



**THE EXPERT ADVISORY COMMITTEE ON DRUGS' (EACD)
ADVICE ON:**

**GAMMA-HYDROXYBUTYRIC ACID AND RELATED
SUBSTANCES ('Fantasy')**

Released December 2001

CONTENTS

Executive Summary	3
Recommendations	4
Substances identification	5
GHB	5
1,4-B	5
GBL	6
GABA	6
How to make GHB	6
Current and proposed legal classification	6
Rationale for proposed classification	7
The Misuse of Drugs Amendment Act 2000	7
Specific effects	8
<i>Pharmacokinetics – absorption, distribution, metabolism, and excretion</i>	8
<i>Effects</i>	9
Likelihood or evidence of abuse	12
Ability to create physical or psychological dependence	14
Potential to cause death	14
Risks to public health	15
<i>GHB and sexual assault</i>	15
<i>Other public health risks</i>	16
Therapeutic value	17
International classification and experience	18
<i>New Zealand’s international obligations under the UN Conventions</i>	18
<i>Other countries’ classification of GHB and its related substances</i>	18
Recommended presumption for supply	19
Implications for harm minimisation principles	19
Other information	20
<i>Is there an antidote?</i>	20
<i>Enforcement provisions of the Act</i>	20
<i>Submitters to EACD</i>	21
References	21

EXECUTIVE SUMMARY

This paper considers gamma-hydroxybutyric acid (“GHB”) and three GHB-related substances:

- 1,4-Butanediol (“1,4-B”)
- Gamma butyrolactone (“GBL”)
- Gamma-aminobutyric acid (“GABA”).

Such substances are commonly called ‘Fantasy’ and all have related ‘class’ effects. Each of the three GHB-related substances can metabolise into GHB in the human body. As such the EACD considered the substances together.

These substances are not controlled under the Misuse of Drugs Act 1975 (“the Act”). After considering the available evidence, the EACD recommends that these drugs should be classified in Part 1 of the Second Schedule of the Act (ie, B1).

Rationale for this general view is provided in this paper. Recently, the availability of GHB has become pronounced in New Zealand and in April 2001 the media reported the first fatality from a GHB-related substance. While at this stage only one death has been attributed to a GHB-related substance in this country, there have been numerous admissions to hospital emergency departments with patients presenting with severe respiratory depression and coma after taking these substances.

GHB and its related substances have a very steep dose-response curve. This means there is only small difference in the dose required to give a recreational user the ‘desired effect’ and that required for an overdose, which may result in coma, convulsions, severe respiratory depression, and death. These substances are unpredictable in their effects, especially when combined with other sedatives/depressants such as alcohol. The induction of vomiting, potential blockage of airways, and dangerously low respiratory depression when a person is unconscious can be potentially fatal. There is individual variability in the dose-response – i.e. equivalent doses can affect different people in different ways. There is also a delayed onset of the effects associated with these substances, which may cause people to consume more of the drug (thinking the original dose is not achieving the desired effect) and risk overdose.

Although many people spontaneously recover from an overdose without assistance, the EACD was also concerned about some inappropriate and potentially dangerous messages circulating about these substances - e.g. leaving unconscious people to ‘just sleep it off’. Such messages may result in a potentially fatal delay in seeking emergency medical care.

These substances are used as recreational drugs in many countries and this year the United Nations Commission on Narcotic Drugs voted to classify GHB under the United Nations drug classification framework. New Zealand has ratified three UN Conventions under this framework and as such has certain obligations under them. A classification of B1 is consistent with New Zealand’s international obligations.

The EACD recognises that some people will experiment with, or continue to consume these substances regardless of their legal status. Therefore, the EACD considers that the implications of classifying these substances on harm minimisation principles are important 'factors in the equation'. In particular, the risk of driving these substances 'underground', increasing their attractiveness to younger people, causing other people to turn to other substitute substances that have not been classified, and the potential for clandestine labs to produce inferior quality 'home produced' versions that have a risk of unknown harmful contaminants, need to be considered.

As such any legal classification, including the status quo, should be supported by complementary measures, such as providing accurate information to empower people, especially those who choose to use these substances, to reduce potential harm to themselves and to others.

RECOMMENDATIONS

After considering all of the information put to the Committee and the classification criteria in the Misuse of Drugs Act 1975, the EACD makes the following recommendations to the Associate Minister of Health:

- (a) GHB and its related substances (including 1,4-B, GBL, and sodium oxybate) should be classified under the Misuse of Drugs Act 1975.**
- (b) GHB and its related substances should be classified in Part 1 of the Second Schedule of the Misuse of Drugs Act 1975 (ie, B1).**
- (c) To capture GHB and all its related substances (including 1,4-B, GBL, and sodium oxybate) wording along the following lines should be inserted in Schedule B1:**

“GHB (gamma-hydroxybutyrate); its salts, esters, amides, ethers and its precursors, including 1,4-butanediol, gamma-hydroxybutyraldehyde, gamma-butyrolactone, and gamma-aminobutyric acid; and the salts of its esters, amides, ethers and precursors, if any; and any substance, preparation or mixture containing any proportion of the said substance or of any such salt, ester, amide, ether or precursor”.

- (d) No presumption of supply should be set for GHB and its related substances.**
- (e) The potential implications of classifying these substances, under the Misuse of Drugs Act 1975, on harm minimisation principles should be considered by the Government.**
- (f) If Parliament decides that these substances should be classified under the Misuse of Drugs Act 1975, this should be complemented with other harm minimisation initiatives such as educating people about the steep dose response curve, potential for severe respiratory depression, and delayed onset of GHB and its related substances.**

- (g) This paper should be made publicly available (eg, posted on the National Drug Policy website www.ndp.govt.nz) as soon as practicable.

SUBSTANCES IDENTIFICATION

GHB

GHB occurs naturally in the human body - primarily in the central nervous system (with highest concentrations in the basal ganglia, Cameron 2001, Li et al 1998). It is a metabolite of the brain neurotransmitter GABA.

Chemically, GHB is called gamma-hydroxybutyric acid, 4-hydroxybutyric acid, or gamma-hydroxybutyrate. Its chemical abstracts registry service ("CAS") number¹ is 591-81-1. GHB's structure consists of a chain of four carbon atoms, with an alcohol group (-C-OH) at one end and a carboxylic acid group (-C-OOH) at the other end (see diagram on page 8).

GHB usually exists as either a free acid (a colourless liquid in its pure form) or as a sodium salt (generally a white powder). The sodium salt is called Sodium Oxybate (CAS 502-85-2) and is soluble in water and methanol. GHB has no chiral centres, so no stereoisomers or racemates are possible.

GHB and its related substances are being used as 'recreational drugs' for their euphoric effects. They have depressant effects on the central nervous system. GHB is most commonly available in a liquid form and is ingested orally. It is also available in putty, powder, capsule, and gel forms. Street names include: Fantasy, Liquid Ecstasy, Liquid X, Liquid E, Grievous Bodily Harm, Georgia Home Boy, Date Rape Drug, Easy Lay, Gamma O, Scoop, Great Hormones at Bedtime, or GH Beers.

1,4-B

1,4-B also occurs naturally in the human body, although in trace amounts (Zvosec et al 2001). Chemically, 1,4-B is called 1,4-Butanediol, 1,4-Butylene Glycol, 1,4-Dihydroxybutane, 1,4-tetramethylene Glycol. Its CAS number is 110-63-4. More commonly it is called 1,4-B or BD. As with GHB it consists of a chain of four hydrocarbon atoms, but it has an alcohol group (-C-OH) at each end (see diagram on page 8).

1,4-B is a liquid and is used as an industrial solvent in polyurethane, marketed as an "organic" cleaner, and used in plastic manufacture. In New Zealand, it has recently been marketed in sachets called One4B, or as a CD or tape cleaner called Puritech. In the United States it has been sold in dietary supplements for bodybuilding, weight loss, and sleep inducement. Most of these products are liquids and include: *Rejuv@Nite*, *Thunder Nectar*, *Enliven*, *Liquid Gold*, *Zen*, *N-Force*, *InnerG*. These have been determined by the Food and Drug Administration to pose a significant public health hazard (FDA 1999b).

¹ An identification number for scheduled substances (eg, lysergic acid is 82-58-6).

GBL

GBL is a lactone-ring analogue of GHB (see diagram below). Chemically, it is called gamma butyrolactone, 2(3H)-furanone dihydro, butyrolactone, 4-butylolactone, dihydro-2(3H)-furanone, 4-butanolide, 2(3H)-furanone, dihydro; tetrahydro-2-furanone, or butyrolactone gamma.

As with 1,4-B, GBL is also used in dietary supplements in the United States and as a cleaner or solvent. Products containing GBL are marketed under various brand names including: *Renewtrient, Revivarant or Revivarant G, Blue Nitro or Blue Nitro Vitality, GH Revitalizer, Gamma G, and Remforce*. They are promoted with claims to build muscles, improve physical performance, enhance sex, reduce stress and induce sleep. Such products have also been determined by the Food and Drug Administration to pose a significant public health hazard (FDA 1999b).

GABA

GABA is the predominant inhibitory neurotransmitter in the brain (Zvosec et al 2001). GABA's structure also has a 4-hydrocarbon chain, but at one end it has an alcohol group (-C-OH) and at the other it has an amine group (-C-NH₂) (see diagram on page 8).

Like the other three compounds it can also be synthesized out of the body. For instance, the New Zealand Custom Service recently intercepted importation of three 100g bottles of GABA.²

CURRENT AND PROPOSED LEGAL CLASSIFICATION

GHB, 1,4-B, GBL, and GABA are not classified under the Misuse of Drugs Act 1975. However, sodium oxybate (GHB's sodium salt) is classified as a prescription medicine in the First Schedule of the Medicines Regulations 1984.

EACD recommends that GHB (including its salt, sodium oxybate), 1,4-B, GBL, and GABA be classified in Part 1 of the Second Schedule of the Act (ie. B1). This is important because some of GHB's derivatives metabolise into GHB once ingested, and classifying only some of these substances would have limited impact if others were still legal.

In order to capture the appropriate GHB-related substances (including 1,4-B, GBL, GABA, and sodium oxybate) wording along the following lines should be used:

“GHB (gamma-hydroxybutyrate); its salts, esters, amides, ethers and its precursors, including 1,4-butanediol, gamma-hydroxybutyraldehyde, gamma-butyrolactone, and gamma-aminobutyric acid; and the salts of its esters, amides, ethers and precursors, if any; and any substance, preparation or

² Personal communication dated 24 April 2001. New Zealand Customs Service.

mixture containing any proportion of the said substance or of any such salt, ester, amide, ether or precursor”.

RATIONALE FOR THE PROPOSED CLASSIFICATION

The Misuse of Drugs Amendment Act 2000

The Misuse of Drugs Amendment Act 2000 effectively ‘changed the rules’ as to how controlled drugs are to be classified under New Zealand law. The Act now requires controlled drugs to be classified according to the risk of harm to individuals or society. Drugs posing a:

- **very high** risk of harm should be scheduled as ‘Class A’
- **high** risk of harm should be scheduled as ‘Class B’
- **moderate** risk of harm should be scheduled as ‘Class C’.

To help assess the ‘risk of harm’ section 4B(2) of the Act also specifies a list of criteria that the EACD has to consider when advising the Minister of Health on each drug. These criteria include:

- specific effects of the drug, including pharmacological, psychoactive, and toxicological
- likelihood or evidence of abuse, including prevalence of the drug, seizure trends, and potential appeal to vulnerable populations
- risk to public health
- therapeutic value of the drug
- potential for death upon use
- ability to create physical or psychological dependence
- international classification and experience of the drug in other jurisdictions
- other matters considered relevant by the Minister
- potential presumption for supply and justification for this.

Such criteria, when taken as a whole, will help guide an assessment of the risk of harm associated with each drug and hence what schedule (if any) is appropriate for the drug in question.

The EACD notes the potential for crossover among the criteria, in that information could conceivably fit under more than one heading. Additionally, comparing a drug before the EACD with drugs that were scheduled in the past has limited value because drugs already in the Act were not scheduled under the new classification criteria. The classification status of drugs already in the Act may well reflect historical factors, political direction, or the state of the knowledge at the time they were scheduled.

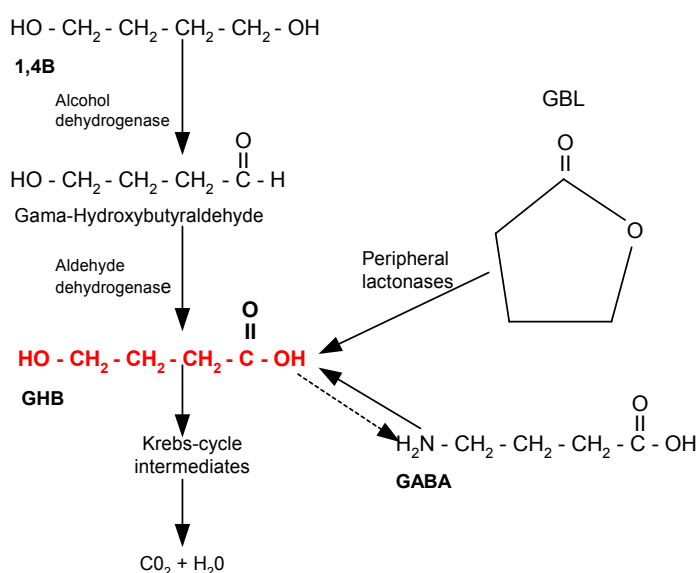
Specific effects of the drug

Pharmacokinetics – the absorption, distribution, metabolism, and excretion of these drugs

GHB is generally ingested orally and is rapidly absorbed from the gastrointestinal tract. The onset of GHB's effects is delayed and systemic effects occur generally within 15 minutes (Dupont and Thornton 2001, Shannon and Quang 2000).

Peak blood/plasma concentrations occur approximately 20-30 minutes after ingesting 12.5 mg/kg and 30-60 minutes with a dose of 50mg/kg (Cameron 2001). Shannon and Quang (2000) cited evidence that peak plasma levels after ingestion of 75 to 100 mg/kg reach 90 and 120 mg/L at 1.5 to 2 hours.

GHB, 1,4B, GBL, and GABA are structurally related. GHB is a metabolite of 1,4-B, GBL, and GABA. Zvosec et al (2001) outline how each of these GHB-related substances is converted to GHB in the human body. 1,4-B is an alcohol, which is broken down in the liver and brain in a two-stage process. First, it is metabolised by the enzyme alcohol dehydrogenase into the intermediate compound gamma-hydroxybutyraldehyde. This intermediate compound is then further metabolised by aldehyde dehydrogenase (another enzyme) into GHB. GBL is metabolised into GHB by lactonase enzymes in the blood. GABA is converted into GHB in the brain and peripheral organs. GHB can also be converted back to GABA. The authors also provide the following diagram outlining these processes:



Elimination half-life is 27 minutes (Shannon and Quang 2000, Cameron 2001, Li et al 1998, Kam and Yoong 1998) and proceeds in a dose-dependant, capacity limited manner (Li et al 1998, Kam and Yoong 1998, Cameron 2001). GHB is eventually eliminated from the body as carbon dioxide and water (Zvosec et al 2001). The primary route of elimination from the body is carbon dioxide (Li et al 1998). Galloway et al (1997) note only 2-5% is eliminated in the urine.

Effects

GHB is a depressant (ie, depresses the central nervous system), which can cross the blood-brain and placental barriers (Cameron 2001, Li et al 1998). The WHO recently described GHB as follows (WHO 2000):

“Pharmacologically, GHB produces sedative and anaesthetic effects at high doses. Such depressant effects appear to be associated with its cataleptic effects and are different from those of barbiturates and benzodiazepines. GHB sedation possessed distinct excitatory properties, which may be due to its effect on the dopaminergic system (increase in intracellular neuronal dopamine). GHB has been found to induce anaesthesia (but does not provide pain relief), (slow-wave) sleep, bradycardia [slowed heart rate], vomiting, random clonic movements, hypothermia, reduction in potassium levels, decrease in ventilatory rate, and apnoea [cessation of breathing, eg when asleep]. However, the respiratory centre remains sensitive to an increase in carbon dioxide”.

Potential adverse effects from GHB are highly variable among individuals. The same dose can affect different people in different ways - for example, a euphoric dose for one person could sedate another person. People using the drug will generally experiment with GHB dosing to obtain the desired effects (O'Connell et al 2000). Such variability, combined with the inherent variability in illicit manufacturing (common to many illicitly made substances), makes GHB a potentially dangerous drug to consume (O'Connell et al 2000).

GHB's effects are dose-related and it has a steep dose-response curve (EMCDDA 2001, Galloway et al 1997, Cameron 2001). A small increase in the dose may cause serious effects, including coma and respiratory depression. In other words, there may be a small margin between the amount needed to produce the 'desired effect' and an overdose. GHB overdose has become a significant cause of patients with drug-induced coma presenting to American emergency departments (Dyer et al 2001).

An oral dose of 10 mg/kg produces short-term amnesia and hypotonia (diminished skeletal muscle tone), 20-30 mg/kg can produce drowsiness and sleep, and doses above 50 mg/kg produce general anaesthesia. Higher doses can produce severe respiratory depression, decreased cardiac output, seizure-like activity, and coma (EMCDDA 2001, Cameron 2001, Kam and Yoong 1998, Dupont and Thornton 2001). Marnell (1999) states that one to two grams make the user physically and mentally relaxed and may reduce social inhibitions. The effects are felt within five to twenty minutes, can last from two to three hours, and depending on the person this dosage can interfere with speech, balance, motor co-ordination, and may induce sleep. Doses of two to four grams can cause a pronounced interference with motor control, balance, and speech. Most users fall asleep at this dosage and the sleep can last three to four hours. A dose of four to eight grams induces a very deep sleep, usually within five to fifteen minutes, which may appear so deep the users cannot be woken up and appear to be in a coma. This deep sleep can last three to four hours, although higher doses can result in a longer sleep.

Hospital admissions and deaths have been linked to GHB ingestion and generally involve the onset of coma and respiratory depression (WHO 2000). Although the risks from severe respiratory depression during coma have

potentially fatal consequences, spontaneous (and often unassisted) recovery from a coma state is common and often occurs within 7 hours because of the short half-life of the drug (Kam and Yoong 1998). Typically, the coma state resolves in 6-8 hours (Cameron 2001, Shannon and Quang 2000). Cameron (2001) observes that some physicians have been surprised when the comatose patient suddenly awakens during an intubation attempt.

As a result of a high incidence of vomiting there is a risk of pulmonary aspiration and so treatment aims to protect the patients airway (Kam and Yoong 1998, Shannon and Quang 2000). Although vomiting often occurs on re-emergence from unconsciousness, it can be a very serious effect if the person is still unconscious or semi conscious. In this regard, a direct correlation has been reported between vomiting and Glasgow Coma Scores ("GCS" - a measure of consciousness). One United States review cites evidence of 85% of vomiting cases having an initial GCS of '8' or less (Shannon and Quang 2000). It has been reported that presenting patients have GCS's of between 3 (severe decrease in consciousness) and '15' (wakeful) (EMCDDA 2001a), and GCS's of '3' are not uncommon (Cameron 2001).

It has also been observed that patients often demonstrate extreme combativeness and agitation despite such profound central nervous system and respiratory depression (Cameron 2001). This has been described as "a drowning swimmer flailing for air" (Li et al 1998) and patients may need to be physically restrained (Shannon and Quang 2000).

Because of its structural similarities to GABA, GHB has been postulated to function as an inhibitory neurotransmitter in the central nervous system (Shannon and Quang 2000). Evidence relating to the activity of GHB on neurotransmitter systems is contradictory (EMCDDA 2001). GHB has an affinity for at least two binding sites in the brain: a GHB specific binding site and the GABA B receptor. It can affect several neurotransmitter systems; increasing acetylcholine and serotonin levels and decreasing norepinephrine concentrations in parts of the brain. It can also inhibit dopamine release, resulting in a build up of dopamine in nerve terminals (WHO 1999), which may be followed by a dose-dependant or time-dependant leakage of dopamine from neurons (EMCDDA 2001). The nature and clinical importance of GHB's effects on brain neuron systems are not fully understood (Zvosec et al 2001). Binding sites are present in the cortex, midbrain, substantia nigra, basal ganglia, and most predominantly, the hippocampus (Cameron 2001, Li et al 1998).

Within the central nervous system GHB mediates the sleep cycles, temperature regulation, cerebral glucose metabolism and blood flow, memory, and emotional control (Li et al 1998).

As there is limited evidence regarding acute or chronic psychological effects of GHB, its effects on cognition, mood, and psychomotor ability is unclear. However, like alcohol, its depressant effects on the central nervous system have implications on the driving ability and operating machinery (EMCDDA 2001).

There are no animal or human data concerning the reproductive toxicity, neurotoxicity, mutagenicity or carcinogenicity potential of GHB (EMCDDA 2001). GHB has been shown to produce an increase in growth hormone in rats and in one small human study, but no study has ever demonstrated weight loss or increased muscle growth (Cameron 2001, Li et al 1998).

The presence of other depressant or sedative drugs (eg, opiates, benzodiazepines, alcohol, and barbiturates) and possibly other psychoactive compounds (eg, amphetamine) may exacerbate the effects of GHB (WHO 2000, EMCDDA 2001a, Galloway et al 1997). This is an issue of concern as other legal and illicit drugs are commonly consumed in environments where GHB is taken (eg, dance parties). The resultant effects of such poly-drug use may 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 (ECMDDA 2001a).

GHB-related substances

Zvosec et al (2001) conclude that the health risks of 1,4-B and GBL are similar to GHB and may include toxic effects that may be fatal, and addiction and withdrawal. Both GBL and 1,4-B are rapidly converted into GHB in the body. In 1999, the FDA noted that some dietary supplement manufacturers were replacing GHB in their products with 1,4-B. However, the effects of ingesting 1,4-B are as dangerous as those of GHB and GBL (FDA 1999).

Despite such similar 'class effects', some studies have suggested differences between GHB and its related substances. First, because GBL and GHB differ in their tissue distribution and bioavailability (the degree to which it becomes available to target tissues etc) after oral ingestion, GBL appears to have greater potency and more prolonged action than GHB (Zvosec et al 2001). Although GBL is rapidly hydrolysed in the blood, it has greater lipid solubility than GHB, which helps it pass through lipid layers of tissues before it can be hydrolysed. Such tissues may act as a 'GBL reservoir' and extend its duration of action as compared to GHB (Kohrs and Porter 1999, Shannon and Quang 2001, Dupont and Thornton 2001).

Second, ingesting 1,4-B in conjunction with alcohol (ethanol) may delay the effects of 1,4-B (Zvosec et al 2001). It has been suggested that alcohol may interfere with the metabolism of 1,4-B because it competes with 1,4-B for the enzyme, which breaks 1,4-B down (alcohol dehydrogenase) (Nelson 2000, Shannon and Quang 2000). Shannon and Quang (2000) refer to animal evidence suggesting that ethanol has a greater affinity for the enzyme than 1,4-B. If so, then this may not only result in delayed GHB toxicity, but also prolonged GHB toxicity from combined ethanol and 1,4-B. In contrast to 1,4-B, it has been suggested that the sedative/euphoric effects of GBL, when consumed with alcohol, may be additive (Nelson 2000).

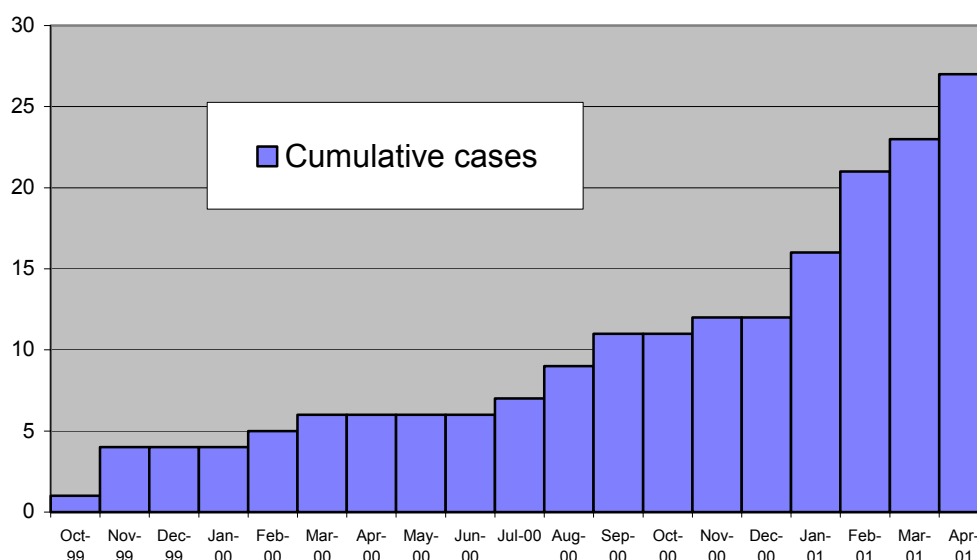
The Committee concluded, on the evidence before it, that GHB and related substances had some similar properties and effects to ethyl alcohol (1,4-B is an alcohol), while there was also some evidence of differences (eg ethyl alcohol dose not have such a steep dose-response curve). The evidence provided by one submitter on the packaging of sachets containing 10 ml of diluted 1,4-B, and a suggestion that it might in future be sold diluted even

further in fruit juice, compared with reported effects from consuming neat 1,4-B, heightened the perceived similarities.

Likelihood or evidence of drug abuse

Although initially used by bodybuilders for its apparent growth hormone promoting properties, the World Health Organization (“WHO”) has noted that GHB’s more recent mode of use worldwide has been for its subjective hypnotic, euphoric, and hallucinogenic effects - especially in the context of the dance music culture (i.e. “raves”) (WHO 2000). Such use is often combined with amphetamine-type stimulants (WHO 1999) or with alcohol. Additionally, users have also claimed to use GHB as an alternative to alcohol (for relaxation), a sexual adjunct, an appetite suppressant, or an anti-ageing product. The serious issue of GHB being used as a ‘date-rape’ drug is also discussed under the Public Health section below.

In 2000, the availability of GHB in New Zealand became pronounced. This was evidenced by a number of people being hospitalised with respiratory depression, high levels of sedation, and coma after using GHB or its precursor 1,4-B. Further, on 28 April 2001, the media reported the first death attributed to a GHB-related substance in New Zealand had occurred in Auckland. The Committee also received evidence from Auckland Hospital’s Department of Critical Care Medicine (DCCM) who advised that between 21 October 1999 (the first case they saw) and 29 April 2001 there were 27 admissions to the DCCM with poisoning due to these agents. In 1999 there were 4, in 2000 there were 8 and in the first four months of 2001 there were 15. The graph below plots cases cumulatively over this time to demonstrate the rate of admissions. Clearly there was an increase in January this year and the DCCM advised that they now admit around one case per week.



There is no record in the New Zealand Drug Survey: *Drugs in New Zealand National Survey, 1998*, about the use of ‘fantasy’. However, GHB (including 1,4-B and GBL) will be surveyed in the 2001 New Zealand Drug Survey

conducted by the Alcohol and Public Health Research Unit in Auckland University.

Two New Zealand suppliers of GHB-related products are being investigated by the Ministry of Health. To date seizures have been limited as the substances have not been classified as controlled drugs under the Act, but the Ministry has recently made seizures of products under the Food Act 1981. International seizure trends vary from country to country, depending on the legal status of the drug in the country concerned.

The EACD is also concerned about the potentially high appeal of these substances to young people – for example as dance party or ‘rave’ drugs. They have also been marketed to appeal to young people and it was noted that people who would usually avoid so-called ‘harder’ drugs may try these substances. Marketing as a ‘new alcohol’, a ‘safe’ drug, or a ‘social’ drug can also send misleading and potentially dangerous messages to people.

In terms of the international situation, the WHO Expert Committee on Drug Dependence recently noted that abuse has been reported in Australia, the United States and many European countries. GBL and 1,4-B have also been abused (WHO 2000).

As at March 2000, the United States Drug Enforcement Agency (“DEA”) had documented over 7,100 GHB overdose events or law enforcement encounters in 45 states (DEA 2000). Data from the Drug Abuse Warning Network and Poison Control Database in the United States show a sharp increase in hospital emergency-room presentations associated with GHB since 1996/97.

A recent GHB risk assessment by the European Monitoring Centre for Drugs and Drug Addiction reported that there have been at least 200 GHB overdose cases in Europe (mainly in Sweden, the United Kingdom, the Netherlands, Denmark, Belgium, Finland, Spain, and Norway (EMCDDA 2001).

The current easy availability of GHB-related substances seems to have contributed to its abuse (WHO 2000). In Europe, the development of a home made ‘kitchen-sink’ GHB industry has been noted because it is easily manufactured and requires no special equipment (EMCDDA 2001).

A brief summary of Customs import information was provided to EACD. A small number of companies are currently importing GHB-related substances under the relevant Customs Tariff number. However, no tariff items were recorded against a number of known New Zealand suppliers, which indicates that some GHB products may be being imported under different tariff codes (eg, generic codes) or the products are being sourced locally.

The Ministry of Health has initiated initial discussions with the New Zealand Chemical Industry Council. Feedback supported the Customs account. The Council has a small number of importing members, who had reported a range of legitimate final products for these substances. The Council had advised the impact of controlling these substances would not be great on industry in New Zealand. However, the implications for potential licensing under the Misuse of Drugs Act 1975 would need to be worked through to assess the impact to industry.

GHB-related substances

The use, manufacture, and sale of GHB was prohibited by the FDA in the United States (with limited exceptions) in 1990. Soon after this GBL and 1,4-B began to be marketed in the United States as “non-toxic” dietary supplements. However, reports of toxic effects and deaths soon led the FDA to issue warnings about both compounds and to designate both as illicit and unapproved new drugs (Zvosec 2001, FDA 1999, FDA 1999a). Despite the FDA’s warnings the use of GHB, GBL, and 1,4-B (sometimes interchangeably) has increased in the United States (Dyer 2000, DEA 2000a).

Ability to create physical or psychological dependence

There have been few studies regarding the dependence potential of GHB (WHO 2000). During studies involving administration of GHB to patients at varying concentrations, no dependence has been observed at low doses of GHB. However, at prolonged high doses a withdrawal syndrome including insomnia, muscular cramping, tremor, anxiety (WHO 2000, EMCDDA 2001), delirium, delusions, and audio and visual hallucinations (Zvosec 2001, Dyer 2001) has been noted upon discontinuation in some cases.

Recent literature also indicates that the long term, frequent use of 1,4-B, GBL, GHB or combinations of these compounds can result in physical and psychological dependence and potentially severe withdrawal syndromes (Zvosec 2001, Miotto and Roth 2001, Dyer 2001, Craig et al 2000, Galloway et al 1997). Due to the rapid absorption and elimination of GHB, prolonged ingestion with short dosing intervals appear to be necessary for the development of dependence syndrome (Zvosec et al 2001, Dyer et al 2001) or the manifestation of withdrawal syndrome (Miotto and Roth 2001). Additionally, while GHB appears to be addictive, non-metabolised 1,4-B may also have effects on dependence and withdrawal syndromes, although such effects are unclear (Zvosec et al 2001).

GHB withdrawal syndrome appears to have some similar aspects of alcohol withdrawal and benzodiazepine withdrawal (eg, prolonged duration of symptoms), but there are also differences (eg, unlike alcohol or sedative-hypnotic withdrawal, initial symptoms of GHB withdrawal appear early, often within the hour and delirium evolves more rapidly) (Miotto and Roth 2001).

In drug discrimination studies in animals, none of the known abused drugs has the ability to fully substitute for GHB. Morphine, dexamphetamine, LSD, and some benzodiazepines produced, at best, partial substitution (WHO 2000).

Potential to cause death

The EACD considered that there was a significant risk of potential death from overdose of GHB-related substances. GHB’s steep dose-response curve, and the potential for vomiting, blocked airways, and severe respiratory depression after overdose was of significant concern to the EACD.

In April 2001, the media reported that the first death in New Zealand attributable to a GHB-related substance. This occurred in Auckland after a man is thought to have consumed a GHB-related substance at a dance party. Auckland hospital DCCM figures reported above indicate the potential for further fatalities from overdose.

Overseas, hospital admissions and deaths have been linked to GHB ingestion. These commonly involve the onset of coma and respiratory depression. GBL, GHB, and 1,4-B have been associated with reports of at least 122 adverse health effects, including three deaths, in the United States (FDA 1999a). More recently, the United States Drug Enforcement Administration has documented 71 deaths associated with GHB; a GHB-related compound was the sole intoxicant in 15 of these cases (Zvosec 2001).⁴ However, the authors caution of the likely underreporting because of lack of knowledge of the toxic effect of GHB on the part of forensic toxicologists and clinicians, the masking effects of other drugs, and the need for targeted analysis to detect GHB.

GHB has been associated with 11 deaths in the European Union between September 1995 and January 2000: four in the United Kingdom, four in Sweden, two in Finland, and one in Denmark. Two deaths have also been reported in Norway (EMCDDA 2001).

Risks to public health

The WHO has concluded that the pattern and consequences of GHB's use in a number of countries in Europe and the United States suggest that its liability to abuse constitutes a significant risk to public health (WHO 2000). Consistent with this, the FDA has determined that GHB and its precursors 1,4-B and GBL pose a significant hazard to the public (FDA 1999a) and the European Monitoring Centre for Drugs and Drug Addiction concluded that GHB posed significant risks to public health (EMCDDA 2001).

GHB and sexual assault

GHB-related compounds have been implicated in sexual assaults (Sturman 2000, EISOHLY and Salamone 1999, IACP 1999, WHO 2000, McKey 2000, Russo 2000, Smith and Temple 2000, Zvosec et al 2001). Low doses may increase libido, euphoria, suggestibility, passivity, and amnesia, which may make victims more susceptible to sexual assault, while higher doses have sedative effects.

The extent to which 'drug rape' drugs are used in New Zealand is unknown. It is not possible to extrapolate from Australian jurisdictions, as data collection around drug-facilitated sexual assault only began in 1998, and initial data are not yet to hand (Russo 2000).

In the United States, the 'vehicle' for classifying GHB as a controlled drug was the *Hillary J. Farias and Samantha Reed Date-Rape Prohibition Act of 1999*.

⁴ A personal communication to the authors from the Drug and Chemical Evaluation Section of the DEA. Note, as at March 2000, the DEA had officially documented 65 deaths which were attributed to GHB (see DEA 2000a).

As at March 2000, the DEA had documented 15 sexual assault cases involving 30 victims under the influence of GHB (DEA 2000). Urinalyses were conducted on samples submitted by the victims of the alleged assaults. Of the 711 drug-positive samples, 48 tested positive for GHB (DEA 2000).

The ease of availability of GHB-related substances, the short life of the drug in the body, and the fact that routine toxicological tests do not detect GHB-related compounds may also be contributing factors in this regard. Targeted analysis with gas chromatography-mass spectrometry is needed to detect and quantify GHB (Zvosec et al 2001). Because of the rapid elimination of sedatives such as GHB, urine has become the analytic specimen of choice in the United States due to the longer window of detection for most sedatives (Dyer 2000).

EISohly and Salamone (1999) attempted to assess the prevalence of drug use in sexual assault cases in which substances were suspected of being involved. Between May 1996 and June 1998, 1179 samples were collected and analysed from 49 American states, Puerto Rico, and the District of Columbia. 468 samples were negative for all substances tested; 451 were positive for ethanol, 218 for cannabinoids, 97 for cocaine, 97 for benzodiazepines, 51 for amphetamines, **48 for GHB**, 25 for opiates, 17 for propoxyphene, and 12 for barbiturates. The authors concluded that although only a small number of drugs have generally been most commonly implicated with sexual assault (including flunitrazepam and GHB), their study demonstrated that at least 20 different substances had been associated with the crime. It is worth noting that, because GHB use has increased in recent years, arguably the ratio of 4 percent (48 positive results out of 1178 samples analysed) may under-represent the current involvement of GHB in sexual assault cases. Another caution is that the presence of the substance did not necessarily indicate the involvement of the drugs in the sexual incident and may reflect usage of the drug before or after the incident of sexual assault.

The use of alcohol (ethanol) is frequently involved in such crimes (Sturman 2000, IACP 1999, LeBeau et al 1999, EISohly and Salamone 1999, Russo 2000). However, when alcohol is used in combination with other central nervous system depressants [eg. GHB] the effects of alcohol are exacerbated (LeBeau et al 1999, Smith and Temple 2000). Additionally, thirty-five percent of drug positive samples in the EISohly study contained multiple drugs. Of the 48 samples that tested positive for GHB, 16 of these also tested positive for alcohol, 10 for benzodiazepines, 10 for marijuana, 6 for amphetamines, 4 for cocaine, 2 for opiates, and 1 for barbiturates (EISohly and Salamone 1999).

Other public health risks

A potential further public health consequence of increased libido or loss of inhibitions caused by these drugs is the risk of unsafe sexual practices (eg, not using contraception). This may increase the risk of transmitting diseases such as hepatitis B, or HIV/AIDS and other sexually transmitted diseases. However, it is unclear to what extent GHB may contribute to such risks. The EACD was unaware of intravenous recreational use of GHB, which may also spread communicable disease. Current information does not suggest that the public health risks associated with communicable disease are a significant

issue at this stage. It was noted that GHB was used intravenously when used as an anaesthetic.

Driving while intoxicated on GHB-related compounds carries personal and public health risks. Zvosec et al (2001) cites evidence of clinical reports of drivers being stopped by Police for driving erratically, being found 'asleep at the wheel' in traffic, losing consciousness while driving, and causing multiple collisions.

GHB-related substances are used or sold for a range of different purposes. They are used in the rave culture, and also as dietary supplements, anti-aging products, sexual adjuncts, appetite suppressants, or for relaxation or anxiety relief. 1,4-B and GBL are also sold as solvents. This wide range of uses may have public health implications as a broader spectrum of the population may be exposed to or use these substances. A related issue is the wide availability of GHB-related substances. Despite regulatory efforts reducing the supply of such dietary supplements in the United States, a shift in marketing tactics has occurred over the internet with GBL and 1,4-B products being marketed as "all natural solvents", "non-toxic cleaners", "chemical samples", and industrial supplies. GHB is also easily made from readily available ingredients.

The risk of harmful effects has been increased by claims that an overdose does not necessitate medical care. The resultant casual attitude towards overdoses has led to fatal delays in seeking medical attention (Zvosec 2001).

Therapeutic value

GHB has been used as an anaesthetic agent and as an aid to alcohol and opiate withdrawal, primarily in France, Italy, and Germany. In the United States and Canada it is currently under evaluation for the treatment of narcolepsy-associated (recurrent, uncontrollable desire for sleep) cataplexy (abrupt attacks of muscular weakness, often triggered by emotional stimuli, and may be associated with diminished skeletal muscles) (WHO 2000).

EACD received information about one New Zealand medical practitioner with extensive clinical experience with GHB as an anaesthetic agent, and who reported such use in New Zealand and Australia. However, although there is evidence of GHB being safely used as a clinical anaesthetic, the EACD emphasised that any anaesthetic agent, including GHB, is potentially very dangerous if used 'recreationally'.

Some authors also suggest GHB's potential use for resuscitation (Li et al 1998, Cameron 2001). The authors outline studies showing a reduction in tissue oxygen requirements and a subsequent reduction in hypoxic cell damage - although the precise mechanism of its tissue protective effect is unclear. Benefit has been noted in a wide range of organ systems and in a number of conditions, including hemorrhagic shock, organ transplant, and heart problems such as myocardial infarction (Li et al 1998, Cameron 2001).

It was noted that scheduling GHB under the Act does not preclude its use for medicinal purposes. A number of other drugs used for therapeutic purposes are classified under the Act.

International classification and experience

New Zealand's international obligations under the United Nations Conventions

The proposed classification for GHB and its related substances (B1) is consistent with New Zealand's international obligations under the United Nations drug classification framework.

In October 2000, the WHO Expert Committee on Drug Dependence submitted an assessment of GHB to the United Nations, along with a recommendation that the drug be classified under Schedule 4 of the United Nations Convention on Psychotropic Substances 1971 (WHO 2000). This followed a pre-review by the WHO in 1999 (WHO 1999).

In March 2001, the United Nations Commission on Narcotic Drugs voted to include GHB in Schedule 4 of the 1971 Convention. New Zealand has ratified the 1971 Convention and is thus obligated to include GHB within its domestic drug control regime. However, New Zealand retains the discretion as to how it classifies substances under its national legislation.

As yet, 1,4-B, GBL, and GABA have not been considered in this international context.

Other countries' classification of GHB and its related substances

Since 1990, GHB has only been legally available in the United States for clinical trials supervised by physicians and approved by the FDA for specialised purposes (thus it cannot be legally marketed, FDA 1999b). However, it was only on 13 March 2000 that GHB was placed in Schedule 1 of the federal Controlled Substances Act by the DEA (DEA 2000a).

In 1999, reports of toxic effects of 1,4-B and GBL led the FDA to issue warnings about the two compounds and designate both as illegally marketed unapproved new drugs (despite many being labelled as dietary supplements) (FDA 1999b). In 2000, GBL (but not 1,4-B) was made a federal List 1 chemical (List 1 and 2 includes similar chemicals, plus some additional ones, to our Schedule 4 in the Misuse of Drugs Act, which 'houses' precursor substances).

The United States legislation also caters for analogues of controlled drugs (substances intended for consumption that are structurally similar or pharmacologically substantially similar, or represented as being similar to a Schedule 1 or 2 substance). As GHB is listed in Schedule 1, then 1,4-B and GBL may also satisfy the definition of a controlled substance analogue (DEA 2000b).

Among the European Community six member countries control GHB under misuse of drugs legislation (Belgium, Denmark, France, Ireland, Italy, and Sweden). It is similarly controlled in Norway. Other European countries

control GHB under medicines legislation (Austria, Finland, Germany, the Netherlands, and the United Kingdom) (EMCDDA 2001). The recent United Nations classification of GHB should result in other signatory countries classifying GHB.

GBL is on the voluntary monitoring list of the Drug Precursors Committee of the European Commission. This list is circulated to the chemical industry who are asked to notify any suspicious enquiries and transactions in the listed chemicals to the authorities. 1,4-B is not on this list (EMCDDA 2001).

Recommended presumption for supply and justification⁵

The EACD does not recommend any presumption of supply be set for these drugs.

Implications for harm minimisation principles

The EACD noted that there is apparently a large number of people prepared to consume GHB or its related substances. After emphasising the risk of harm from unknown or variable concentrations or doses, the EACD discussed the other possible effects of classifying these substances under the Misuse of Drugs Act.

As with other scheduled substances, there is a potential for driving the drugs 'underground'; increasing the attractiveness of the substances to some young people; encouraging the introduction of alternative un-regulated substances; and prompting the illicit manufacture of inferior 'home produced' versions of the controlled substances that have a risk of unknown harmful contaminants. Such effects would impact on harm minimisation principles. However, the Committee concluded that it did not currently have sufficient evidence to weigh up these risks against the deterrent effect of scheduling these substances under the Misuse of Drugs Act.

The EACDA agreed that any legal classification, including the status quo, should be supported by complementary measures, such as providing accurate and evidence-based information to empower people, especially those who choose to use these substances, to reduce potential harm to themselves and to others. Key messages include:

- The steep dose-response curve (ie, a small increase in dose can have more serious effects).
- The specific health effects including the potential overdose effects (eg severe respiratory depression).
- The individual variability in the dose-response – i.e. equivalent doses can affect different people in different ways.

⁵ The Act contains provisions for setting a presumption for supply for controlled drugs (section 6(6)). This is a threshold where the simple possession of a specified amount of a drug is deemed to be for the purpose of supplying it to other people. Once the threshold is reached the onus is on the person to prove they were not in possession of the drug to supply other people. The EACD may decide to recommend a presumption for supply.

- The delayed onset of the effects associated with these substances, which may cause people to consume more of the drug (thinking the original dose is not achieving the desired effect) and risk overdose.
- The unpredictability of the effects - especially when combined with other sedatives/depressants such as alcohol. Likewise, some GHB substances may be more potent (such as GBL).
- How to care for an unconscious person who has taken these substances (safeguarding the airway, positioning the person in the 'recovery position', 'mouth-to-mouth' breathing, and to call for immediate medical assistance).
- People who have taken the drug should not drive a vehicle, operate heavy machinery, or engage in water-related activities.
- People should not take these substances alone, or with strangers.
- People should not take drinks from strangers, or leave their glasses unattended because someone might 'spike' their drink.

The EACD agrees that as a starting point, this paper should be made publicly available (eg, posted on the National Drug Policy website www.ndp.govt.nz) as soon as practicable.

Other relevant information

Is there an antidote?

The reversal of GHB-induced central nervous system depression is a controversial issue. Viera and Yates (1999) note that although there is no definitive antidote for GHB-related products, neostigmine and physostigmine have shown promise as potential reversal agents. Similarly, Shannon and Quang (2000) report there is no known antidote for GHB overdose and treatment is largely supportive with attention to airway management. The authors advise that while physostigmine and naloxone have been reported to reverse some effects of GHB, further investigation is needed to establish the safety and efficacy of these agents for GHB toxicity.

Regarding physostigmine, some experts consider that the risks of such antidotes (eg, bradycardia or seizures) outweigh the benefits in most GHB ingestions and they should be reserved for selected cases, if used at all (Cameron 2001). In a recent article Caldicott and Kuhn (2001) argued the potential for physostigmine to be used in some cases of severe GHB overdose/sedation.

Enforcement provisions of the Act

The classification of GHB and its related substances into schedule B1 of the Act will impact on Police and Customs officers enforcement powers. For example, under section 13 of the Misuse of Drugs Amendment Act 1978, a Police or Customs Officer can detain a person if they have reasonable cause to believe that the person has any Class A controlled drug or Class B (whether B1, B2, or B3) controlled drug secreted within that person's body for any unlawful purpose.

However, other enforcement provisions of the Act distinguish between different Parts of a Class. A good example is section 18, which provides the Police with search and seizure powers without a search warrant for controlled drugs in Class A, B1, or C1 only.

Submitters to EACD

The Committee also considered a number of written submissions, by or on behalf of:

- The Brenner family / Chen and Palmer
- Outerspace Limited
- The Department of Critical Care, Auckland Hospital
- The New Zealand Drug Rape Trust
- Dr Allan Pelkowitz.

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