1,4-Butanediol

Expert peer review on pre-review report

35th Expert Committee on Drug Dependence, Hammamet, Tunisia
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1. Comment based on the review report

a. Evidence on dependence and abuse potential
Pharmacology of 1,4-butanediole is tightly coupled to that of GHB, to which it is metabolized. Thus 1,4-BD has a significant abuse potential but its positively reinforcing effects are likely to be weaker than with the highly abused drugs. There is some evidence on tolerance and withdrawal in animals, and because of the drug is converted to GHB, it can be inferred that in humans its features could be similar to GHB withdrawal. Information on 1,4-BD, that would allow its separation from GHB and GBL, the other important precursor, is currently limited in almost every aspect but growing.

b. Consequences to individual and society because of misuse
Safety margin is narrow for the drug as used for recreational purposes, the overdose risk is great, and it can bring about loss of consciousness, respiratory depression, coma and death. Withdrawal reactions may be severe. The effects of 1,4-BD are reported to be subject to high inter-individual variability. Thus, to the individual the consequence of 1,4-BD abuse can be very serious. At the societal level the impact is minor as the abuse prevalence has remained low.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)
With the present knowledge it is difficult to separate the abuse of 1,4-BD from that of GHB. The compound is manufactured in ton quantities and is readily available in most countries and via the internet. Information on misuse and smuggling of 1,4-BD comes from a few countries, such as the Unites States of America, Australia, and several countries of Europe. Reports on clandestine manufacturing and smuggling are very rare.

d. Need of the substance for medical (including veterinary) practice
No need of the substance for medical practice.

e. Need of the substance for other purposes (e.g. industrial)
The substance is extensively used by industry and appears not being in process of replacement by any alternative. It is widely used in the medicine industry, the organic and fine chemical industry, the textile industry, the paper making industry, the automobile industry.

f. Measures taken by countries to curb misuse
1,4-BD is not subject to the 1988 UN Convention that covers precursor chemicals. Only a few states have declared 1,4-BD as a controlled substance as scheduling seems difficult considering its legitimate industrial applications. Some countries are controlling one or both precursors of GHB under drug control or equivalent legislation, and the European
Community and the Member States have taken additional voluntary measures to prevent its diversion.

g. **Impact if this substance is scheduled**
   Impact of scheduling is hard to predict without more detailed information on patterns of use.

2. **Additional information to the pre-review report**

While hardly any data are available on the prevalence of use of 1,4-BD specifically, internet drug forums and data from analysis of drug samples from amnesty bins and forensic science services suggest that use and availability to the users of 1,4-BD remains limited (Wood DM et al., Acute toxicity and withdrawal syndromes related to gamma-hydroxybutyrate (GHB) and its analogues gamma-butyrolactone (GBL) and 1,4-butanol (1,4-BD). Drug Testing and Analysis, 2011, 3: 417–425).

Human volunteer studies have shown that there is significant inter-individual variation in the rate of metabolism of 1,4-BD to GHB, possibly related to ADH-IB G143A polymorphism resulting in differences in activity of alcohol dehydrogenase (Thai D et al., Clinical pharmacology of 1,4-butanol and gamma-hydroxybutyrate after oral 1,4-butanol administration to healthy volunteers. Clinical Pharmacology and Therapeutics 2007, 81: 178-184). Experiments on baboons suggest that administration of 1,4-BD (and GBL) can raise plasma GHB levels faster than treatment with GHB itself, and the quick onset and longer duration of action with this compound may result in having greater abuse liability than GHB (Goodwin AK et al., Behavioral effects and pharmacokinetics of gamma-hydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanol (1,4-BD) in baboons. Psychopharmacology 2009, 204: 465-476).

3. **Other comments or opinions**

None.

4. **Expert reviewer’s recommendation for the need for a critical review**

Abuse rate of 1,4-BD is low but because 1,4-BD pharmacology is intrinsically linked to that of GHB, and has the potential to be abused in place of GHB, surveillance of patterns of its use appears important. Some recent evidence suggests that pharmacokinetic differences between administered GHB and 1,4-BD, including interaction with ethyl alcohol, may be significant. Doses used for intoxication are close to toxic doses and the risk of overdosing is high. Thus to gain more insight a critical review is recommended.