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Gamma-hydroxybutyrate (GHB): A New Generation of Drugs from the Chemical Shelf

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Abstract: The drug gamma-hydroxybutyrate (GHB, 'liquid ecstasy') reached Switzerland in 1998. We describe the analyses of seized liquids and body fluids, legal aspects, forensic cases (overdosing and car driving), effects and adverse effects, pharmacology and toxicology of GHB.

Keywords: Gamma-hydroxybutyrate · GHB · Forensic case reports · Driving under the influence · Toxicology

1. Introduction

Drug dealers and underground chemists recently discovered a new source of drugs: the catalogue of chemicals! The most common representatives of this new kind of drugs of abuse are gamma-hydroxybutyric acid (GHB, 'liquid ecstasy') and benzylpiperazine (A2). Such drugs are easy to obtain and remain outside the jurisdiction of the drug laws, at least for a certain period of time.

GHB has been abused in the USA since the beginning of the nineties. In Europe the first reported cases were in 1995 [1]. The main abusers are young people at raves, discos, and on the drug scene, where GHB is popular for its euphorigenic and sedative properties. Furthermore, it is taken as an alleged anabolic agent by bodybuilders. Criminals use it to narcotize potential victims [2]. In Switzerland the first described cases of GHB intoxication occurred in 1998 [3] and the first cases of driving under the influence in 2000 [4].

Low doses of 1–2 g GHB have an euphoric effect; the consumer feels at ease, relaxed, and slightly inebriated. Higher doses lead to sleepiness, dizziness, nausea, vomiting, convulsions, cramps, bradycardia and hallucinations. The intake of 3–4 g (50 mg/kg bw) normally leads to unconsciousness within minutes, and doses of more than 4–5 g to deep coma [1][3][5][6].

2. Production and Supply

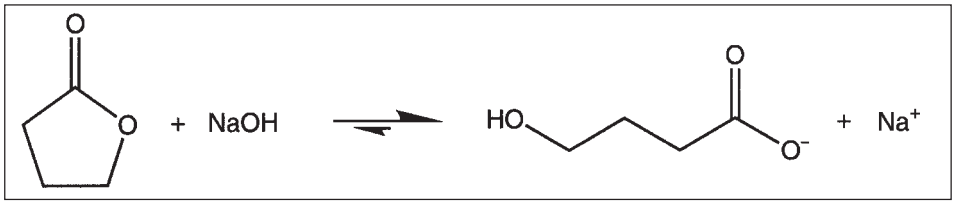
To produce gamma-hydroxybutyrate sodium salt (Na-GHB) underground chemists mostly use gamma-butyrolactone (GBL, abbreviated butyrolactone) as an educt. The lactone group is simply hydrolyzed by heating the educt in an alcoholic sodium hydroxide solution (Scheme 1). This solution is finally diluted with water and usually colored with food dyes. Inadequate handling of the reaction can lead to an excess of sodium hydroxide, leading in turn to corrosion of the mouth and throat area, of the esophagus, and maybe even the stomach and colon tract [7][8].

The drug is supplied mainly from so-called 'alternative shops', at parties, on the street, or through the Internet, where in addition to GHB itself, manufacturing kits from GBL are also on offer.

Relatively little is known about the addictive properties of GHB. To date, a small number of physical [9–11] and one probable case of psychic addiction [12] have been described. Withdrawal can lead to sleeplessness, muscle cramps, tremor and anxiety attacks [11].

3. Analysis of Seized GHB Liquids

As the GHB concentration in seized liquids is high, these samples can simply be diluted and then analyzed after a method developed by Mesmer and Satzger [13] using a high pressure liquid chromatograph coupled with a UV diode array detector (HPLC-DAD). The two analytes GHB and GBL can be determined in the same run at a wavelength of 215 nm. Salts normally consist of either Na-GHB or K-GHB. Therefore it might be required to use atomic absorption spectrometry (AAS) for the determination of the alkaline metal present.



Scheme 1. Reaction scheme for the production of gamma-hydroxybutyrate sodium salt (Na-GHB) from gamma-butyrolactone (GBL).

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In Zurich last year, the street price for a normal 5 ml dose of GHB (containing about 2.4 g Na-GHB and 0.2 g GBL) was approximately CHF 20.—. GHB is normally orally consumed in the form of its sodium salt dissolved in an aqueous solution (Fig. 1).

Fig. 1. Picture taken from different GHB samples sold in 'alternative stores' in Switzerland. Each tube represents a single oral dose and contains about 2.4 g of Na-GHB.

4. GHB Analysis in Blood and Urine

We conduct GHB analyses by a modified method of Couper and Logan [14]. 100 µl of whole blood, serum or urine and 25 µl of the internal standard GHB-d6 are added into a 1 ml Eppendorf tube. Then 25 µl of sulphuric acid (0.1 N) are added and the sample is vortexed. 400 µl of ethyl acetate are added and the sample is vortexed again, then centrifuged (12000 rpm, 5 min). The organic supernatant is evaporated to dryness under a stream of nitrogen at room temperature. For silylation 20 µl MSTFA are added, vortexed and kept at room temperature for one hour. Gas chromatography-mass spec-trometry (GC-MS) analyses are per-

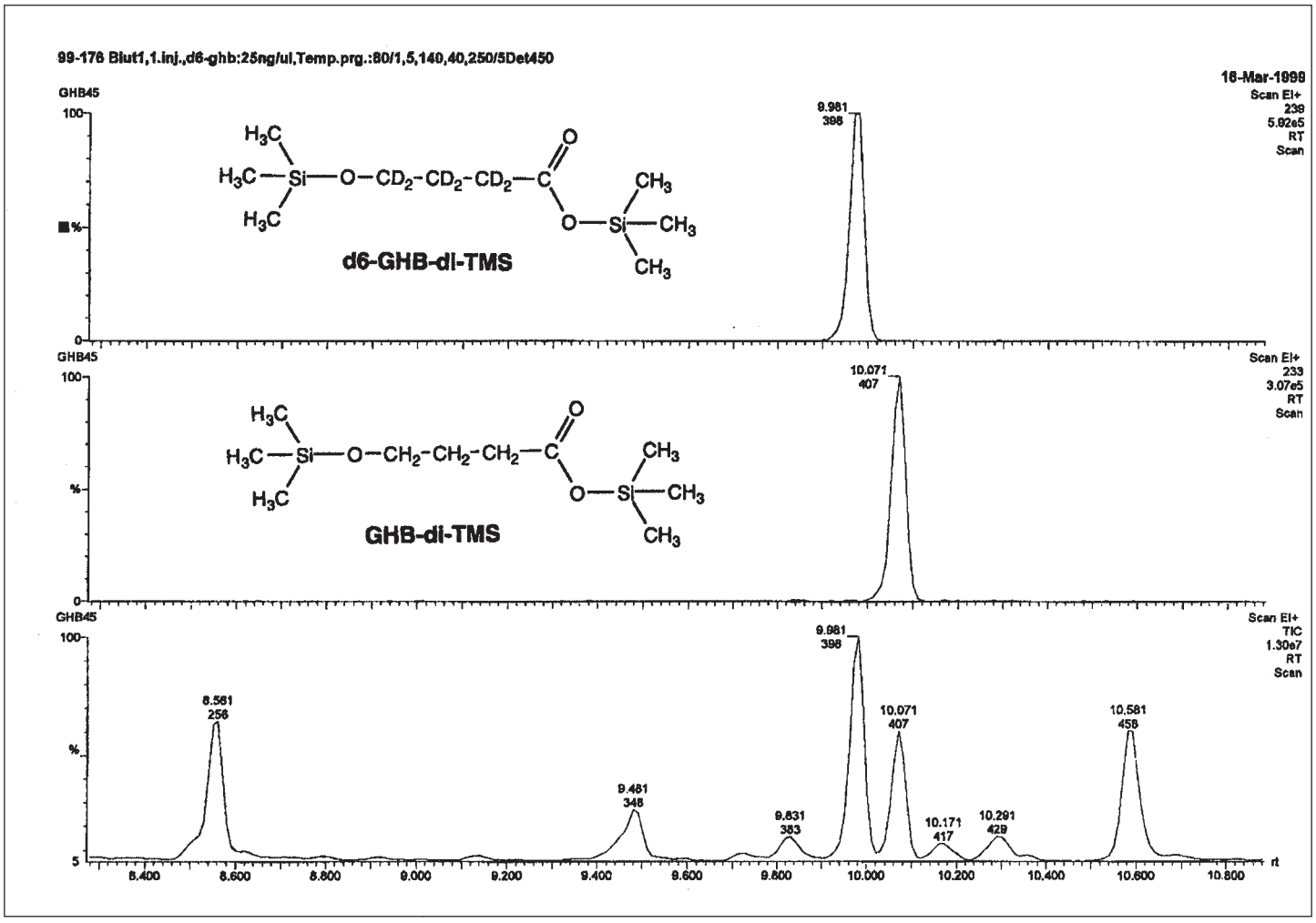


Fig. 2. GC-MS analysis (full-scan mode) of a whole blood sample of a case. Chromatogram of the characteristic mass of TMS-derivatized d6-GHB (top, m/z = 239) and GHB (middle, m/z = 233) and of the total ion current (TIC, bottom), respectively.

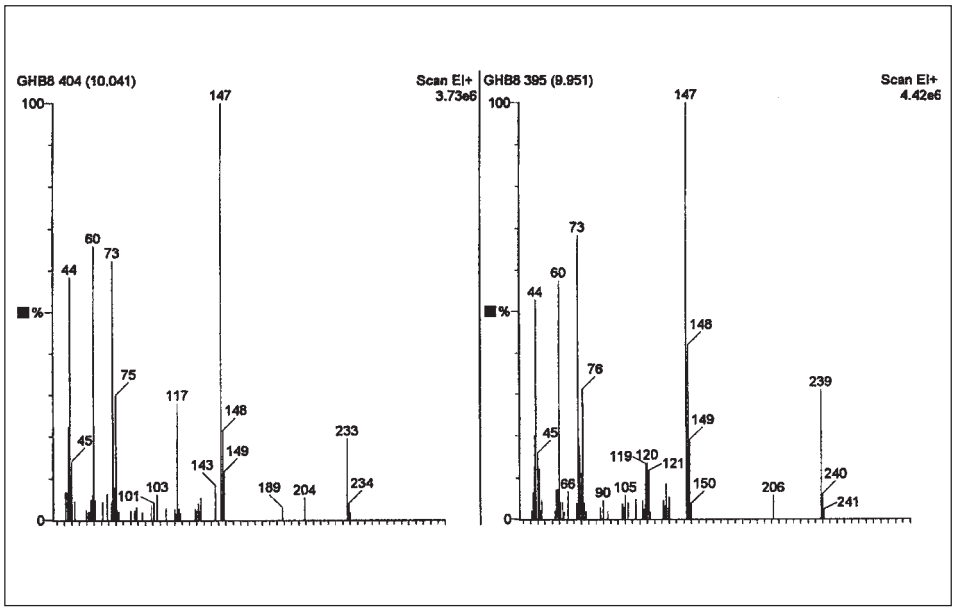


Fig. 3. EI mass spectra of GHB-di-TMS (left) and d6-GHB-di-TMS (right).

formed with a Fisons MD 800, full scan mode, electron ionization (70 eV). A DB5-MS column (J & W Scientific, 30 m, 0.25 mm i.d., 0.25 μm film thickness) is used. The injection port temperature is 230 °C, the interface temperature is 250 °C and the temperature in the ion source is 200 °C. 1 μl of sample is injected into the GC-MS. The initial column temperature is at 80 °C, hold 1 min, ramped at 5 °C/min to 140 °C, and then ramped at 40 °C/min to 280 °C with a final hold of 5 min. Helium with a pressure of 80 kPa is used as the carrier gas. The mass m/z 233 for GHB and m/z 239 for GHB-d6, respectively, are used for quantitation, see Fig. 2 and 3.

5. Narcotics Law, Poisons Law

Due to increasing abuse, GHB was classified as a Schedule one drug in the USA. The classification applied initially to several states in 1997 (*e.g.* in Florida [15]) and was extended to the whole of the USA in 2000 [16]. Since December 31, 2001, in Switzerland the salts of gamma-hydroxybutyric acid are subject to the Federal Narcotics and Psychotropic Substances Law (Betäubungsmitttelgesetz) [17]. However, gamma-hydroxybutyric acid itself, gamma-butyrolactone, and 1,4-butanediol have still not been scheduled. In the Swiss Poisons Law (Giftgesetz) the sodium salt of gamma-hydroxybutyric acid (Na-GHB) belongs to poison class 2 (Giftklasse 2) and gamma-butyrolactone to poison class 4 (Giftklasse 4) [18]. In Switzerland gamma-hydroxybutyric acid is not listed in the Poisons Law.

6. Forensic Cases

In forensic practice, it is important to be able not only to analyze the products of illicitly manufactured GHB samples, but also to identify and quantify GHB in body fluids of recreational consumers as well as of offenders and victims of criminal offences, *e.g.* of people taking GHB at parties, of car drivers, or of people committing crimes under the influence of GHB. The following examples of our casework show the dramatic effects of GHB. For further details see [3][4].

Case #1

A 33-year-old man driving a Jeep-Cherokee through Zurich in the evening rush hour suddenly veered across the road, forced oncoming cars to brake, and drove onto the opposite pavement. There, he drove on, causing several pedestrians to jump aside, then crossed another street and onto a second pavement, which he then left, forcing a bus to a full stop. On the main road he crashed at full speed into a car. The drivers of both cars remained unhurt, but the driver at fault was completely disoriented. The police found four ampoules of an orange GHB-containing liquid in his possession and stated that he was unable to co-operate, became comatose (GCS 3) and was admitted to hospital. All physiological parameters were unobtrusive (blood pressure 126/78, pulse 54) with the exception of miosis. After more than an hour he regained consciousness and left the hospital soon after. When interrogated, he claimed that he had bought five ampoules of GHB around noon and had immediately drunk the contents of one of them. Further, he confessed that he had consumed cocaine and alcohol that afternoon and that he occasionally consumed cannabis. Our results (see Table 1) show that his driving capabilities were clearly impaired by GHB; cocaine had probably had an additional but minor effect. The high blood concentration of GHB proves that the last GHB intake occurred shortly before the accident and not during the time period claimed by the reckless driver.

Case #2

A 21-year-old man parked his car at a bus stop in Zürich around 9 a.m. When checked by the police, he showed symptoms of drowsiness, aggressive behavior and slowed reactions in addition to which he was trembling, unsteady on his feet, had slurred speech and was very tired. He had reddened and watery eyes. In his car four full and eight empty GHB-containing bottles were found. During the interrogation he confessed that he had ingested GHB between 6 and 8 p.m. on the previous evening but denied the abuse of other substances. Our results (Table 1) prove that he had recently consumed amphetamine, and also cannabis at an earlier period. The data also show that his last GHB intake occurred shortly before he was checked by the police. The GHB and amphetamine blood levels show that this driver was clearly unfit to drive a car.

Case #3

A 27-year-old man drove on the wrong side of the main road along lake Zurich at midnight. Oncoming cars had to drive on the pavement to avoid collision. A police car stopped him with great difficulty. Completely disorientated and unsteady on his feet, he showed symptoms of drowsiness, had slurred speech, and was depressed. When interrogated he explained that he had ingested GHB and carbamazepine – an antiepileptic – 2 h before the incident. According to the driver carbamazepine acts as a mood enhancer, which seemed to be the only reason why it was ingested. The GHB blood concentration can explain the odd driving pattern in this case (Table 1).

Table 1. Overview of the results of the three cases of car drivers

	Case #1	Case #2	Case #3
Time span between incident and blood sampling	1 h 25 min	2 h 16 min	48 min
GHB in whole blood	135 mg/l	53 mg/l	68 mg/l
GHB in urine	2700 mg/l	1800 mg/l	1050 mg/l
GHB content in the liquid	3 ampoules of 5 ml liquid, each containing 2.4 g Na-GHB		
Other substances in whole blood	cocaine 70 μg/l, ecgonine methyl ester 60 μg/l, benzoylecgonine 1150 μg/l, THC not detectable, THC-COOH 4.5 μg/l, no ethanol	amphetamine 45 μg/l, THC not detectable, THC-COOH 5.5 μg/l, no ethanol	carbamazepine 2'900 μg/l, no ethanol

Case #4

A 26-year-old man was admitted to a hospital in a deeply comatose state in the early morning hours. He remained in this state – during which time even his motor reflexes remained unresponsive – for about 3 h. After this period of time he suddenly regained consciousness, was fully orientated and did not sustain any after effects. He stated that he had spent the night in several discos and had ingested alcohol, amphetamine, cannabis and ecstasy (MDMA). Later that night he ingested an unknown amount of a clear liquid, which he had ordered under the name of 'Blackout' on the Internet. Within 10 min he started to show loss of balance, then his entire body began to jerk and he later became comatose. A 40 ml 'Blackout' bottle, still containing a small amount of the remaining liquid was found on the patient. While a concentration of 0.5 g/ml GHB was determined in the liquid, no other substances could be identified in the sample. The comatose state of the patient could have been attributed to his ingestion of the missing volume of liquid. As neither blood nor urine samples were available, it could not be clarified as to whether or not any of the other substances mentioned played a contributory role in the patient's condition.

Case #5

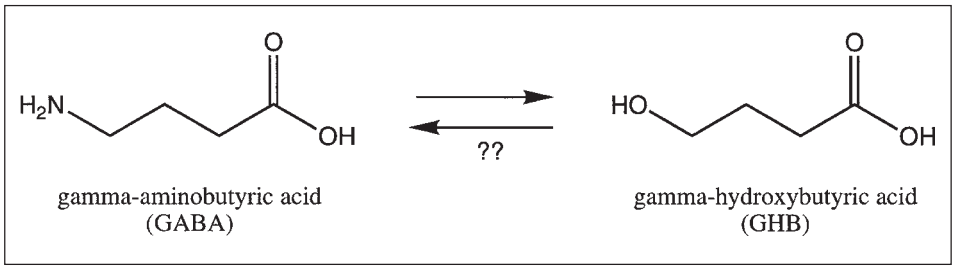
A 23-year-old man was admitted to a hospital in the early morning hours. He was unconscious, agitated, showed uncontrolled defensive movements of all extremities and made pronounced lip-smacking sounds with his mouth. 5 h after admission he regained consciousness, was fully orientated but had no memory of what had happened. He stated that he had been at a techno party, where he allegedly ingested amphetamine and ecstasy (MDMA). Sometime after midnight he drank a clear liquid. He had no memory of what happened afterwards until he woke up in hospital in the late morning. The blood analysis revealed that besides GHB, MDMA and a very high amphetamine concentration were present, and played a substantial role in the state of intoxication of the patient.

7. Pharmacology and Toxicology of GHB

GHB is a metabolite of the neurotransmitter gamma-aminobutyric acid (GABA) and is also probably metabolized to GABA [19] (Scheme 2). GHB seems to affect gabaergic, opioid, dopaminergic and cholinergic neurotransmitter-systems in the brain [19][20].

As physiologically normal for humans, GHB concentrations of approx. 0.1 mg/l in plasma [21] and of 0–7 mg/l in urine [22] were described. Ingested GHB is quickly resorbed, metabolized and eliminated. The terminal half-life is approx. 30 min and with high doses (>50 mg/kg bw) both resorption and elimination are slowed down [21][23]. A dose of approx. 1 g leads to a maximum plasma concentration of approx. 25 mg/l [23]. In the awakening phase Helrich *et al.* [24] were able to establish a good correlation between plasma concentration and effects: deep coma at GHB concentrations >260 mg/l, spontaneous blinking and responses occurred to deep pressure at 160–260 mg/l, spontaneous movements with occasional opening of eyes at 50–160 mg/l and awakening with concentrations below 50 mg/l.

Single doses of 1–2 g have an euphoric effect; the consumer feels at ease, relaxed and slightly inebriated, the senses are intensified, the wish to contact other people is increased and a stronger physical sensitivity is noticed [8][11][15]. It is also suggested that it acts as an aphrodisiac [11][15]. Doses of approx. 2.5 g lead to sleepiness, dizziness, nausea, vomiting, convulsions, cramps, bradycardia and hallucinations [5][6]. Intake of 3–4 g (50 mg/kg bw) normally leads to unconsciousness within minutes, and doses of more than 4–5 g (doses up to 30 g have been described) to deep coma [1][5][6]. In almost all cases the coma is reversible and the patient free from after effects [1][5][25][26]. There is a rapid onset of unconsciousness in addition to a rapid awakening [1][12][26][27]. The observed amnesia is evidently anterograde. Particularly for the inexperienced consumer the steep dose-response curve can be fatal as the doubling of a normal dose can lead to coma instead of the desired euphoria. One should take into account that the dosing of GHB – particularly in its liquid form – is difficult because the consumer normally does not know the concentration.



Scheme 2. Metabolism of the neurotransmitter gamma-aminobutyric acid (GABA) to gamma-hydroxybutyric acid (GHB) and probably *vice versa* from GHB to GABA.

Ingestion of GBL or 1,4-butanediol leads to a GHB inebriation because GBL as well as 1,4-butanediol are very quickly metabolized to GHB in the body (Scheme 3). For example the half-life for the transformation of GBL to GHB in the rat is about 1 min [28].

In rats the LD50 is 1.7 g/kg bw, the cause of death is respiratory depression [29]. In humans the lethal dose is so far unknown. Until now, very few credible lethal cases attributed solely to GHB have been documented [30][31]. However, there are some documented lethal cases where GHB was consumed together with other centrally depressing substances [32–35]. Not to be omitted are lethal cases caused by the intake of 1,4-butanediol, which must also be considered as GHB cases since this substance is quickly metabolized to GHB [36–38]. To our knowledge there are no described fatalities due to GBL.

So far there has not been a breakthrough in the use of GHB for medical purposes. As early as the sixties, its use as an intravenous anesthetic had been evaluated [29] unsuccessfully, because of its lack of analgesic properties and the fact that it caused frequent episodes of cramps and vomiting [8][20]. In the USA in 1989 its use as a weight reduction substance was forbidden by the FDA [39]. GHB has been considered as a medication for the treatment of withdrawal symptoms in alcoholics and opiate addicts [40][41]. It is currently being studied as a treatment for narcolepsy [42][43].

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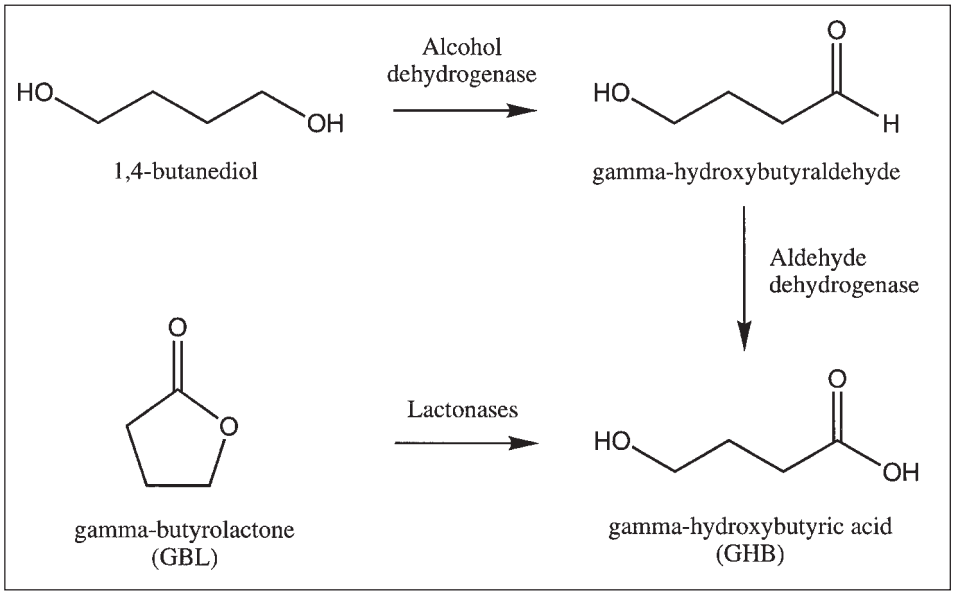

Scheme 3. The metabolism of 1,4-butanediol to GHB includes the formation of the intermediate gamma-hydroxybutyraldehyde, whereas the metabolism of GBL to GHB occurs in one step only.