent to about 1g of GHB.

GHB is absorbed within 10–15 minutes and in adverse circumstances neither flumazenil nor naloxone appear to be effective. GHB cannot be detected in blood or urine by means of routine toxicological analysis, nor does it react with the reagents in commonly used field-test kits. Suitable methods of identifying GHB in the laboratory are NMR and infrared spectroscopy.

Information on the frequency, circumstances and/or quantities in which GHB is encountered

In Austria, although there have been no reported seizures or hospital treatment episodes attributed to GHB, there is some anecdotal evidence of use among very small, closed groups.

In Belgium there are regular seizures, particularly during the summertime, of small quantities of GHB in liquid form and, incidentally, in capsules. In

September 1999, there was a report of two cases of hospitalisation near the French border. GHB was suspected but results from blood sample analysis have not been made available yet.

In Finland, 757 millilitres of GHB were seized in seven incidents in 1998. In 1999, the Finnish forensic laboratories analysed samples of GHB relating to total seizures of over 3 800 grams. Also, over 5 litres of the precursor GBL were seized.

In France, there have been few seizures reported and no reported fatal or non-fatal intoxications. A survey, which compared 900 young people who regularly attended techno party events with a control group matched for age and sex of people who do not attend such events, found that 4 % of techno party attenders said they had taken GHB. Among the control group, consumption of GHB was non-existent indicating that the use is not widespread.

According to the French Centre d'Evaluation et d'Informations sur les Pharmacodependances, abuse of 1,4-butanediol as a substitute for GHB has increased since the classification of the latter under French legislation, in April 1999. The substance 1,4-butanediol is being sold as 'ecstasy'.

In Denmark, there have been five seizures of GHB since June 1999 and in the same period 12 patients with non-fatal intoxications associated with GHB have been treated in hospital.

Germany reports some incidents of seizures of small, insignificant quantities of GHB.

In Ireland, one seizure of GHB in liquid (25 millilitres) and one in powder form were reported.

In the Netherlands, there were a number of small seizures from discotheques. At least eight hospitalised, non-fatal intoxications associated with GHB have been recorded. Producers of GHB are thought to be involved in the production of controlled drugs, with dealers possibly having links to ecstasy producers. They are individuals with a criminal background or members of small groups, rather than criminal networks.

In Spain, the first seizure took place in Madrid in January 1996. From 1996 to November 1999, a total of 16 small seizures were reported. Since 1995, one non-fatal intoxication was registered. On the basis of current evidence, GHB use in Spain is thought to be very limited (Cabrera et al., 1998).

In Sweden, seizures have found GHB in connection with other seizures of narcotic drugs and anabolic steroids. In 1997, one seizure of 50 kg was

reported, and in 1998 one seizure of 13.5 and 20 litres as well as some small seizures.

In the United Kingdom, London, the North-West, the Midlands and South Wales have been identified as the main areas of production and supply. GHB is mainly distributed through retail outlets and over the Internet. Proactive enforcement against sale and supply of GHB via retail outlets has curtailed the overt advertising and supply of GHB, particularly in London's sex shops. The disruption of overt supply has led to distribution patterns similar to those of illicit drug networks. In addition, the Medicines Control Agency (MCA) has taken action against a number of unlicensed operators. There is little evidence of widespread use or that illicit use is increasing. GHB is supplied to bodybuilders via mail order and in gyms. Seizures are rarely submitted for laboratory examination. The Forensic Science Service handles less than 10 cases each year. There is no current intelligence regarding international trafficking of GHB into or from the United Kingdom. There is intelligence that the precursor, GBL, is being sourced from other Member States, for example Belgium, to be used in GHB production. The high profit margins and the comparatively limited penalties encourage the involvement of organised criminal groups. There is evidence of criminals involved in controlled drugs also being involved in the production and supply of GHB.

A first indication of the possible risks associated with GHB

In small doses (10 mg/kg body weight) GHB diminishes tension but in marginally larger doses (50–70 mg/kg body weight) it can cause nausea, vomiting, confusion, convulsion, anaesthesia, apoplexy, respiratory depression and coma.

It has been stated that adverse effects occurred both when GHB was used alone or in combination with other drugs and alcohol (Williams et al., 1998). The risks of GHB consumption are more severe when taken with alcohol and drugs such as benzodiazepines, barbiturates, opiates, anti-convulsants, and antihistamines.

GHB use could lead to the development of physical dependence (Galloway et al., 1997).

The earliest recorded indications of illicit use of GHB were in Sweden and in the United States during the early 1990s. At that time in Sweden, the small number of GHB overdoses was associated with bodybuilders.

Since 1995, eight deaths linked to GHB use have been reported within the European Union [6]. In September 1995, March 1996, November 1997 and January 1999, four deaths were reported from the United Kingdom. In February 1996 and in March 1997, two deaths were reported from Sweden. Alcohol was implicated in each of the deaths in Sweden and the United Kingdom. In 1998 and in 1999, two deaths were reported from Finland.

A substantial number of hospital admissions and comas associated with a combination of GHB and alcohol were reported from the United Kingdom, Sweden and the Netherlands. In the Netherlands, the conclusion of the risk assessment on GHB for continued monitoring was based mainly on the danger the drug presented for individual health, due to the fact that the desired effect and the dosage to cause unconsciousness or reversible coma are closely linked to each other.

Information on chemical precursors

The precursor to GHB is gamma-butyrolactone (GBL), a solvent widely used in industry and commercially available. GHB is easily manufactured by adding aqueous sodium hydroxide to gamma-butyrolactone (GBL). No special equipment is required for this process. A major technical difficulty facing control of GHB is that the chemical reaction above is reversible. The precursor can simply be recovered from a GHB solution by adding acid to neutralise the sodium hydroxide. Because of the wide use of these chemicals, the monitoring of sales in Europe does not offer a feasible method of identifying illicit production.

Information on the mode and scope of established or expected use of GHB as a psychotropic substance

Effects of GHB are more similar to those produced by alcohol, marijuana and diazepam, than they are to MDMA and other stimulant drugs. Although GHB may be distributed through the same market as ecstasy, it is not likely to be purchased as or mistaken for ecstasy because of its distinguishing physical appearance and effects. GHB dissolves easily and is colourless, odourless and sometimes tasteless. Therefore, it can be taken easily and unobtrusively in social settings where alcoholic drinks are served. The comparatively low price of GHB may provide a cheap alternative to alcohol for young people on low incomes.

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[6] In 1993, one death, which occurred in association with heroin use, was recorded in Italy.

The reasons given by the techno party attenders in the French survey for taking GHB included the effects induced by taking it. Additional reasons were that in association with other substances it enhanced the overall effects or facilitated the 'come down' from taking stimulant drugs.

There is little evidence that GHB is abused on a wide scale in any Member State. In parts of the United Kingdom, GHB use is reported as being established on the 'gay scene' and it is thought to have made some inroads into the 'heterosexual scene'. Anecdotal and media reports have suggested that GHB has widespread potential for being surreptitiously added to drinks for sexual purposes, including rape.

Books about GHB are available and information about recipes, taste, effects and where to purchase supplies is commonly exchanged via the Internet.

Information on other use of GHB and the extent of such use

There are claims that GHB has anabolic properties and bodybuilders therefore use it. Internet discussion groups and other media provide evidence that GHB is used outside of the 'dance scene' for a number of reasons such as: to induce sleep, as a substitute for alcohol, and for sexual purposes and relaxation.

Drafted by Europol and EMCDDA
17 March 2000

Use of GHB as a medicinal product (EMEA)

As part of the preparation for the risk assessment of GHB, the European Agency for the Evaluation of Medicinal Products (EMEA) asked for information on the national situation of this product in terms of authorisation and therapeutic value.

According to the responses received, GHB is authorised only in four countries: in Italy and Austria for alcohol craving, and in France and in Germany as an anaesthetic. In Germany it was put on the market before the German Medicines Act came into force in 1978. Sales figures were not provided but it can be assumed that they are low. GHB is subject to restricted prescription in France and is regulated as a psychotropic substance in Italy.

Review of the pharmacotoxicological data on gamma-hydroxybutyric acid (GHB) [7]

This report was commissioned by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as a background paper for the risk assessment of the compound GHB. The report follows the structure of Annexes A and B of the risk-assessment guidelines developed by the Scientific Committee of the EMCDDA.

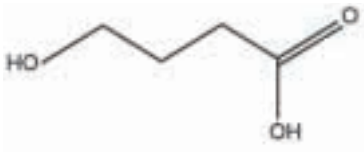
Pharmacotoxicological evidence

Chemical/pharmaceutical information

Chemical description

Gamma-hydroxybutyric acid (shown below) refers to the protonated form whereas gamma-hydroxybutyrate refers to the deprotonated form of the carboxylic acid moiety. The abbreviation GHB refers to both of these chemical names. Other chemical names include oxybate, 4-hydroxybutanoic acid, and 4-hydroxybutyric acid. The chemical structure is shown in Figure 2.

Figure 2: Chemical structure of GHB



Molecular formula:	$C_4H_8O_3$
Molecular weight:	104.11

The chemical abstracts registration (CAS) number for 'free' gamma-hydroxybutyric acid (GHB) is [591-81-1] and [502-85-2] for GHB sodium salt

[7] This report was written by S. P. Elliott of the Regional Laboratory for Toxicology (City Hospital NHS Trust, Birmingham, United Kingdom) for the risk-assessment meeting on GHB; Lisbon 25 and 26 September 2000, EMCDDA.

(NaGHB). GHB sodium salt is a white solid, soluble in water and methanol. GHB salts other than sodium can also be formed, for example GHB potassium salt (KGHB).

Precursors

There are various chemical precursors to GHB. Gamma-butyrolactone (GBL) and 1,4-butanediol have both been found to undergo in vivo conversion to GHB in animals and humans. The hydrolysis of GBL to GHB is catalysed in vivo by a lactonase (Roth et al., 1966). In rat whole blood the half-life conversion of GBL was only 1 minute, with serum more active than plasma (Roth et al., 1966). 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. GHB formation from GBL is chemically a reversible reaction and appears to be pH dependent. Under acidic conditions, GHB can be converted to the lactone, GBL, a process that has been exploited for gas chromatographic analysis of the compound (Vree et al., 1976). No endogenous GBL has been detected in plasma or urine, therefore, it is assumed that this conversion does not occur in vivo. 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) (Maxwell et al., 1971; Roth et al., 1968).

Methods 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 (Ward et al., 1998).

IDENTIFICATION

The analytical profile of GHB has been described in numerous papers. In particular, data pertaining to gas chromatography with mass spectrometry (GC-MS) and gas chromatography with flame ionisation detection (GC-FID) are described (Vree et al., 1976; McCusker, et al., 1999; Ferrara et al., 1993; Couper et al., 2000); analysis usually requires conversion to γ-butyrolactone (GBL) or chemical derivatisation. A chemical (colour reaction) spot test has been developed which also requires the conversion of GHB to GBL (Badcock et al., 1999). GHB is not detectable using traditional field-test kits.

Legitimate uses of GHB

GHB has been used in various pre-clinical and clinical trials since 1960. GHB was originally evaluated as an anaesthetic particularly in France and Germany (as Gamma OH™ and Somsanit™, respectively). It has also been assessed in the treatment of narcolepsy and associated disorders such as cataplexy, in addition to its use as an aid to opiate and alcohol withdrawal in Italy (as Alcover™). There are no known reported industrial uses of GHB, however, GBL and 1,4-butanediol are used as solvents in various industrial processes.

Pharmaceutical form

GHB is available as either a liquid formulation or as a powder (either loose or sometimes in a capsule). It has various street names including 'liquid ecstasy', 'liquid E', 'GBH', 'easy lay', 'scoop', 'liquid X', 'fantasy' and 'cherry meth'.

Seized GHB material in Europe appears to consist of both powder and liquid preparations. Seizures of GBL and 1,4-butanediol are predominantly in liquid form. The following is a list of some common (mostly previously available) GHB-related products usually sold as 'nutritional or dietary supplements' (http://www.erowid.org).

'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.

Route of administration and dosage

As GHB is invariably obtained in the form of a powder or liquid formulation, 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. 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 web sites and books which advocate GHB use suggest that an individual 'finds the dose they are comfortable with' and 'takes GHB on an empty stomach for a more rapid effect' (Ward et al., 1998). This is due to the fact that GHB appears to 'effect different people in different ways' — a euphoric dose for one person could be a sedative dose for another (Kam et al., 1998). The steep dose-response curve of GHB — where a small increase in the dose can cause sedation as opposed to just nausea — could also cause problems in terms of the user selecting the required dosage or taking subsequent doses in quick succession. However, it is generally suggested that a 0.5 g dose be taken for relaxation and disinhibition, a 1 g dose for euphoric effect and a 2–3 g dose for deep sleep (Ward et al., 1998; http://www.erowid.org; http://www.lycaeum.org).

Toxicology and pharmacology in animals and humans

Pharmacodynamics and preclinical safety data

NEUROPHARMACOLOGY

GHB was first synthesised in 1960 by Laborit (1964) in an attempt to study the effects of butyric acid and GABA (γ-aminobutyric acid), producing a compound which would interfere with β-oxidation and would cross the blood-brain barrier. Bessman and Fishbein (1963) later discovered that GHB is an endogenous compound existing as a proposed metabolite of GABA. During these studies GHB was isolated in the brain of both rats and humans. Some researchers postulated that GHB was also a putative neurotransmitter or neuromodulator (Mandel et al., 1987; Cash, 1994).

There have been many studies detailing the effects of GHB on various neurotransmitter systems, particularly serotonin (5-HT, 5-hydroxytryptamine), 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, for example, dynorphin (Hechler et al., 1991).

Giarman and Schmidt (1963) noted that at relatively high doses of GHB, ACh levels were increased in certain regions of the brain. Early work by Gessa et al. (1966) studied the effect of GHB on 5-HT, NA and DA in the brains of rabbits and Long-Evans rats. Rabbits were injected intravenously (i.v.) and rats were injected intraperitoneally (i.p.) with varying doses of GHB ranging from 250 mg/kg to 2 000 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 2 000 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 2 000 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 2 000 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 (Walters et al., 1973; Bustos et al., 1972; Spano et al., 1971; Cheramy et al., 1977; Godbout et al., 1995). It appears that there is an initial inhibition of DA release at the synapse but an increase in neuronal DA production. After this intracellular increase in DA there is either a time-dependent (DA increases with time) or dose-dependent non-functional leak of DA from the neurone (low doses inhibit, high doses stimulate). Both theories ultimately result in a pronounced increase in brain DA concentration. However, Feigenbaum and Howard (1996) 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.

GHB was also found to have an affinity for two receptors in the brain — a possible GHB-specific receptor and $GABA_B$ receptor. GHB appeared to have no affinity for the $GABA_A$ receptor. Evidence for a GHB-specific receptor came from experiments by Benavides et al. (1982) and Maitre et al. (1990) involving radiolabelled GHB ((^3H)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. 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_i or G_o family of proteins (Ratomponirina et al., 1995). Godbout et al. (1991) reported that there is an increase in spontaneous firing in prefrontal cortical neurones after administration of low doses of GHB. 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, $GABA_B$ (Nissbrandt et al., 1996; Bowey, 1989; Xie et al., 1992; Williams et al., 1995). GHB has been found to be only a weak agonist of this receptor, exhibiting a binding affinity of 1 000 times less than GABA and 1 000 times less than binding to the GHB-specific receptor (Mathivet et al., 1997). Studies using a $GABA_B$ antagonist, CGP 35348, indicated that GHB activation of the $GABA_B$ receptor produces hyperpolarisation (Williams et al., 1995). A Na^+ dependent GHB transport has also been discovered which is thought to remove GHB from the synaptic cleft following neuronal release (Benavides et al., 1982).

Neuroendocrinology

Following an intravenous 2.5 g dose of GHB in six male human volunteers, a significant increase in both plasma prolactin and growth hormone (GH) was observed at 30, 45, 60 and 90 minutes post dose (Takahara et al., 1977). Five of the six patients fell asleep. These effects were not observed in the saline controlled group. As DA is known to inhibit prolactin production, the results suggested there was a GHB-induced reduction in DA. However, as growth hormone secretion is known to be increased by dopaminergic stim-

ulants, 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 humans (Kato et al., 1974; Smythe et al., 1975). 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 stimulates or blocks the release of GH-releasing or GH-release inhibiting and prolactin-release inhibiting hormones. The slow-wave and REM (rapid eye movement) 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 (Chin et al., 1992).

Cardiovascular and respiratory effects and thermoregulatory responses

Laborit (1964) 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). 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 (1964) also observed a strong hepatic and renal vasodilating action, particularly during haemorrhagic shock in animals, indicating that GHB has 'antishock activity'. In humans, after a 2–4 g injection of GHB there appeared to be no effect on blood pressure, unless during surgery when, in the absence of adequate neuroplegic premedication, a progressive hypertensive episode occasionally occurred. In addition, there were no unfavourable effects observed in 50 human atherosclerotic patients under GHB anaesthesia. However, a frequent decrease in the amplitude of the *T*-wave was noted, but this appeared to be due to the hypokalaemia (reduction in serum potassium levels) associated with GHB (Laborit, 1964). 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 (Laborit, 1964).

Laborit also observed in both animals and humans 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 apnoea, often observed in coma patients); however, the respiratory centre remained sensitive to an increase

in carbon dioxide (pCO_2). Both Laborit and Gessa (1966) 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).

Effects on brain function

Many researchers have recorded the effects of GHB on brain function in animals and humans using an electroencephalogram (EEG) (Laborit, 1964; Winters et al., 1967; Marcus et al., 1967; Scotti et al., 1978; Mamelak et al., 1977; Metcalf et al., 1966; Entholzner et al., 1995). 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 (Laborit, 1964).

Based on behavioural and electroencephalographic criteria, GHB-induced sleep has been described as being indistinguishable from natural sleep, that is unlike coma. The natural stages of sleep 1–2–3–4–REM (rapid eye movement) all occur in their normal sequence (Mamelak et al.,1977). GHB has been noted to lengthen 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.

Toxicology

At present there are no animal or human data concerning reproductive toxicity, neurotoxicity or the mutagenicity and carcinogenic potential of GHB.

Toxicity in animals

Laborit (1964) 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.). In rats, the LD_{50} (i.p.) was 1.7 g/kg and the LD_{100} was 2 g/kg. The cause of death was reported to be respiratory depression; however, using artificial respiration rabbits tolerated doses up to 7 g/kg. With respect to weight, bone marrow, liver and kidneys, there were no significant differences observed between controls and rats receiving 0.17 g/kg GHB daily for 70 days.

During the course of the various experiments involving the administration of GHB to animals at numerous doses, the following observations 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

Early reviews concerning the use of GHB, particularly in anaesthesia, suggested that GHB was non-toxic (Laborit, 1964). Short amnesia and hypotonia have been associated with an oral dose of 10 mg/kg GHB (Chine et al., 1992). REM sleep can be induced in humans using an oral dose of between 20-30 mg/kg GHB (Mamelak et al., 1986; Yamada et al., 1967). 50–70 mg/kg GHB given intravenously produces hypnosis but has little analgesic effect (Appleton et al., 1968). This dose may also cause hypotonia, bradycardia, nausea, vomiting, random clonic movements of the face and extremities and Cheyne-Stokes respiration (Laborit, 1964; Chin et al., 1992). 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 (Vickers, 1968). High oral doses of GHB (greater than 60 mg/kg) can also result in coma, usually lasting up to 4 hours (Mamelak, 1989). Table 1 shows a summary of resultant concentrations following various GHB doses.

Table 1: Reported concentrations 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., 1993
75 mg/kg (oral)	Sleep	90 mg/l (peak plasma) 2 hours 9 mg/l (plasma) 6 hours	Hoes et al., 1980
50 mg/kg (i.v.)		170 mg/l (peak blood)	Helrich et al., 1964
100 mg/kg (oral)		1 100 mg/l (peak urine) in 4 hours	Hoes et al., 1980

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.

Interactions with other drugs or medicines

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 apnoea, vomiting and random clonic movements (sometimes reported as being seizures) (Kam et al., 1998; Chine et al., 1998; Li et al., 1998a; Li et al., 1998b). Presenting patients have been reported to have initial GCS scores (Glasgow coma score) of between 3 (severe decrease in consciousness) and 15 (wakeful) (Chin et al., 1998; Williams et al., 1998). There have been no detailed studies concerning the interaction of GHB with other drugs or medicines. However, it is believed the adverse effects of GHB intoxication are exacerbated by the presence of other sedatives or depressants such as opiates (e.g. heroin or morphine), benzodiazepines, barbiturates or alcohol (e.g. ethanol) and possibly other psychoactive compounds (e.g. amphetamine). Depending on the nature of the interaction, resultant effects may also depend on the order in which the drugs are administered — for example, there may be potential problems if amphetamine is ingested after GHB due to the resultant release of neuronal dopamine.

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 (Mamelak et al., 1986; Yamada et al., 1967; Vickers, 1968). 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 (Mamelak et al., 1986). An investigation by Henderson et al. (1976) showed that intravenous physostigmine was effective in reversing the anaesthetic action of GHB in 25 patients. These results were confirmed by Schöntrube et al. in 1993. 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) (Appleton and Burn, 1968). 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

As GHB is not usually detected during routine toxicological analysis (Badcock and Zotti, 1999; Williams, 1998; Elliott, 2000) the evidence for GHB or related product ingestion (e.g. GBL or 1,4-butanediol) is usually based on anecdotal or circumstantial evidence.

There have been many reported cases of intoxication linked to GHB, however, there also appear to be many more unconfirmed/anecdotal reports (http://www.erowid.org; http://www.lycaeum.org). 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 (CDC, 1999; Dyer et al., 1997; Rambourg-Schepens et al., 1997). This is consistent with the reported in vivo conversion of these compounds to GHB (Poldrugo and Snead, 1984; Lettieri and Fund, 1978).

The majority of reported cases have occurred in the United States (Couper and Logan, 2000; Chin et al., 1992; Chin et al., 1998; Li et al., 1998; Stokes and Woekener, 1998; CDC, 1999; CDC, 1997; FDA, 1990; FDA, 1997; CDC, 1990; CDC, 1997; Dyer et al. 1991; Steele and Watson, 1995; Dyer, 1991; Viera and Yates, 1999; Eckstein et al., 1999) and Europe (http://erowid.org; Williams et al., 1998; EMCDDA; Elliott, 2000; Kouagie et al., 1997; Vandevenne et al., 2000; Hovda et al., 1998; Personne and Landgren, 2000; Knudsen, 2000; Hunderup and Jorgensen, 1999) although abuse of GHB has also been reported in Australia (Australian Drug Foundation). Based on documented cases and reports to Reitox national focal points, it can be estimated that there have been at least 200 presumed GHB overdose cases in Europe (EMCDDA); global estimates range from hundreds to thousands of cases (CDC, 1997a; FDA, 1990; FDA, 1997; CDC, 1990; CDC, 1997b). In Sweden and the United Kingdom alone, there have been at least 100 apparent GHB-related hospital admissions since 1996. Eight cases have been reported in the Netherlands, 12 cases in Denmark, two cases in Belgium, two cases in Finland, three cases in Norway and one case in Spain (EMCDDA).

Williams et al. (1998) reported six cases of probable GHB intoxication occurring between 1995 and 1996 in London, United Kingdom. These cases are summarised in Table 2. The clinical observations in these cases confirm those of other cases where it appears that patients present in various states ranging from initial confusion, dizziness or euphoria, leading to collapse, vomiting and loss of consciousness/coma (Chin et al., 1992; Chin et al., 1998; Li et al., 1998; Li et al. 1991; Dyer et al., 1991; Steele and Watson,

1995; Dyer, 1991; Viera and Yates, 1999; Eckstein et al., 1999). Administration of naloxone and flumazenil did not appear to have a significant 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 usually ascertained/analysed. Furthermore, in these particular cases 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.

Table 2: Six cases of United Kingdom reported hospital admissions implicating GHB ingestion and toxicity

Case No	Patient details	Reference and country of occurrence	Clinical presentation	Comments
1	32 yr M	Williams et al., 1998 (United Kingdom)	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 nitrite.
2	28 yr M	Williams et al., 1998 (United Kingdom)	Collapsed, unconscious. GCS 3, BP 100/60, pulse 90 bpm. Naloxone given — no effect. Discharged 10 hours after arrival.	One capsule of GHB at nightclub. Reported to have also taken MDMA.
3	29 yr F	Williams et al., 1998 (United Kingdom)	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.
4	20 yr M	Williams et al., 1998 (United Kingdom)	Collapsed, naloxone given at scene — some recovery. In hospital — decreased level of consciousness. BP 135/70, pulse 60 bpm. Discharged following morning (approximately 6 hours after arrival).	Unknown dose. Heroin user, reported to have taken methadone then GHB to aid opiate withdrawal.
5	25 yr M	Williams et al., 1998 (United Kingdom)	Collapsed, unconscious. GCS 3, BP 82/50, pulse 56 bpm. Naloxone given — no effect. Discharged 4 hours after arrival.	Unknown dose. Bodybuilder, GHB powder dissolved in drink with 2 pints of lager.
6	20 yr M	Williams et al., 1998 (United Kingdom)	Collapsed, unconscious. GCS 3, BP 110/45, pulse 74 bpm. Naloxone given — no effect. Discharged 5 hours after arrival.	Unknown dose. First use of GHB, powder dissolved in drink with a large amount of alcohol.

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 (Couper and Logan, 2000; Elliott, 2000; Louagie et al., 1997; Vandevenne et al., 2000, le Gatt et al., 1999; Baselt, 2000; Dyer et al., 1994). A selection of these cases is presented in Table 3.

Table 3: Collection of confirmed hospital admissions involving GHB ingestion and toxicity

Case No	Patient details	Reference and country of occurrence	Drugs detected	GHB concentration	Comments
1	13 yr M	Elliott, 2000a (United Kingdom)	GHB	Serum > 100 mg/l	At school
2	33 yr M	Elliott, 2000a (United Kingdom)	GHB + morphine + 6-MAM	Urine/serum > 100 mg/l	Heroin user
3	32 yr M	Elliott, 2000a (United Kingdom)	GHB + MDMA + amphetamine	Urine/serum > 100 mg/l	
4	44 yr M	Elliott, 2000a (United Kingdom)	GHB + MDMA + cocaine	Urine/serum > 50 mg/l	Nightclub
5	23 yr M	Vandevenne, 2000 (Belgium)	GHB + MDMA + cocaine + amphetamine (no ethanol detected)	Urine = 34 mg/l Serum = 133 mg/l	Ingested an 'unknown' clear liquid, found to be GBL
6	F	Louagie, 1997 (Belgium)	GHB + ethanol (134 mg/dl)	Serum = 125 mg/l	Party

Fatal cases

Approximately 65 deaths in the United States have been linked to GHB since 1990 (FDA, 1997a). In Europe, approximately 11 deaths in which GHB has been implicated have been reported since 1995. United Kingdom (four deaths — September 1995, March 1996, November 1997 and January 1999), Sweden (four deaths — February 1996, March 1997, 1998–2000), Finland (two deaths — 1998 and 1999) and Denmark (one death — January 2000) (http://www.erowid.org; http://www.lycaeum.org; EMCDDA; Elliott, 2000). However, recently there have been a further two unconfirmed cases in the United Kingdom and one case in Sweden (EMCDDA; Mixmag, 2000). Table 4 shows reported cases involving GHB or GBL ingestion. Due to in vivo conversion of GBL to GHB, only GHB is usually detected in biological fluids analysed in such cases. The majority of cases have involved the 'recreational' abuse of GHB for its apparent euphoric or 'high' effects, primarily by young people.

Table 4: Collection of reported fatalities involving GHB ingestion and toxicity

Case No	Patient details	Reference	Drugs detected	Concentration(s)	Comments
1	42 yr M	Ferrara et al. (Italy, 1993)	GHB + morphine + 6-MAM ([1])	Blood GHB = 12 mg/l Urine GHB = 258 mg/l Blood morphine = 770 g/l Blood 6-MAM = 29 g/l	Heroin user, used GHB (Alcover™).
2	21 yr F	Hale (United Kingdom, 1995)	GHB + ethanol	Blood GHB = 356 mg/l Blood ethanol = 47 mg/dl	At a party ingested GHB product 'Seventh Heaven'.
3	31 yr F	Erowid and EMCDDA (Sweden, 1996)	GHB + ephedrine + ethanol		
4	31 yr M	Erowid and EMCDDA (Sweden, 1997)	GHB + ethanol		
5	17 yr F	EMCDDA (Finland, 1998)	GHB + ?		
([1]) 6-MAM = 6-monoacetylmorphine (heroin metabolite)					

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

- The presence of other drugs (particularly alcohol and opiates/opioids e.g. heroin, codeine, methadone and morphine).
- Some researchers describe the presence of GHB in post mortem blood specimens, in cases where there has been no evidence of GHB.
- The GHB concentration found is sometimes low.

The mode of abuse of GHB frequently involves the use of other drugs such as alcohol or MDMA, therefore, deaths involving solely GHB appear to be rare. The presence of alcohol and other depressant 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. (1995) reported a death involving GHB and heroin (diacetylmorphine). A high concentration of morphine was detected in the blood (770 mg/l). In most of the other reported GHB deaths, ethanol has also been involved at significant concentrations (EMCDDA; Hale; Davis, 1999). In the United Kingdom case in 1995 involving both GHB and ethanol, the mechanism of death was stated to be respiratory depression (Hale).

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 (Fieler et al., 1998; Anderson and Kuhwahara, 1997; Stephens et al., 1999). In 1998, Fieler, Coleman and Baselt detected GHB in 15 out of the 20 post mortem blood specimens analysed. 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 eight post mortem urine specimens analysed. They suggested 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. 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. If confirmed by further studies this phenomenon has profound implications for the interpretation of post mortem GHB concentrations.

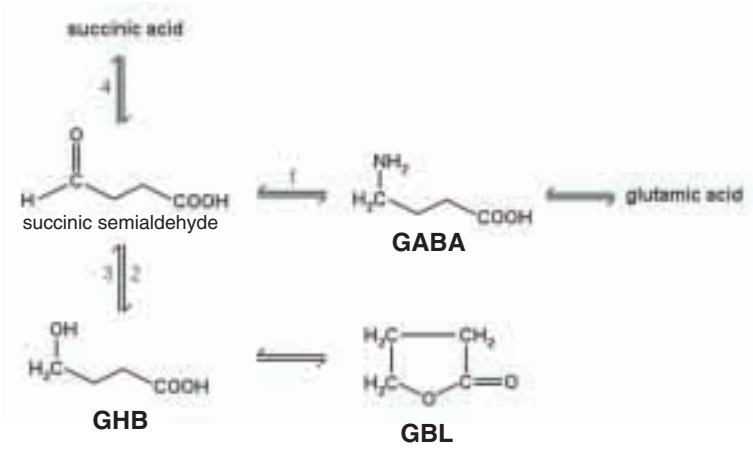
In the majority of GHB-related deaths the concentration in post mortem blood has been found to be 'high', however in several cases the concentration was found to be relatively low, e.g. less than 50 mg/l. Such concentrations are within the range of GHB concentrations apparently produced post mortem, 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.

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

Pharmacokinetics

In 1969, Roth and Giarman demonstrated that [^{3}H]GABA is converted to [^{3}H]GHB via succinic semialdehyde (intermediate compound) in brain tissue. This was later confirmed by Anderson et al. (1977). The conversion is catalysed by the enzymes; GABA aminotransferase and succinic semialdehyde reductase (Figure 3).

Figure 3: Proposed biochemical pathway of GHB synthesis and metabolism



Enzymes:

1	GABA aminotransferase
2	succinic semialdehyde reductase
3	GHB dehydrogenase/GHB-ketoacid transhydrogenase
4	succinic semialdehyde dehydrogenase

Succinic semialdehyde reductase has been found to be different between species; in human and pig brain the enzyme is dimeric (M_R 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. As previously mentioned, GHB can also be produced after administration of γ-butyrolactone (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) (Kaufman et al., 1979; Nelson and Kaufman, 1994). Although GHB has the potential to produce GABA, this was not observed after injecting mice with radiolabelled GHB (De Feudis and Collier, 1976). Laborit (1964) also postulated that GHB 'orientated' glucose-6-phosphate (G6P) into the pentose phosphate pathway (produces ribose for nucleic acid synthesis and NADPH).

In humans, GHB is rapidly absorbed, with peak plasma concentrations (C_{max}) occurring within 20–60 minutes post oral dose (t_{max} = 20–60 min.). This is consistent with the onset of effects occurring approximately 15 minutes after an oral dose and can last for up to seven hours, depending on the dose (Galloway et al., 1997). Effects of intravenous dosage have been reported to occur within minutes, post administration (Takahara et al., 1977). Following a 12.5 mg/kg dose, the half-life was 20 minutes (Vickers, 1969). Only 2–5 % is eliminated as unchanged drug in urine (Laborit, 1964; Hoes et al., 1980).

Clinical experience

Clinical safety data

Preclinical studies

- Laborit (1964) 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. Furthermore, in 1962, Barrier reported that GHB was beneficial in obstetric surgery due to the absence of respiratory depression in the infant and its anti-shock property against possible cardiac anoxia (Laborit, 1964).
- 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 (Laborit, 1964). However, a large proportion of reports regarding GHB's anti-anxiety effects appear to remain anecdotal.
- In 1972, Laborit remarked on GHB's 'aphrodisiac' actions in humans. 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 intensity of orgasm.
- The clinical evidence pertaining to GHB's possible antidepressant effects are largely anecdotal. However, Laborit (1964) 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.

Clinical studies

GHB as an anaesthetic agent

In the 1960s, early work involving GHB assessed its potential as an anaesthetic agent (Laborit, 1964; Appleton and Burn, 1968; Vickers, 1969). Anaesthetic doses within the range 60–70 mg/kg were given intravenously to a patient. GHB has been reported to be involved in over 6 000 cases in general anaesthesia, and 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_2 is maintained, anti-shock 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 and poor pain control. The autonomic nervous system remains active — therefore, as for other anaesthetics, administration of other agents are required such as opioid analgesics. Mainly because of the unpredictable duration of action, GHB was nearly displaced as an anaesthetic agent. However, owing to the rapid metabolism of GHB and the reliable induction of sedation and anaesthesia without depressing either respiratory or cardiocirculatory parameters or liver and kidney function, GHB is being re-evaluated as an agent in emergency and critical care medicine, mainly in long-term sedation of patients (Diedrich et al., 1996; Kleinschmidt et al., 1995; Pichlmeier and Schneck, 1991; Pospiech and Schmidt, 1993).

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 (Mamelak et al., 1986; Broughton and Mamelak, 1979; Scarf et al., 1985; Scrima et al., 1990; Delay et al., 1993) due to its sleep-inducing properties. 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) (Mamelak et al., 1986). 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). Symptoms appeared to intensify during periods of stress, however, few adverse effects were observed. 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 in the morning such as 'Dexedrine' (d-amphetamine) as part of their treatment regimen, in order to achieve the optimal levels of sleep at night and wakefulness during the day. 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 (Mamelak et al., 1986; Scarf et al., 1985).

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-addicted rats with either GHB (at various doses), ethanol or a placebo, 8 hours after the last dose of alcohol. The degree of withdrawal tremor was observed. It was found that GHB appeared to reduce the tremor over a 2-hour period. Gallimberti et al. (1989) assessed the effectiveness of a solution of GHB (Alcover™) in 23 alcoholic humans. One group received 50 mg/kg of GHB and the other group received a similar tasting placebo. A withdrawal symptom score was obtained at baseline and 1–7 hours after treatment. The score was based on the occurrence of tremors, sweating, nausea, depression, anxiety and restlessness. It was found that GHB-treated patients had a significantly consistent reduced withdrawal score, post treatment, compared to the placebo control group. These results appeared to support those observed in rats. In an additional study involving 82 patients, Gallimberti et al. (1992) showed that GHB was effective in reducing alcohol consumption and craving for alcohol. However, no long-term outcome was evaluated.

Further evidence for the effectiveness of GHB in the treatment of alcohol withdrawal syndrome has involved randomised, controlled clinical studies to compare GHB with well established benzodiazepines. In one single blind study involving 60 alcoholic patients, an oral dose of 50 mg/kg GHB was compared with 0.5–0.75 mg/kg diazepam for 10 days (Addolorato, 1999). No significant difference in the overall efficacy was observed. A second study involving 43 alcoholic patients, compared an intravenous GHB dose (50 mg/kg then continued by 10–20 mg/kg/h per infusion) against intravenous flunitrazepam (0.2–2 mg bolus continued by 0.015–0.08 mg/kg/h) for up to 30 days in intensive care patients (Lenzenhuber et al., 1999). If necessary, clonidine and haloperidol were administered to treat autonomic

signs of withdrawal and hallucinations, respectively. Again, no difference in overall efficacy was observed between the two compounds. However, GHB-treated patients required significantly higher haloperidol (possibly due to hallucinogenic properties of GHB) and lower doses of clonidine.

In 1993, Gallimberti et al. treated 27 heroin and methadone-dependent patients with 25 mg/kg of GHB. All patients were in withdrawal and an additional 14 patients were used as placebo controls. A similar withdrawal score to that used for the alcohol study was obtained up to 3 hours after treatment and finally assessed on the eighth day of treatment, before and after administration of naloxone. The results showed that GHB was effective in reducing all the signs of opiate withdrawal symptoms, except for diarrhoea and insomnia, over the 8 days. Although three methadone-dependent subjects and two heroin-dependent subjects reported transient dizziness or vertigo on the second/third day, no other side effects were attributable to the administration of GHB. One limitation of the use of GHB for withdrawal was noted to be its short duration of action, as frequent doses of GHB would be required.

Non-clinical use of GHB (including subjective effects in humans)

It appears that GHB or related products (e.g. GBL and 1,4-butanediol) are used by various groups of people. The use and abuse of GHB has increased since 1990 and has been accompanied by an increased presence of GHB-related web sites 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 or related web sites. 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.
- 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 in an attempt to normalise their sleep patterns.
- Some groups have actively promoted (again usually via the Internet) the potential anti-ageing effects of GHB due to claimed indirect anti-oxidant

properties of the compound by stimulating the glial cell pentose phosphate pathway producing NADPH for the reduction of oxidised glutathione (South, http://www.smartdrugs.com).

- 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'.

- The apparent 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' and may use it as an alternative to alcohol, 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 been found to be associated with social gatherings such as parties, nightclubs, music events (e.g. 'raves' or festivals), 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 allegedly been used for illicit sexual activity or 'date rape', due to the potential incapacitating and sleep-inducing effects of GHB (and GBL or 1,4-butanediol) (Smith, 1999; Sohley and Salamone, 1999). 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 (Ward et al., 1998). 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.

Dependence potential in humans

Dependence potential

There have been few studies regarding the dependence/abuse potential of GHB. However, during the numerous studies involving administration of

GHB to patients at varying concentrations, no dependence has been observed at low doses of GHB. At prolonged high doses, however, physical dependence as evidenced by a withdrawal syndrome has been noted in some cases and includes symptoms of insomnia, muscular cramping, tremor and anxiety (Galloway et al., 1997).

Further studies indicated that GHB maintained self-administration marginally above saline and water (in monkeys and rats, respectively) (Colombo et al., 1995). Studies of the reinforcing and discriminative stimulus effects of GHB in monkeys and rats have indicated that GHB was partly substituted for by morphine, LSD, chlordiazepoxide and GABA-mimetics such as muscimol, GBL, baclofen and 3-aminopropane sulfonic acid in rats (Winter, 1981). GHB did not appear to substitute for d-amphetamine, pentobarbital, diazepam and triazolam in rhesus monkeys (Woolverton et al., 1999). Woolverton et al. (1999) concluded that GHB has, at most, a low abuse potential.

Psychological risk assessment (cognition, mood and mental functioning)

Acute and chronic effects

In general, there are few published data concerning specific psychological effects of GHB either acutely or chronically. However, recently, Ferrara et al. (1999) studied the effects of single dose GHB on psychomotor performance and monitored the patients' subjective feelings. GHB at doses of 12.5 mg per kg and 25 mg per kg, including placebos were given to six male and six female volunteers. The subjects' psychomotor performance was evaluated at baseline and at 15, 60, 120 and 180 minutes post dose using critical flicker fusion, response competition test, critical tracking task, choice reaction time and visual vigilance task. The subjects' mood was assessed before and 120 minutes after treatment using 16 visual analogue scales. The results indicated that GHB at either dose had no effect on vigilance, attention, alertness, short-term memory or psychomotor coordination. Calmness increased at the lower dose and the subjects apparently felt more contented at both dose regimens. Observed adverse effects consisted of subjective dizziness and dullness but these feelings disappeared 30–60 minutes after administration.

Various observations made in studies involving the administration of GHB to patients include relaxation, nausea, agitation and sedation/coma (London

Toxicology Group; Takahara et al., 1977; Chin et al., 1992; Mamelak et al., 1986; Vickers, 1969). No long-term effects have been reported. After awakening patients are usually alert and feel 'refreshed', however, there have been some reported instances of transient mental disturbance (Steel, 1968). Galloway et al. (1997) reported that one patient using GHB (dose unknown) described effects similar to those experienced after alcohol ingestion and also that it impaired his ability to drive. Two cases have been reported where GHB has been detected in the blood and urine of drivers. In one case the driver was found asleep at the wheel after stopping in a traffic lane (Stephens and Baselt, 1994) and a second driver involved in a road traffic accident was reported to be confused, combative and delirious (Baselt, 2000).

Other researchers have evaluated the effect of GHB in the treatment of schizophrenia as it was thought that GHB-induced inhibition of dopamine neuronal firing would be beneficial to afflicted individuals. Levy et al. (1983) and Schulz et al. (1981) in two separate studies generally did not observe any significant antipsychotic efficacy of GHB.

Conclusions

- GHB is not a new synthetic drug. It was synthesised in 1960 by Laborit but was later found to be a naturally occurring compound in mammalian brain and other tissues.
- Evidence relating to the activity of GHB on neurotransmitter systems is largely contradictory, however, it appears that GHB is a hyperpolarising compound that blocks dopamine release at the synapse and produces an increase in intracellular (neuronal) dopamine.
- GHB has been reported to produce enhanced slow-wave/delta sleep without a decrease in oxygen consumption while the respiratory centre remains sensitive to carbon dioxide. It also induces anaesthesia but does not provide pain relief. An increase in growth hormone and prolactin release has been reported in one study of six human subjects.
- GHB can cross the blood-brain barrier and can be produced in vivo as a product of GABA metabolism and after administration of GBL (γ-butyrolactone) or 1,4-butanediol. GHB is rapidly absorbed and metabolised, possessing a plasma half-life of approximately 20 minutes and has a steep dose-response curve. Following an oral dose, effects usually occur after 15 minutes and can last up to seven hours, depending on the dose.

- GHB has been evaluated for various potential therapeutic uses including obstetrics, anaesthesia, alcohol/opiate withdrawal and treatment of narcolepsy and cataplexy.
- Reports indicate that GHB is used 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), relaxation and antidepressant effects, postulated anti-ageing properties and more recently its apparent euphoric ('high') effects. There have also been reports of GHB allegedly being used in cases of so-called 'date rape'.
- There is limited published data concerning specific psychological effects of GHB either acutely or chronically, therefore the exact effect of GHB on cognition, mood and psychomotor ability is unclear.
- Animal and human studies indicate that GHB toxicity is dose-dependent and can result in coma, random clonic movements, decrease in body temperature, hypotonia, nausea, vomiting, bradycardia, respiratory depression and apnoea. A possible physical dependence has been observed at prolonged high dosage.
- Other depressant or sedative drugs (e.g. opiates, benzodiazepines, alcohol and barbiturates) and possibly other psychoactive compounds (e.g. amphetamine) may exacerbate the effects of GHB.
- In humans, non-fatal instances of intoxication and also deaths implicating GHB have been reported.

Sociological and criminological (Europol) evidence on the risks of GHB

Introduction

GHB was developed in the early 1960s as a human anaesthetic but medical use was limited due to unwanted side effects. Its non-medical use as a sleep aid and bodybuilding supplement in the 1980s, and as a recreational psychoactive drug in the 1990s lead to growing concerns and GHB has been scheduled in the United States and in some European Member States. This report summarises the relevant data required by the Technical Annex C of the *Guidelines for the risk assessment of new synthetic drugs.* In the absence of systematic studies of illicit use of GHB, the sociological and criminological evidence for this report is based on limited information collected from:

- the Reitox national focal points in the 15 EU Member States (1);
- Europol's contribution to the risk assessment of GHB (2);
- EMEA's contribution to the risk assessment of GHB (3);
- the Qualitative European Drugs Network (QED) (4);
- the literature (5);
- key European forensic scientists (6);
- key toxicologists in the United Kingdom (7);
- telephone interviews with key experts in the field of recreational drugs (8);
- the Internet (English-language searches) (9); and
- youth and mass media (English-language searches) (10).

Table 5 presents the topics covered in this annex by briefly indicating the extent and type of evidence that is available. The numbers as in the list above are used in the table to code the sources of information. Where information is available, it is presented and examined under the main category headings. In general, there is insufficient information, or too much overlap, to address each of the subheadings in the text.

Table 5: Sociological and criminological evidence for GHB

Topics	Recorded evidence (see text for details)
Social consequences for the user	Mainly related to the steep dose-response curve and unpredictable dose resulting in loss of physical control and consciousness and to the ingestion of caustic soda. (6, 7, 9, 10)
Primary relations and/or family problems	No evidence but legal sanctions may result in criminal records, distress and stigma for the users and their families, etc. (5, 8)
Education and employment problems	No evidence but legal sanctions may result in users being dismissed from work or education. GHB also offers an opportunity for inebriation without detection to people who are undergoing drug or alcohol treatments or monitoring. (8,9)
Marginalisation	Mainly related to legal controls and sanctions which vary depending on the countries and the sanctions applied. (1, 4, 5, 8, 9)
Consequences on the social behaviour of the user	As above.
Drug-related disorderly conduct	Anecdotal evidence of clumsy behaviour, vomiting and loss of consciousness in dance settings which is regarded unfavourably by music promoters, club owners and youth media journalists. (8, 10)
Drug-related acquisitive crime	No evidence.
Drug-related violence	Reports on the use of GHB for drug-assisted sexual assault. (5, 6, 9, 10)
Drug-related traffic offences	High potential for accidents. (6, 7, 8, 9)
Other social consequences	The ease with which GHB can be acquired, or manufactured, allows more consumer power than that usually found in illicit drug markets in the EU. (8, 9) The use of GHB to induce relaxation and sleep promotes the concept of illicit drug use for self-medication purposes rather than hedonism. (7, 8, 9)
Presence or absence of major value conflicts	The similarity to alcohol regarding effects and route of administration may facilitate diffusion i.e. in the absence of major value conflicts about use. (8, 9)
Implications for social institutions (school, labour, recreational, etc.) and community services	In view of the pharmacological effects and known health risks there are implications for a number of social institutions: the media, drug outreach workers, research institutes, hospital emergency departments, community drug and rape services, police. (4, 5, 6, 8, 9, 10)
Wholesale production and distribution	Distribution of GHB has been identified in 10 Member States, although on a limited scale. Three Member States, France, the Netherlands and the UK, have information on illicit production of GHB.
Violence in connection with wholesale production and distribution	No reliable information available.
Money-laundering aspect	No reliable information available.
Involvement of (international) organised crime	The Netherlands and the UK report on the role of organised crime in the production and trafficking of GHB. Producers are thought to be involved also in the production of controlled drugs. They are individuals with a criminal background or members of small groups, rather than criminal networks.

Table 5 (cont.)

Topics	Recorded evidence (see text for details)
The retail market	GHB has marketing authority in three countries, Italy, France and Germany, for alcohol craving, general, and other anaesthetic. Licit and illicit retail markets provide a range of products for different consumer groups. (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)
Non-commercial 'private' consumption market among users	A home-made 'kitchen-sink' illicit industry has developed due to ease of access to precursors, information and ease of manufacture, but little is known about the nature and extent of this industry and market. (6, 8, 9, 10)
Semi-public subculture consumption market (discos, etc.)	In dance settings GHB is frequently sold in liquid form in small 3 ml plastic bottles containing approximately 3 g of GHB, where it is used socially for relaxation, mild euphoria or post-party for sleep. Licit, pharmaceutical-grade GHB is also available through the Internet, catalogue sales and specialist shops in some countries. The licit market has recently been curtailed by legislation and bad publicity. (1, 6, 8, 9)
Existence and characteristic of street markets	No evidence.
Violence, public order and nuisance implications	No evidence.
Social factors that increase the probability of harm	A range of factors such as low price, ease of availability and administration, lack of information, the need for sedation following heavy stimulant use, and careless media coverage, increase the probability of GHB diffusion and consequent harm. Other factors, such as antisocial effects, relatively short duration, low status image, mitigate against widespread diffusion and so decrease the probability of harm. (1, 4, 8, 9, 10)

Social consequences for the user

The main social consequences of GHB for the user are linked to two different factors: its pharmacological effects and its legal status.

Nausea, vomiting, and loss of physical control and consciousness sometimes resulting from use of GHB may result in unpleasant or expensive consequences ranging from social embarrassment to hospital admission and the sort of invasive medical procedures, which are often used in cases of opiate overdose, such as tracheal intubation. Home-made, 'kitchen-sink' GHB products have been reported to have caused burns to mouth and lungs as a result of large amounts of caustic soda.

Under the current laws in the European Union, the social consequences of taking the drug or supplying friends is significantly greater in countries which have placed GHB under drug control law, such as Denmark, France, Italy,

Ireland and Sweden, than in other countries without legal controls over use. For example legal sanctions can result in dismissal from work, criminal records distress and stigma for the users and their families.

Consequences on the social behaviour of the user

The described loss of physical control associated with the use of GHB has obvious consequences on the social behaviour of users and presents a high risk for driving, cycling or operating machinery. According to outreach workers in the Netherlands:

> *[GHB] has a very negative effect on the atmosphere … people trying to talk and not being able to … not a nice trend, not at all.*

A particular consequence that has been linked with GHB by some media and police reports is the potential for GHB to be used surreptitiously — by adding it to other people's drinks — for sexual purposes, including rape (Sturman, 2000). Such reports are difficult to substantiate because GHB is frequently taken, knowingly, in alcoholic drinks and together with other drugs. Also, the majority of individuals who reported sexual assault to the police also reported that they had been in the assailant's company and had consumed alcohol and/or other drugs prior to the assault. GHB-assisted sexual assault cases had not been drawn to the attention of the drug outreach workers interviewed and, in the United Kingdom, GHB has been detected in only two alleged drug rape samples submitted to the forensic science services. In the United States, successful convictions have been based on circumstantial rather than laboratory analyses.

Other social consequences

Firstly, the ease with which GHB can be acquired, or manufactured, allows more widespread entrepreneurial opportunity and consumer power than in the illicit 'ecstasy' markets in the EU. This development can be linked to developments in communication via the Internet. Secondly, the promotion of GHB for health — anti-ageing and bodybuilding — through Internet sites promotes the idea of illicit drugs being used for self-medication purposes rather than hedonism. The representation of GHB for relaxation, sexual enhancement and inducing sleep is strong and there appears to be a lobby of users who wish to defend the right to use GHB for these purposes.

However, the size of this lobby is unknown and the vested interests of GHB producers and distributors may play a part in its visibility on the Internet.

In view of the social and health risks relating to GHB, the widespread availability of GHB and its precursors, and the ease with which it can be prepared for consumption presents a number of implications for social institutions. Responses by some social institutions are already evident in some Member States.

Press and mainstream media

A recent American emergency room television series episode addressed the issue of there being no effective intervention for treatment for an overdose of GHB. In this episode, a doctor's instructions regarding a patient brought in who was known to have consumed GHB was to leave the patient in the corridor to sleep it off.

Some types of media coverage are thought to inadvertently promote the use of GHB. Careless coverage has been described in negative terms by drug researchers, police and service providers. In particular, concerns have been expressed about media coverage of GHB use in sexual assault. There is a potential for such coverage to increase harm in the form of 'copy-cat' crime. This is said to have occurred in Australia (Sturman, 2000). One example of such coverage is in an article about GHB in the August 2000 issue of Cosmopolitan (a women's magazine with large international circulation figures). The article was entitled 'The new date rape drug' and had a subtitle 'From health pill to rapist's tool'. One drug worker interviewed reported that he actively discourages journalists from covering issues such as this in mainstream magazines and newspapers.

Research institutions

Social research on illicit use of GHB is being initiated in some countries and questions about the use of GHB have been inserted into a music magazine survey and a gay magazine survey in the United Kingdom, and into a magazine in Australia.

Information for drug outreach workers

Drug outreach workers are a key source of information for users. Compared with other synthetic drugs and alcohol, the sleep dose response curve of GHB and the unpredictable effects depending on what else has been con-

sumed have lead to the dissemination of targeted information. Both written and verbal information highlight specific dangers about dose and about drug and alcohol combinations to serve as a warning to users and potential users. Information about contraindications for using GHB has also been provided.

Internet sources, which appear to be American, have advised people who are going to use GHB to mark their hand with the letters 'G' or 'GHB' to identify a reason for loss of consciousness, if it occurs. Admission to hospital unconscious may lead to routine interventions for opiate overdoses, such as intubation, and this can be very costly. By indicating that an overdose has been caused by GHB, users have a better chance of avoiding high ambulance and hospital fees.

Other advice to GHB users and 'kitchen-sink' producers has been to add blue food colouring to GHB in order to help users identify it, and to prevent both inadvertent use and/or deliberate use in drug-assisted assault.

Hospital personnel

Pharmacotoxicological information about GHB for hospital personnel may, in some circumstances, help to prevent the adoption of unnecessary medical procedures.

Community

In a number of urban areas, community drug and rape services have been alerted about the use of GHB and provided with up-to-date information. Advice to people who believe that they have been victims of drug-assisted sexual assault is to provide a urine sample as early as possible (Sturman, 2000).

Workplace

Employees undergoing drug or alcohol treatment or screening may be particularly vulnerable to the use of GHB in order to avoid detection.

Police

Police doctors are usually responsible for obtaining blood and urine samples but, in the United Kingdom, some police forces have recently advised police constables to obtain urine samples from people reporting as victims of sexual assault as soon as possible in order to increase the possibility of identifying the presence of GHB (Sturman, 2000).

Wholesale production and distribution [8]

Violence in connection with wholesale production and distribution

Member States did not provide data on violence in connection with the production, trafficking and distribution of GHB.

Money laundering aspects

No reliable data are available on the volume of money laundering in relation to the production, trafficking and distribution of GHB.

Involvement of (international) organised crime

Contributions of Member States' law enforcement agencies

Austria, Greece, Italy and Luxembourg have reported that until now there have been no seizures of GHB, nor is there any information on (large-scale) production, trafficking and distribution of GHB or on the role of organised crime in these activities.

In Belgium, seizures of GHB are increasing considerably and in particular during summertime, where there was an increase in seizures of small quantities of GHB in liquid form and, incidentally, in capsules. In Finland, 757 millilitres of GHB were seized in seven incidents in 1998. In 1999, the Finnish forensic laboratories analysed samples of GHB relating to total seizures of over 3 800 grams. Also, over 5 litres of the precursor GBL were seized. In France, a 'kitchen-type' laboratory was discovered in the region of Paris and 4 kilograms of GHB were seized in August 1998. In September 1998, 503 grams of GHB were seized and in September 1999 a 'kitchen-type' laboratory was discovered in Bordeaux and 80 centilitres of GHB were seized.

In Denmark there have been five seizures of GHB since June 1999. Germany reports 11 incidents of seizures of small, insignificant quantities of GHB. The limited number of seizures does not allow for an assessment of the level of production, trafficking and distribution or the role of organised crime. In Ireland, one seizure of GHB in liquid form (25 millilitres) was reported.

In the Netherlands there were a number of small seizures in 1999, totalling 76 capsules of GHB. Producers of GHB are thought to be involved in the production of controlled drugs, with dealers possibly having links to ecstasy

[8] Europol's contribution to the risk assessment.

producers. They are individuals with a criminal background or members of small groups, rather than criminal networks. However, in January 1999, a criminal organisation was dismantled that had been engaged for a number of years in the production and trafficking of 'designer drugs', including GHB. In Portugal, one seizure of 1 100 litres of the precursor GBL took place in November 1999.

In Spain, 34 seizures took place in 1999, in Zaragozza (31) and Ibiza (three). In Sweden, abuse of GHB is increasing and GHB and GBL have been found in seizures of narcotic drugs and anabolic steroids. It is believed that GBL is being imported into Sweden.

In the United Kingdom, London, the North-West, Midlands and South Wales have been identified as the main areas of production and supply. There is intelligence that the precursor, GBL, is being sourced from other Member States, for example Belgium, to be used in GHB production. GHB is mainly distributed through retail outlets, the Internet, via mail order and in gyms. The disruption of overt supply has led to distribution patterns similar to illicit drug networks. There is no current intelligence regarding international trafficking of GHB into or from the United Kingdom. The high profit margins and the comparatively limited penalties encourage the involvement of organised criminal groups. There is evidence of criminals involved in controlled drugs also being involved in the production and supply of GHB.

Conclusions

- No Member State has information on large-scale production, trafficking and distribution of GHB. Seizures of GHB in the European Union are very small when compared to seizures of 'regular' types of synthetic drugs such as amphetamine, MDMA and MDA.
- Three Member States — France, the Netherlands and the United Kingdom — have information on illicit production of GHB in their country. Production in France seems to be incidental and limited to two kitchen-type facilities.
- Two Member States — the Netherlands and the United Kingdom — report on the role of organised crime in the production, trafficking and distribution of GHB. In both countries producers of GHB are thought to also be involved in the production of controlled drugs, with dealers possibly having links to ecstasy producers. They are individuals with a criminal background or members of small groups, rather than criminal networks.

The retail market

The retail market appears to consist of both pharmaceutical grade GHB and a wide range of home-made varieties serving a market historically predominated by homosexual men but which is making inroads into the heterosexual population, and in particular that of recreational drug users.

GHB is authorised only in three countries: in Italy for alcoholic craving and in France and Germany as an anaesthetic ([9]). In France and Italy, the commercial sales figures for GHB have decreased. In France they more than halved (from 35 547 in 1988 to 12 456 in 1999) and in Germany no sales figures are available but it is assumed that market sales are very low (EMEA, 2000).

In some countries such as the Netherlands and the United Kingdom, GHB has been available for a number of years through retail outlets such as smart shops, sex shops, gyms and through mail order (Stichting Adviesburo Drugs, 1990). GHB and GHB-making kits have been widely available through Internet sales but, in 2000, concern about the drug's safety and changes in marketing authorisation have led to restricted advertising and sales. GHB kits are no longer openly sold on the Internet and in August 2000, only two English-language Internet sites openly marketing GHB were identified. GHB sold in this way is generally in powder form in quantities ranging from 75 g upwards and suppliers provide strong assurances of quality (assays above 99 % , measured using gas chromatography) and discretion with regard to packaging, encrypted transactions, and guaranteed deliveries are assured. One laboratory appeared to be based in the United States and offered worldwide shipping. The other, a South African-based laboratory, excluded supply to Australia, New Zealand, Norway, South Africa or the United States.

Although Internet sales of GHB have been curtailed, a number of bodybuilding, anti-ageing and smart-drug web sites continue to advertise GHB under other names such as gamma-OH, ProK, Genetika, Alcover, ReActive and Renewtriant and Furanone Di-hydro. These GHB-type products are generally advertised as dietary supplements providing therapeutic benefits for: inducing sleep, mood enhancement, treatment of drug and alcohol addiction, sexual enhancement, athletic performance and to combat ageing. The sites that promote the use of GHB usually provide strong cautions with regard to doses and contraindications.

([9]) Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992 and that Article 12 of Directive 75/319/EEC of 20 May 1975 regulated through the Committee for Proprietary Medicinal Products (CPMP) the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with Pharmacovigilance.

A home-made, 'kitchen-sink' industry developed due to the fact that GHB is easily manufactured and no special equipment is required for this process. A book about GHB has been published and information about recipes, taste, effects and where to purchase precursors is exchanged via the Internet in many different languages (Ward, 2000). In February 2000, a web site dedicated to GHB alone was established.

GHB dissolves easily and is generally colourless, odourless and relatively tasteless. Therefore, it can be taken easily and unobtrusively in social settings where alcoholic drinks are served. In recreational drug settings, GHB is most frequently sold in liquid form in plastic opaque bottles or screw cap doses and in Europe, GHB synonyms in these settings include 'GBH' and 'liquid ecstasy', 'happiness drops' and 'liquid loving'. Although GHB sometimes appears in the same market place as ecstasy it is not likely to be purchased as, or mistaken for, ecstasy because of its distinguishing physical appearance and its effects, which are more similar to those produced by alcohol and other sedatives than MDMA or other stimulant drugs. The United Kingdom focal point reported that 30 ml bottles contain about 3 g of GHB and one of these is typically sold for approximately EUR 15. In Spain and Sweden, prices of GHB reported by the focal points are considerably lower than in the United Kingdom but the defining units or price sources may be different. For example, Internet or catalogue sales prices for bulk orders are lower than 'street level' sales prices.

A major technical difficulty facing control of the GHB retail market is that the precursor gamma-butyrolactone (GBL) is used industrially and is commercially available at low prices and the precursor can simply be recovered from a GHB solution by adding acid to neutralise the sodium hydroxide. In Sweden, in 1998 approximately 40 products containing GBL in substantial amounts were identified and 11 of them were commercially available as consumer products. The Swedish focal point reported that a dialogue with major importers of GBL was planned in order to trace possible leaks to clandestine production.

Social factors that increase the probability of harm

A major social factor that increases the probability of harm is linked to the steep dose response curve of GHB (Elliott, 2000). Firstly, the variable and unknown GHB content available on the illicit market makes it impossible for individuals to assess their dose on the basis of past experience in the way

that they do with alcohol. Secondly, there exists a small, but significant, minority of 'innovators' or 'extreme' users who take large quantities of drugs and alcohol as part of their social lifestyle. This group may continue to use GHB because of its availability, low price and other factors, even if more accurate and reliable information about dose was available to them.

With regard to the potential wider dissemination of GHB use, it appears that GHB may have a significant role in the recreational drug scene as a self-medication drug used to counteract some of the negative influences of stimulant drugs such as sleeplessness and tension. Here the demand for GHB, or a similar drug, is linked with the heavy or regular use of stimulants. The comparatively low price of GHB also provides a cheap alternative to alcohol for young people on low incomes. The similarities of GHB to alcohol both in terms of oral administration and effects allows easy experimentation among mainstream youth without any major value conflict. These factors, combined with perceived lack of hangover effects, could lead to widespread dissemination among young people. Socially excluded populations may be the most vulnerable to widespread dissemination (EMCDDA, 2000). Mitigating factors against widespread diffusion are the relatively low status of GHB due to: its low price, its association with heavy alcohol use and its anti-socialising effects. The relatively short-acting effects of GHB compared with drugs such as MDMA also mitigate against the drug gaining widespread popularity as does the high purity and low price of MDMA that is currently evident on the market.

Finally, another social factor that increases the probability of harm is the role of the media in promoting harm, if inadvertently. This relates particularly to media coverage of GHB use for the purposes of sexual assault which could promote a small, but significant, number of 'copy-cat' crimes.

Public health risks of GHB — epidemiological evidence

Introduction

The earliest recorded indications of health risks associated with non-medical use of GHB were in Sweden and in the United States during the early 1990s. At that time in Sweden, the small number of GHB overdoses was associated with bodybuilders. In the absence of systematic studies of non-medical use of GHB, the epidemiological evidence regarding the public health risks of GHB for this report is based on limited information collected from:

- the Reitox national focal points in the 15 EU Member States (1);
- Europol's contribution to the risk assessment of GHB (2);
- EMEA's contribution to the risk assessment of GHB (3);
- the Qualitative European Drugs Network (QED) (4);
- the literature (5);
- key European forensic scientists (6);
- key toxicologists in the United Kingdom (7);
- telephone interviews with international experts in the field of recreational drugs (8);
- the Internet (English-language searches) (9); and
- youth and mass media (English-language searches) (10).

Table 6 presents the topics covered by this annex by briefly indicating the extent and type of evidence that is available. The numbers in the list above are used in the table to code the sources of information. Where information is available, it is presented and examined in the text under the main category headings. In general, there is insufficient information, or too much overlap, to address each of the subheadings in the text.

Following the EMCDDA request to all 15 Reitox national focal points for information about GHB, four responded stating that they were unable to

Table 6: Topics for public health risks — epidemiological evidence

Topics	Recorded evidence (see text for details)
Availability and quality of product on the market	
Availability at consumer level (extent/quantities)	Some seizures and limited targeted survey data indicate relatively low availability and use. (1, 2, 4, 6, 8)
Sources (at consumer level)	Pharmaceutical laboratory and 'kitchen-sink' GHB available. (6, 7, 8, 9, 10)
Trends in availability	Increase in legal sanctions has reduced supply via the Internet and illicit laboratories. (6, 9)
Average dose and degree of variability	250 mg for relaxed energy enhancement – 3 g for profound sleep. (1, 5, 6, 9, 10)
Purity levels and presence of adulterants	No evidence.
Other active ingredients	No evidence.
Typical price and range	Up to approximately EUR 5 per dose. (1, 6, 8)
Knowledge, perceptions and availability of information	
Availability of scientific information on product	See pharmacotoxicological review.
Availability of information on effects of product	Ranges from mild energy enhancement to unconsciousness. Hangover effects comparatively low. (4, 5, 8, 9, 10)
Level of awareness of product among drug consumers in general	Relatively low awareness and experimentation in Europe.
Level of knowledge of product, effects and perceptions among consumers of product	Lack of reliable knowledge about dose concentrations but the Internet coverage suggests high levels of information available among regular users. (6, 7, 8, 9, 10)
General population	No evidence but appears low.
Prevalence and patterns of use	
Extent of use of product	Targeted surveys of party/dance scenes indicate limited prevalence but it is probably higher among some male homosexual populations. (1, 4, 8)
Frequency of use	No evidence.
Route(s) of administration	Usually orally in liquid form but anecdotal reports of limited use by inhaling. (8)
Other drugs used in combination with product	Alcohol and stimulants. (4, 8)
Geographical distribution of use	Has been analysed by forensic or toxicology laboratories in 11 Member States. (1, 2)
Trends in prevalence and patterns of use	Some evidence of spread into heterosexual recreational drug-using population. (8, 10)

Table 6 (cont.)

Topics	Recorded evidence (see text for details)
Characteristics and behaviour of users	
Age and gender of users	Anecdotal evidence for it being historically more prevalent among male homosexuals. (1, 8)
Social groups where product available/used	Recreational dance scene, heavy alcohol users, bodybuilders.
Risk behaviours associated with use	Physical accidents and unconsciousness.
Special concerns about vulnerable groups	Low income and socially excluded, drug and alcohol dependence. Children who may drink GHB inadvertently are vulnerable. (1, 3, 5)
Trends in characteristics/behaviour of users	Association with anti-social behaviour, vomiting, lack of control, sleep and unconsciousness. (8, 9, 10)
Indicators of health consequences	
Hospital emergencies	Five countries report non-fatal hospital admissions associated with GHB.
Deaths (direct and indirect)	Deaths associated with GHB reported in four countries.
Traffic accidents	No evidence.
Requests for treatment/counselling	No evidence.
Other health indicators	Concerns expressed by drug outreach workers, club owners, music promoters, journalists about use of GHB in dance settings. (10)
Content of use	
Risk factors linked to circumstances and rituals of consumption	Steep dose response curve and anaesthetic effects make it very dangerous in physically active settings, particularly for driving. Home-made 'kitchen-sink' varieties may carry added risks of too much caustic soda. The close affinity to alcohol in terms of effect and mode of consumption could make diffusion to mainstream populations more probable. (7, 8, 9, 10)
Implications for the non-using population	Increase in negative atmosphere (vomiting, slurring, staggering and unconsciousness) in social recreational settings. (10)

provide any formal evidence of GHB use in their countries (Austria, Greece, Italy and Luxembourg). All except one of these had anecdotal reports of its use.

Laboratory analysis of samples of GHB, or its precursors, were reported by all, except four, countries, either by focal points or by Europol. The information provided is not always consistent in its detail and forensic analyses of GHB samples has been, generally, very limited. The number of seizures and quantities of GHB identified by laboratory analysis range from 3 800 grams in Finland to a single small sample of a GHB precursor identified by the criminal police in Portugal in 2000.

There have been 11 reported deaths in which GHB was associated as cause in the European Union between September 1995 and January 2000. The majority of these were reported from the United Kingdom and Sweden and most, but not all, also involved alcohol. Non-fatal hospital admissions associated with GHB are difficult to assess in the absence of routine screening for GHB by hospital toxicology laboratories but, as with deaths, the highest number of reports also comes from the United Kingdom and Sweden.

Table 7 summarises key data on GHB including the indicators used.

Availability and quality of product on the market

GHB has marketing authority ([10]) in only three countries: in Italy for alcoholic craving and in France and Germany as an anaesthetic (EMEA, 2000). Growing concern about non-medical use of GHB in the United States, Australia and Europe has prompted a number of countries to introduce new and more stringent drug controls on GHB. Since 1998, six Member States have put GHB under permanent control: Belgium (Decree 21.1.1998), Denmark (Euphoriant Act, 16.12.1999), France (Decree 28.4.1999), Italy (Decree 266, 11.11.1999), Ireland (Misuse of Drugs Act, May 1999) and Sweden (Narcotics Act, 13.1.2000). In the United Kingdom, the Netherlands, Austria and Finland GHB continues to be controlled by the Medicine Act and monitoring is in progress. In the United Kingdom, the Medicines Control Agency (MCA) has taken action against a number of unlicensed operators.

The effect of these changes is evident in the withdrawal of open sales of GHB from gyms, sex shops and smart shops and in the reduced level of advertising and open supply on the Internet of GHB and kits for making GHB at home. More discrete methods have been adopted by suppliers of GHB alongside the appearance of substitutes for GHB in name or content. For example, in August 2000, one bodybuilding site was marketing Furanone Di-hydro as a product named 'ReActive', claiming that it was not GHB. Smart drug and anti-ageing sites also market products with similar effects as GHB under a range of different names. The disruption of overt supply has lead to distribution patterns similar to illicit drug networks.

([10]) Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992 and that Article 12 of Directive 75/319/EEC of 20 May 1975 regulated through the Committee for Proprietary Medicinal Products (CPMP) the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with Pharmacovigilance.

Availability at consumer level (extent/quantities)

In addition to GHB being made available via the Internet and other discrete retail outlets, a home-made 'kitchen-sink' GHB industry has developed due to the fact that it is easily manufactured (Elliott, 2000) and no special equipment is required for this process.

Seizures

Austria, Greece, Italy and Luxembourg have reported that until now there have been no seizures of GHB. In Belgium, there are regular seizures, particularly during the summertime, when there is an increase in seizures of small quantities of GHB in liquid form and capsules. GBL is more commonly found than GHB and seizures usually occur near the Dutch border. In 1999, Spain reported 31 seizures in Zaragozza and three in Ibiza. In Sweden, police seizures have found GHB in connection with other seizures of narcotic drugs and anabolic steroids. In Denmark, since June 1999, there have been five seizures of GHB providing six samples. In 1999, the Finnish forensic laboratories analysed samples of GHB relating to total seizures of over 3 800 grams. Germany reported 11 seizures of small insignificant quantities of GHB. In 1999 in the Netherlands there were a number of small seizures totalling 76 capsules of GHB. In the United Kingdom the forensic science service handles less than 10 cases each year. In Ireland two seizures were made, one of GHB in liquid form and one in powder. In France there have been few seizures reported (Europol, 2000).

Dose and price

In recreational drug settings, GHB is most frequently sold in liquid form in plastic opaque bottles or screw-cap doses and samples found to contain GHB, which have been analysed by the DIMS project in the Netherlands are commonly submitted already mixed with alcohol. Police sources in Europe have made seizures in liquid, powder and capsule form.

Advised doses range from 250 to 500 mg for energy enhancement, 500 to 1 000 mg for euphoria/libido enhancing effects, and up to 3 grams for profound relaxation and sleep. The United Kingdom focal point reports that standard 30 ml bottles contain about 3 g of GHB but the amount of GHB contained in the bottles consumed in recreational dance settings and elsewhere across Europe is likely to vary considerably. There have been some reports of burns to mouths due to high caustic soda content in home-made varieties.

The liquid form is generally taken in capfuls by cautious users or 'swigged' from the bottle, less cautiously by others. In the United Kingdom, one of these bottles is typically sold for approximately EUR 15. In Spain and Sweden, prices of GHB reported by the focal points are considerably lower but this is likely to be the result of different unit definitions and different sources. For example, the number of doses in a 3 ml bottle varies and prices for Internet or catalogue bulk order sales are lower than the 30 ml bottle price at 'street level'.

Knowledge, perceptions and availability of information

Knowledge and availability of information

The scientific knowledge about GHB is summarised in the review of pharmacotoxicological data on GHB (Elliott, 2000).

The knowledge and perceptions of GHB among the general EU population are not known, but are probably limited and subject to a low level of media reporting. The most significant lack of information about GHB is with regard to the variable strengths and quantities of GHB contained in 'street sales' and the lack of predictable effects for individuals.

For the populations who use recreational drugs, smart drugs or bodybuilding drugs information about GHB is mostly made available through the social networks which serve those populations. A vast number of Internet sites and newsgroups (4 300 in the English language identified from one search engine) feed into these networks and promote the use of GHB for a wide range of purposes including inducing sleep, mood enhancement, treatment of drug and alcohol addiction, sexual enhancement, athletic performance and combating ageing. One anti-ageing site reproduced a graph of a Japanese clinical study that showed that a dose of 2.5 grams of GHB dramatically increased growth hormone levels 16 times within 60 minutes. Information about recipes, taste, effects and where to purchase supplies and alternatives to GHB is available in many different languages and many offer warnings with regard to doses and highlight the contraindications for use. In February 2000, a web site dedicated to GHB was established (www.ghb.org) and a book specifically about GHB has been published and distributed through major bookstores in the United States and via the Internet (Ward, 2000).

Perceptions

There appears to be a lobby of GHB users and promoters, visible in Internet discussion groups, which has recently put forward a conspiratorial view of the American government and pharmaceutical industry's strategies regarding trials with GHB. Whilst government sanctions against the use of GHB are increased, the GHB trials may result in FDA approval for GHB to be authorised as a prescription drug for treating sleep disorders.

Within recreational drug settings, anecdotal reports suggest that the negative effects of GHB with regard to associated nausea, unpredictable doses, subsequent risks of losing physical control or consciousness and its generally negative low-status image will restrict its popularity in widespread social settings. Unlike MDMA, it appears to be considered an antisocial drug among mainstream trend setters, music promoters, club owners and outreach workers. For example, an outreach worker in Amsterdam described it as having:

a very negative effect on the atmosphere — we don't like it

In the United Kingdom, club promoters and youth magazines are beginning to speak out about the use of GHB. The April 2000 issue of Mixmag gave four full pages to the coverage of information about GHB with the subheading: 'Some call it the nastiest drug in Britain, others offer prayers at its alter. What's the truth about GHB? And what's it doing to you'.

Prevalence and patterns of use

There are no data specifically on prevalence or on patterns of the use of GHB and at present there is little evidence that GHB is used on a wide scale in any EU Member State. However, there is evidence of its use predominantly in the male homosexual social scene in the past and of it now making inroads into heterosexual sub-populations for recreational purposes, into the wider ecstasy market and into post-party settings (Newcombe, 1999). According to the risk assessment conducted in the Netherlands, GHB is most commonly found in Germany, the Netherlands and the United Kingdom (CAM, 1999).

In the Netherlands, some use of GHB in party settings has been reported by drug workers.

In parts of the United Kingdom, use of GHB is reported as having an affinity with heavy alcohol users. However, a Liverpool study of 100 United Kingdom clubbers over the Christmas period 1999–2000 found that nobody had used GHB. A survey in France conducted in 1998 found that 3 % of regular techno party goers said they had taken GHB but among a matched control group consumption of GHB was non-existent, indicating that the use of GHB is also not widespread in France (Médecins du Monde, 1999). The French survey indicated that GHB was not only taken for the effects it induced but that, in association with other substances, it enhanced the overall effects or facilitated the 'come down' from taking stimulant drugs. The Swedish report also indicates that GHB is not the drug of choice but used as a complement to other drugs. A survey in Helsinki conducted in May 2000 suggested that the popularity of GHB had decreased since 1998 because of supply restrictions and relatively short effects compared with MDMA (www.qed.org).

Social research on illicit drug use is generally limited to recreational dance or treatment settings, yet anecdotal and Internet evidence suggests that use of GHB may not be confined to recreational party drug settings. Some specific sub-populations appear to use GHB for specific effects — for example, both gay and heterosexual men for its perceived muscle building and sexual enhancement properties, stressed professionals to induce sleep, and middle-aged populations for anti-ageing and sexual benefits. The Austrian focal point reinforced this view with some anecdotal evidence of use among very small closed groups outside the dance drug setting. Internet postings and outreach workers suggest that GHB can also be used as a substitute for alcohol or drugs to achieve inebriation whilst avoiding detection tests in treatment, the workplace and for driving. Some police sources and media coverage have expressed concern about the ease with which GHB may be used to facilitate sexual assault. In this regard, Internet newsgroups discussions, not infrequently, counter suggestions that GHB is tasteless by addressing the issue of the bitter or unpleasant taste experienced by users.

It is clear that there is a considerable amount of information about GHB on the Internet, in magazines, and media. However, the significance of this information for the task of estimating the prevalence of its use is difficult to interpret for a number of reasons. Also the role that media reports play in reflecting or promoting harmful drug trends is not well understood.

Characteristics and behaviour of users

The limited information that is available about the characteristics and behaviour of users has been reported above. However, it should be noted that the comparatively low price of GHB provides a cheap alternative to alcohol and when used for illicit purposes the effects of GHB are much closer to those produced by alcohol, marijuana and diazepam than they are to MDMA and other stimulant drugs. One drug worker in the United Kingdom observed that the use of GHB was more prevalent among heavy alcohol users and another in the Netherlands commented that he did not understand why young people wanted to use GHB for going out. Compared with alcohol, the physical incapacity and unconsciousness resulting from a relatively small increase in GHB doses demonstrates that health risks in relation to road traffic or operating machinery are particularly high.

Indicators of health consequences

Deaths

There have been 11 deaths in which GHB was implicated in the European Union. In the United Kingdom between September 1995 and January 1999, four deaths occurred in the United Kingdom associated with GHB in combination with alcohol. In Sweden, the official number of fatal GHB intoxications is four and in a fifth death GHB was identified but not considered to be the cause of death. In Finland, two deaths have been reported and in January 2000 one death was reported in Denmark (concentration of 34 mg GHB/kg and alcohol blood content of 0.27). The majority of deaths also involved alcohol.

Non-fatal hospital admissions

Non-fatal hospital admissions are difficult to assess in the absence of routine screening for GHB by hospital toxicology laboratories (Hernandez M. et al., 1998). From April 1996 to mid-1999, over 150 non-fatal intoxications were reported in the United Kingdom. In 1997, following six hospital admissions involving GHB in the Netherlands a study was conducted. The study analysed blood and urine samples from 50 patients with suspected ecstasy intoxication and consumption of GHB was confirmed in three patients out of the 50.

More recently, since mid-1999, the United Kingdom reports that approximately 60 non-fatal intoxications involving GHB are treated in hospital each year, whereas in the Netherlands none have been reported. In Denmark there have been 12 reported non-fatal intoxications involving GHB since mid-1999: in three of these cases the patients were unconscious on arrival and in three cases GHB had been consumed in combination with alcohol. In Sweden over 20 non-fatal hospital admissions were reported. The most recent reports have come from Belgium where two non-fatal intoxications were reported in July 2000. The French have not provided figures for GHB intoxications or deaths associated with illicit use but the Pharmacovigilance report submitted by the EMEA highlights the existence of overdose reports, dependence and accidental poisoning of children (EMEA, 2000).

In 1998, the Advisory Council on the Misuse of Drugs considered whether GHB should be controlled and concluded that it did not present a sufficient social problem and in 1999 a risk assessment of GHB conducted in the Netherlands also recommended continued monitoring (CAM, 1999).

Context of use

An important factor with regard to context of use is the lack of reliable indications of dose accompanying sales of GHB at 'street level'. However, the steep dose response curve of GHB makes it risky for recreational use even where dose is both accurately measured and known (Elliott, 2000). The combination of GHB with other drugs, particularly alcohol and other sedative drugs also increases substantially the risks related to taking GHB as does taking GHB when suffering medical conditions such as epilepsy, hypertension and diabetes. GHB taken at home for relaxation or sleep without combining it with other drugs or alcohol reduces the risks of physical accidents and the social/psychological harm associated with the drug. The continued and heavy use of stimulant drugs which creates the need for the type of sedative effects offered by GHB is likely to increase the demand for GHB. Also the close affinity of GHB to alcohol, in terms of effect and mode of consumption, could make diffusion to mainstream populations more probable, particularly to those with low incomes and with drug or alcohol problems.

Implications for the non-using population

At present, the main implications for the non-using population appear to be the increasingly negative atmosphere (vomiting, slurring, staggering and unconsciousness) described in social recreational settings.

In the absence of traffic controls to prevent GHB users from driving there is a risk for road users.

Table 7: Summary of key data on GHB

	Date	Place	Comment
Illicit use first identified	Early 1990s	Sweden	4–5 cases per annum of non-fatal overdose among bodybuilders
		United States	57 overdoses in 5 months
	1991	United Kingdom	First came to attention
	April 1994	Spain	Came to attention in a study of synthetic drugs
	1995	Belgium	Sold in smart shops
		Netherlands	Six overdoses in Rotterdam
Marketing authority	Current	Italy	Authorised for alcohol craving
		France	Authorised for surgery and alcohol treatment
		Germany	Authorised for general anaesthesia
Legal controls	1996	Netherlands	Controlled under Medicines Act — now being monitored
	1998	United Kingdom	Controlled under Medicines Act. ACMD recommended monitoring but not control
		Austria	Controlled under Medicines Act
		Finland	Controlled under Medicines Act
	Jan. 1998	Belgium	Control under Royal Decree
	May 1999	Ireland	Decision to control under Misuse of Drugs Act
	Nov. 1999	Italy	Control under drug law and GBL scheduled
	Dec. 1999	France	Control under Narcotic Act entered into force
	Dec. 1999	Denmark	Control under Euphorians Act
	Feb. 2000	Sweden	Control under Narcotics Act entered into force
Large seizures	Aug. 1998	France	4 kilograms of GHB
	1999	Finland	3 800 grams and over 5 litres of GBL
	Nov. 1999	Portugal	1 100 litres of GBL
Small seizures /chemical analyses	1996–99	Spain	34 seizures — mainly in Zaragozza
	1998	Finland	Seven incidences amounting to 757 millilitres
	1999	Netherlands	Small seizures from geographically-spread discotheques
	Aug. 1998	France	One small 'kitchen-sink' laboratory
	May + Sept. 1999		Two single sample seizures in different regions and one small 'kitchen-sink' laboratory
	July 1999	Denmark	Five seizures
	To date	Germany	11 incidents of small seizures
	To date	Sweden	GHB found in association with narcotics and steroid drugs
	To date	Belgium	Regular seizures especially in the north near the Netherlands
	To date	Ireland	Two individual samples

Table 7 (cont.)

	Date	Place	Comment
Laboratory investigations	To date	Netherlands United Kingdom	Illicit production identified 10 reports of illicit/attempted manufacture by unlicensed operators
Deaths associated with GHB	1996–99 1995–99 1998–99 Jan. 1999	Sweden United Kingdom Finland Denmark	Four deaths in different cities Four deaths Two deaths (one remains open) One death
Non-fatal intoxications	1996–97 1996–97 June 1999 1999 July 2000	Netherlands United Kingdom Denmark Sweden Belgium Italy France	Nine patients admitted to hospital — six in Rotterdam Approximately 150 people treated 12 patients treated in hospital 20 cases in nine months Two cases Two cases Child/children admitted with accidental poisoning (EMEA Pharmacovigilance)
Source notes — There are few data on seizures because in most EU Member States it is not, or has not been, a controlled drug. Records of hospital admissions are subject to variations in practice, nevertheless the recorded incidence of intoxications associated with GHB is notably higher than those associated with ketamine and MDMA with higher prevalence use.			
Pattern and effects — GHB is unlikely to be mistakenly consumed as ecstasy. Effects are much closer to alcohol than to MDMA and, unlike MDMA, it is usually taken orally in liquid form, often in alcohol.			
Health risks — The main concern is the steep dose-response curve. When combined with alcohol, or other sedative drugs, risks are increased.			
Diffusion — Reports suggest GHB is not widely used in Europe. Highest use appears to be in the United Kingdom, Sweden, Germany and the Netherlands. Among small groups it may be used for recreational nightlife, bodybuilding, inducing sleep, an alcohol/drug substitute, sexual relaxation and disinhibition.			

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