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REPORT

from :	European Monitoring Centre for Drugs and Drug Addiction
to :	Horizontal Working Party on Drugs
Subject :	Report on the Risk Assessment of Ketamine and GHB in the framework of the Joint Action on New Synthetic Drugs

Please find herewith aforementioned report drawn up upon request on 17 April 2000 of the Portuguese Presidency.

The assessment was made by a special meeting on 25/26 September 2000 in Lisbon under the auspices of the Scientific Committee.

EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION

Direction

Lisbon, 3 October 2000
Dir (00) LWE - D/115

Mr Javier Solana
Secretary General
Council of the European Union
Rue de la Loi 175
BE- 1048 Bruxelles

Dear Secretary General,

It gives me great pleasure to provide you with the Reports of the Risk Assessments of KETAMINE and GHB in the framework of the Joint Action on New Synthetic Drugs.

On 17 April 2000, the Portuguese Presidency formally referred the drugs KETAMINE and GHB to the EMCDDA for risk assessment under Article 4 of the Joint Action on New Synthetic Drugs adopted by the Council on 16 June 1997. The risk assessment reports were drawn up by a special meeting held in Lisbon 25-26 September 2000 and convened by the EMCDDA under the auspices of its Scientific Committee, extended with experts nominated by the Member States and representatives of the Commission, Europol and the European Agency for the Evaluation of Medicinal Products.

May I draw your attention to the fact that this exercise is the second phase of the Joint Action which consists of three stages. The first consists of an Early Warning System involving the collection and exchange of information by the EMCDDA and Europol concerning a new synthetic drug. The second phase involves the risk assessment of the substance by a special meeting convened under the auspices of the Scientific Committee of the EMCDDA.

The third phase foresees that the Council may, on the basis of an initiative to be presented within a month from the date on which the report of the results of the risk assessment is established and acting in accordance with Article K.3 (2) (b) of the Treaty, adopt unanimously a decision defining the new synthetic drug or drugs which will be made subject to necessary measures of control.

If the Commission deems it necessary to propose that a new synthetic drug or drugs be controlled, it is expected to present an explanatory report to the Council.

Once the decision that the Council may take becomes public, the EMCDDA will publish the work that it has undertaken.

Please accept, Sir, the assurance of my high consideration.

Georges ESTIEVENART
Director

Cc : Ms Nicole Maestracci, President of the Horizontal Drugs Group of the Council of the European Union.

Report on the Risk Assessment of Ketamine in the Framework of the Joint Action on New Synthetic Drugs

On 17 April 2000, the Portuguese Presidency of the European Council formally notified KETAMINE (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) to the EMCDDA for risk assessment under Article 4 of the Joint Action on new synthetic drugs of 16 July 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 Ketamine, was held on 25-26 September 2000.

The meeting considered the following documents:

I. Technical Annexes A and B: The Pharmacotoxicological Report on Ketamine, 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 of Ketamine
V. EMEA contribution to the risk assessment of Ketamine

These documents in conjunction with further information and comments from the expert participants formed the basis of the Risk Assessment which is reported below.

1. CHEMICAL DESCRIPTION

The chemical name of Ketamine is 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, a arylcycloalkylamine. It is structurally related to phencyclidine (PCP–'angel dust') and cyclohexamine. It occurs in racemic form and also as the S-enantiomer.

Registered names (medical) are: KETALAR, Ketamine PANPHARMA, MAH, KETOLAR, KETANEST-S.

Registered names (veterinary) are: KETALAR, Ketaminol Vet., Clorketam, Imalgene, Anesketin, Ketamine Ceva, Vetalar Vet., NARKETAN, MAH, KETASET.

Ketamine is known in Member States under the street names: K, Special K, KitKat, Tac et Tic, Cat Valium, Vitamine K, Ket, Super K, and others.

2. PHARMACEUTICAL DESCRIPTION

Ketamine was first synthetized in 1962 and patented in Belgium in 1963. As an anaesthetic and analgesic, Ketamine has a recognized unique therapeutic value in veterinary practice and, to a lesser extent, in human medicine. Clinically, Ketamine usually is administered intravenously or intramuscularly. In recreational use, typical doses are: 75-125 mg intramuscularly or subcutaneously; 60-250 mg intranasally; 50-100 mg intravenously; and 200-300 mg orally.

Ketamine is manufactured by the chemical industry for use in the manufacture of pharmaceutical products using as precursors cyclopentyl bromide, *o*-chlorobenzonitrile, and methylamine. Due to the complicated multi-step synthesis, and the difficulty of purchasing the necessary precursors and numerous solvents and reagents, Ketamine sold illicitly for recreational use appears to be mostly obtained by diversion of legitimate supplies of either the bulk drug or of pharmaceutical preparations containing it.

Pharmaceutical products may be injected or may be modified by evaporation after which the resultant powder may be snorted in pure form or mixed with other drugs and/or inactive components. In powder form, combination with cocaine has been observed.
In the form of tablets, the concentration of Ketamine and other substances are mostly unknown by users. These tablets are sold as 'ecstasy' in some Member States. Other substances reported to be present in Ketamine-containing tablets are pseudoephedrine, ephedrine, caffeine, amphetamine, methamphetamine and MDMA. As the effects of Ketamine are dose-dependent, the uncertainty about Ketamine concentration in the powder, and *a fortiori* in fake 'ecstasy' tablets, poses a risk in recreational use.

Preparations containing Ketamine hydrochloride are used as an anaesthetic and analgesic agent in human and veterinary medicine, with important clinical applications in paediatric and ambulatory anaesthesia, treatment of burned wound patients, and for short anaesthetic procedures. However, the human use of Ketamine in the EU is restricted to special indications, due to the occurrence of emergence reactions. Outside the EU, the ease of use gives Ketamine a major advantage under difficult circumstances (developing countries and remote areas). Its use in veterinary anaesthesia, especially in small animals, is widespread and considered by several Member States and by the Federation of Veterinarians of Europe as indispensable in veterinary medicine.

3. HEALTH RISKS

(Documents I, II and V)

3.1. Individual health risks

(a) Acute effects

Ketamine is a dissociative anaesthetic. The term 'dissociative' has a twin meaning. Firstly, it refers to an effect on the brain, inducing a lack of responsive awareness, not only to pain but also to the general environment. Secondly, it refers to a feeling of dissociation of the mind from the body ('out of body experience'). Ketamine would be expected to block or interfere with sensory input to centres of the central nervous system (CNS) in a way the drug selectively interrupts association pathways of the brain before producing somesthetic (sensation of having a body) sensory blockade.

Ketamine differs from most anaesthetic agents in that it appears to stimulate the cardiovascular system**,** producing changes in heart rate, cardiac output and blood pressure. In recreational Ketamine users, presenting to an emergency department, tachycardia was the most common finding. As a mild respiratory depressant, Ketamine is unlikely to produce respiratory depression at recreational doses, even if it cannot be wholly excluded. Cardiovascular effects usually do not pose a problem, but is contraindicated in patients with significant ischaemic heart disease and is to be avoided in those with a history of high blood pressure or cerebrovascular accidents.

The findings of neurotoxicity in the rat may indicate cause for concern in recreational users of Ketamine. These users may not take Ketamine in combination with protective agents like benzodiazepines. Moreover, compounds increasing the neurotoxic potency of Ketamine (like alcohol) might be co-administered. Recreational use also implies repeated exposure, whereas clinical use is mostly incidental. Long-term adverse effects in chronic users of Ketamine have been reported, though they are scarce, and include persisting impairment of attention and recall and a subtle visual anomaly**.** The Report on Risk Assessment of 4-MTA noted that Ketamine increased the neurotoxicity of 4-MTA in mice. Neurotoxicity of Ketamine in primates including humans has not been studied.

(b) Clinical effects

Ketamine is considered as an anaesthetic with a good safety profile, based on extensive clinical experience**.** The major drawback, limiting clinical use, is the occurrence of emergence reactions in patients awakening from Ketamine anaesthesia. These reactions include hallucinations, vivid dreams, floating sensations and delirium. However, preclinical data may be of greater importance for recreational use which, contrary to clinical practice, may present cases of long-term use.

A total of 12 deaths in which Ketamine was identified, have been noted between 1987-2000 including seven from the USA. Only three reported fatal cases involving Ketamine alone were identified. Two reports concern mixed drugs fatalities. In one case, Ketamine had only a minor role. For the remaining six cases, insufficient details were available to be evaluated properly. In the three cases involving only Ketamine, the routes of administration were intramuscular or intravenous and the cause of death was mainly due to overdose (multiple intramuscular doses or accidental intravenous overdose), in line with preclinical findings. In the other cases involving Ketamine mixed with other drugs, lower Ketamine concentrations indicates that drug interaction may have contributed to these deaths. Substances with CNS/respiratory depressant effects, like ethanol, opioids, barbiturates, and benzodiazepines or drugs with cardiostimulant effects, like cocaine or amphetamines, may increase Ketamine acute toxicity.

Regarding non-fatal intoxications, potential dangerous interactions may also arrise when different drugs are combined. Ketamine has sympathomimetic properties. Inhibition of central catecholamine re-uptake and increased levels of circulating catecholamines are believed to cause the cardiovascular stimulant effects. Serious side effects such as hypertension and pulmonary oedema have been reported, but such adverse effects appear to be rare and may be related to the combination of Ketamine with other drugs, such as amphetamines and its analogues, ephedrine and cocaine.

(c) Dependence

Tolerance, dependence and withdrawal signs have been observed in a number of animal studies. Tolerance to the desired effects of Ketamine develops quickly and may result in an escalation of the dose, the toxicological implications of which are unknown. A risk associated with the recreational use of Ketamine, is the potential of the drug to cause psychological dependence in some individuals based on case reports and information from users. The prevalence of long-term use is unknown. There is no evidence that Ketamine causes an abstinence syndrome in humans.

(d) Psychological effects

Ketamine may be experienced by the recreational user as an altered, 'psychedelic' state of mind ('the K-hole') that allows the user to travel beyond the boundaries of ordinary existence. The intensity of 'psychedelic effects' is dose-related. Ketamine in subanaesthetic doses produces a clinical syndrome which both neurophysiologically and behaviourally resembles that of a schizophrenic psychosis. Ketamine acutely affects cognitive performance, profoundly affects perception of the body, time, surroundings and reality.

The main effects of Ketamine are neurobehavioural: anxiety, agitation, changes of perception (e.g., loss of notion of danger, visual disturbance) and impairment of motor function and the analgesic effects. In such a condition, the user may be at risk of injury to themselves (burns, falls) or to others (accidents).

3.2. Public health risks

(a) Availability and Quality

Ketamine preparations have marketing authorizations in most countries of the EU, except in Greece where the marketing authorization was recalled in 1998 [1].

Seizure data suggest mostly low levels of availability of Ketamine for illicit use within different Member States, with a decrease occurring in the UK and an increase in two other Member States. A large proportion of Ketamine seizures are in tablet form and the tablets carry the same logo as those often found in ecstasy tablets. It may also be found in powder form and sold as a stimulant such as amphetamine or cocaine. Forensic laboratories have found Ketamine in variable doses mixed with manitol, caffeine, ephedrine and pseudo-ephedrine, MDMA, methamphetamines and amphetamines. In Belgium, 89 kilos of pure Ketamine in powder were seized in September 1999 and a further 3 kg in January 2000. Four Member States (Belgium, Ireland, the Netherlands and the UK) seized significant amounts of Ketamine. However, seizures of Ketamine are small when compared to seizures of 'regular' types of synthetic drugs such as amphetamine, MDMA and MDA.

(b) Knowledge and Perception of Ketamine Among Users

There is apparently low awareness of and experimentation with Ketamine in Europe compared with drugs such as cannabis, MDMA, amphetamine and cocaine. Lack of information about the dose content of the Ketamine on the market may be an important factor. Anecdotal reports from France and the UK indicate growing awareness among consumers about how to manage doses to achieve sought after effects and to avoid negative ones. A survey in a dance setting in Austria found that the respondents, using regularly MDMA and amphetamines, considered the psychological risks attached to Ketamine as very high.

[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.

At low doses, Ketamine is sometimes reported to have a stimulant effect: this could be the result of stimulant effect of other drugs or active cutting agents (like caffeine) or because Ketamine is often snorted with amphetamines and/or cocaine or taken with other drugs in the illicit drug scene. There is some indication that Ketamine has an up-market image as an esoteric drug for experienced drug users.

(c) Prevalence and Patterns of Use

Surveys of selected groups of drug users in dance settings have shown that a significant number of people experiment with Ketamine but the level varies between sub-populations and geographical areas. A London club survey in 1997 found that up to 40% of the 200 respondents had experimented with Ketamine and were to use it the same evening. A large French survey conducted the same year found that 15% of the 900 respondents in techno party settings had experimented with Ketamine. Recently, a large school survey conducted in the North East of England found that 1% of 13/14 years old children and 2% of 15/16 years old had ever tried Ketamine compared to 2% and 5% respectively who had tried cocaine.

The most popular route of administration is to snort Ketamine as a powder and to inject liquid preparations, and there have been reports of it being swallowed, smoked or inserted rectally.

(d) Characteristics and Behaviours of Users

Although there is evidence of use by younger people, targeted surveys and anecdotal reports from the Netherlands and from Australia, indicate that prevalence may be higher in older, highly educated, experienced, MDMA users, particularly in the free party/new age travellers scene, in the gay club scene, and among small groups of self-exploratory individuals. Among 'closed' groups in Europe, initiation into Ketamine use is often ritualised.

The most vulnerable groups are those who take Ketamine under the illusion they are taking MDMA or some other stimulant drug. The volume of seizures of Ketamine in tablet form with ecstasy-type logos reflects the scope for this scenario and the need for better information about drug contents and harm reduction. Ketamine does not react with commonly used field tests (e.g., Marquis reagent) although other drugs present in the tablet may produce a positive reaction.

(e) Indicators of Health Consequences

In the EU since 1996, there have been four deaths reported to the EMCDDA in which Ketamine was found by laboratory analysis, of which two occurred in 1996 in Ireland. In neither of the Irish cases, Ketamine was considered to be the main cause of death. One death of a 19 year old male has been reported in France in which Ketamine, LSD and ecstasy were implicated. The fourth death, also reported from France, was a polydrug user.

There has been a notable lack of reporting about hospital emergencies in Europe. A recent report in France presents some data on 17 cases of intoxication associated with Ketamine.

An important factor of health risk is the lack of reliable indications of dose accompanying sales of Ketamine at street level. In the absence of advice, first time users of Ketamine will tend to follow similar consumption patterns as those previously adopted for other drugs. This uninformed use of Ketamine increases the risk of both physical and psychological problems. The existence of tolerance may increase a tendency to move to injecting Ketamine, with the risks associated with injection.

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(f) Context of Use

The implications for the non-Ketamine using population appears to be phenomenon of Ketamine entering the recreational drug market in the guise of ecstasy, or other stimulant drugs. This means that someone expecting to take MDMA, cocaine or amphetamine may find themselves taking Ketamine inadvertently, without warning, knowledge or support.

Compared with the effects of stimulants, the rapid physical incapacity rendered by Ketamine consumption has serious implications for driving.

4. SOCIAL RISKS: sociological/criminological aspects

(Documents III and IV)

4.1. Sociological aspects

4.1.1 Social Consequences

Social consequences for the user stem firstly from its anaesthetic properties and loss of physical control if too high a dose is taken, and secondly from reported psychological effects of regular, or heavy, use which include dependency. In addition to the loss of physical control it may cause tension due to the introspective quality of effects, other psychological symptoms, and compulsive use by a small minority

4.1.2 Consequences for the Social Behaviour of the User

Main consequences on social behaviour stem directly from Ketamine's effects and a tendency towards compulsive use by some users.

4.1.3 Other Social Consequences

In dance settings Ketamine often appears in the form of well-made tablets, which are visually similar to MDMA and usually mixed with a stimulant ranging from caffeine to amphetamine. It is also found as liquid, powder and capsules. Ketamine has also been used as a cutting agent for drugs such as cocaine, amphetamines and heroin and may be taken by problem opiate users. The chosen route of administration for a small minority is by injection which raises a value conflict in a drug using culture which is strongly against injecting.

A range of social factors increase the probability of use, such as the existence of a large market of long term ecstasy users seeking new drug experiences, a rather intellectual trend-setting image and low price. However, other factors mitigate against widespread diffusion, such as the anaesthetic effects, marked discomfort with intranasal use, the short action, acute psychological reactions when taken without due knowledge about dose or effects, psychological dependence, and negative effects on social relationships.

In view of potential anaesthetic and numbing effects, psychological disturbances and compulsive use there are implications for: drug services, research institutes, hospital emergency departments and the press.

4.2. Criminological aspects

The seizure of considerable amounts in Belgium, Ireland, the Netherlands and the UK could suggest an involvement of organised crime. In the UK, it is believed that Ketamine raw material is imported in bulk from legitimate suppliers in Europe. A number of sources, close to the user, suggest that there may be diversion from licit sources or foreign purchase, particularly from Asia.

5. POSSIBLE CONSEQUENCES OF PROHIBITION

5.1. Legal Status

Ketamine is subject to control in five Member States: Belgium, France, Greece, Ireland (to be scheduled in the Misuse of Drugs Act) and Luxembourg. It is controlled through general medicines legislation in all Member States. Due to the fact that Ketamine preparations, as medical and veterinary products, have marketing authorization in most Member States and have a recognized unique therapeutic value, the major concern appears to be the diversion from legitimate supply to the black market.

The complex routes of synthesis for manufacturing illegally Ketamine reduce the potential impact on the illegal market for Ketamine of targeted measures to control Ketamine precursors. Illegal production of Ketamine is unlikely to develop due to these conditions. However, the implication of organised crime in the production and supply of Ketamine in tablet form, with the possible health risks due to sales of Ketamine tablets with ecstasy logos, represents a particular matter of concern.

5.2 Possible Consequences of Prohibition

The possible consequences of prohibition discussed at the meeting included the following:

- The EMEA highlighted the fact that changes in the conditions of marketing authorizations for Ketamine containing medicinal products proposed by the meeting should be referred to the CPMP and CVMP.
- Introducing penalties for use would be unlikely to deter use in groups where illegal drugs are already well-established.

- Concern was expressed about the effects of prohibition and control measures on informal information and harm-reduction networks.
- One opinion was that control measures might draw unnecessary attention to the drug thus increasing its attractiveness to potential users.
- In discussions on possible mechanisms of control, differences between control of the bulk drug and of medicinal products containing Ketamine were mentioned. In this regard, there was a strong support that the view of the chemical and pharmaceutical industry about possible measures of control be sought.
- The view that as a common minimum approach, medicines legislation should be used as a control measure received strong support.
- Another opinion expressed at the meeting was that stronger measures of control to deal with diversion, trafficking and inadvertent exposure (i.e. through fake 'ecstasy'-tablets) were necessary.
- The meeting noted the concern of the Federation of Veterinarians of Europe that placing Ketamine under the same stringent restrictions as opioids could be detrimental to good veterinary medicine. It was noted that the same concern could apply to the use of Ketamine in human medicine.

6. CONCLUSIONS

The Scientific Committee of the EMCDDA enlarged 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 Ketamine and in accordance with Article 4 of the Joint Action submit the following conclusions:

6.1 Ketamine is not a new synthetic drug. While it has a significant therapeutic use, it is also being used in recreational settings.

6.2 The meeting noted the main risks of the recreational use of the drug, such as the psychological dependence, loss of self-control, and the risk of acute intoxications. To date, the use of Ketamine has been reported as associated with mortality or morbidity in small number of cases.

6.3 An opinion which received strong support at the meeting was that as a common minimum, Ketamine should be subject to control under the medicines legislation in Member States.

6.4 Another opinion expressed at the meeting was that stronger measures of control to deal with diversion, trafficking and inadvertent exposure to the drug were necessary.

6.5 The meeting recommends that both the EMCDDA and Europol should further monitor the manufacture, trafficking, distribution, patterns of use and health consequences of Ketamine, particularly the fatalities and non-fatal emergencies.

6.6 The meeting recommends that a study on possible neurotoxicity of Ketamine in primates should be considered in the context of the 5th Framework Research Programme of the European Commission.

6.7 The possibility for improving control of diversion should be discussed with the chemical and pharmaceutical industry in order to ensure the continued availability of Ketamine for medical and veterinary use.

6.8 The meeting recommends that consideration should be given to how appropriate information be disseminated to the most vulnerable risk groups.

Lisbon, 25 September 2000

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 which is 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.

It has various street names including 'Liquid Ecstasy', 'Liquid E', 'GBH', 'Easy Lay', 'Scoop', 'Liquid X', 'Fantasy' and 'Cherry Meth'.

2. LEGITIMATE USES OF THE PRODUCT

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 in only four Member States. There are no known reported industrial uses of GHB, however, GBL and 1,4-butanediol have many uses in various industrial processes.

3. 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).

4. HEALTH RISKS

(Documents I, II and V)

4.1 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-β 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 psychoactive effects of GHB have implications for the ability to drive and operation of machinery.

4.2 Public Health Risks

(a) Availability and Quality

Preparations containing GHB have marketing authorization[1] 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 drug 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.

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, 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.

A.

B. *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.*

C. *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. 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 make 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.

5. SOCIAL RISKS: Sociological/criminological aspects

(Documents III and IV)

5.1 Sociological aspects

5.1.1 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.

5.1.2 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.

5.1.3 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, police.

The retail markets provide a range of products for different consumer groups. 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.

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.

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.

5.2 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, including rape.

6. POSSIBLE CONSEQUENCES OF PROHIBITION

6.1 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.

6.2 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 authorized medicines containing GHB in four Member States and the possibility of an application for Orphan Drug Status for GHB being submitted. The EMEA also highlighted the fact that changes in the conditions of marketing authorizations 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.
- 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 authorizations were in place and it was recommended that this point should be further investigated.

7. 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:

7.1 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.

7.2 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.

7.3 An opinion which received support was that control through medicines legislation is sufficient.

7.4 Another opinion which received significant support at the meeting was that this substance should be subjected to more stringent control measures.

7.5 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.

7.6 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.

7.7 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.

7.8 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