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 GHB to the EMCDDA 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 EMEA to assess the health and social risks as well as the possible consequences of prohibition of GHB, was held on 25-26 September 2000.

The meeting considered the following documents:

I. Technical Annexes A and B: The Pharmacotoxicological Report on GHB, Report to the EMCDDA
II. Technical Annex D: public health risks: epidemiological evidence, EMCDDA
III. Technical Annex C: sociological/criminological evidence, EMCDDA
IV. Europol contribution to the risk assessment on GHB
V. EMEA 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-hydroxybutyric acid. GHB can also form various salts (e.g., 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 byproduct 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.


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
   (Documents I, II and V)

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 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 6 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 UK, 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: Sweden, UK, 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 operation of machinery.

3.2 Public Health Risks

(a) Availability and Quality

Preparations containing GHB have marketing authorisation 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 USA 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 homemade preparations.

In dance settings, GHB is frequently sold in liquid form in small 3ml plastic bottles containing approximately 3g 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 0.5g dose be taken for relaxation and disinhibition, a 1g dose for euphoric effect, and a 2-3g dose for deep sleep.

---

1 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 Internet sites and newsgroups promote the use of GHB for a wide rage of purposes including: inducing sleep, mood enhancement, treatment of drug and alcohol withdrawal, sexual enhancement, bodybuilding 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, 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. Therefore, it can be taken unobtrusively in social settings where drinks are served.

(d) Characteristics and Behaviours of Users

There is limited information available about 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 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 UK, 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: Sweden, UK, 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 increase substantially the risks related to taking GHB.
4. SOCIAL RISKS: Sociological/criminological aspects
   (Documents III and IV)

4.1 Sociological aspects

4.1.1 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 ingestion of caustic soda.

4.1.2 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.

4.1.3 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: press, drug outreach workers, research institutes, hospital emergency departments, community drug and rape services, and 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 duration, 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 be involved also 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 control 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 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 discussed at the meeting included the following:

- 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. 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 was sufficient because it could permit seizure of products and prevent advertising of such products and also their sale. 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 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 recommends that the Drug Precursors Committee set up under Article 10 of Regulation 3677/90 and Directive 92/109/EEC should strongly consider the inclusion of 1,4 butanediol within the monitoring system.

6.6 The Committee recommends 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 recommends 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