Bromazolam:
Report to the Expert Advisory Committee on Drugs

Prepared by the Ministry of Health

Meeting of 27 February 2024

Contents

1 EXECUTIVE SUMMARY

Bromazolam is a central nervous system depressant classified in New Zealand as a benzodiazepine. As a group, all benzodiazepines are regulated as prescription medicines under the Medicines Act 1981. However, some benzodiazepines are also scheduled as controlled drugs under the Misuse of Drugs Act 1975. Since 1 December 2022, bromazolam has been subject to a temporary class drug order (TCDO). Whilst subject to a TCDO, bromazolam is treated as a Class C1 controlled drug under the Misuse of Drugs Act 1975. The Expert Advisory Committee on Drugs (the Committee) is required to review the scheduling of bromazolam and provide advice to the Minister of Health while the TCDO is in place. The TCDO for bromazolam was renewed for a year, effective from 1 December 2023.

Bromazolam was reviewed by the World Health Organization Expert Committee on Drug Dependence (ECDD) in October 2023, and was recommended to be scheduled in Schedule IV of the Convention on Psychotropic Substances of 1971.

Growing international evidence indicates that bromazolam is a notable novel psychoactive substance of abuse. Illicit use of bromazolam was first identified in Sweden in 2016 and in New Zealand in 2020. Bromazolam has been identified in samples seized by the New Zealand Police and the New Zealand Customs Service. Additionally, both the Institute of Environmental Science and Research, and KnowYourStuffNZ (a drug checking service) have identified bromazolam in samples domestically. Internationally, as a proportion of all toxicology samples in which novel benzodiazepines are detected, the prevalence of bromazolam is increasing. It is possible that bromazolam is being produced to circumvent the legislation which restricts access to benzodiazepines and benzodiazepine derivatives internationally and domestically.

Bromazolam has a similar potency to some other benzodiazepines. User reports associate bromazolam with sedation, loss of consciousness, memory loss and disinhibition (effects shared with other benzodiazepines), and an increased risk of undesirable effects at higher doses. There is also an increased risk of severe adverse effects or death when used alongside other central nervous system depressants. International data demonstrates that the use of benzodiazepines alongside opioids is common.

Dependence can develop with prolonged use of benzodiazepines. Withdrawal from benzodiazepines can be life threatening when not managed appropriately.

2 INTRODUCTION

2.1 Purpose

This report provides an overview of bromazolam to be presented to the Expert Advisory Committee on Drugs (the Committee) for their consideration and subsequent scheduling recommendations under the Misuse of Drugs Act 1975.

2.2 Substance classification

The Ministry considers that bromazolam is captured as a benzodiazepine derivative and is therefore classified as a prescription medicine under the Medicines Regulations 1984. Bromazolam was placed under a temporary class drug order (TCDO) on 1 December 2022. This temporarily specified bromazolam as a Class C1 controlled drug under the Misuse of Drugs Act 1975 for a period of one year (unless otherwise renewed or revoked). The TCDO for bromazolam was renewed for a year, effective from 1 December 2023.

2.3 Why is this substance being considered?

Bromazolam is being considered by the Committee because it is subject to a TCDO. As required under section 4E of the Misuse of Drugs Act 1975, the Minister must seek advice about the appropriate classification of a drug while a TCDO is in place.

The TCDO request for bromazolam was submitted by the National Drug Intelligence Bureau (NDIB) in June 2022 following evidence of the growing domestic presence of bromazolam and the associated risk it poses to New Zealand society. The original TCDO request is provided alongside this technical paper. Data from NDIB demonstrates bromazolam seizures by New Zealand Police (Police) and New Zealand Customs Service (Customs), and detections in drug testing data (NDIB 2022a).

3 SUBSTANCE IDENTIFICATION AND CHEMISTRY

3.1 Identification

IUPAC Name: 8-bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

CAS Number: 71368-80-4

Molecular weight: 353.2 g/mol

Molecular formula: $C_{17}H_{13}BrN_4$

Appearance: a crystalline solid or a white powder (when pure) (Cayman Chemical 2022; EMCDDA 2021a)

Solubility: soluble in dimethylformamide (30 mg/mL), dimethyl sulfoxide (20 mg/mL), and ethanol (10 mg/mL); partially soluble in methanol (1 mg/mL) (Cayman Chemical 2022).

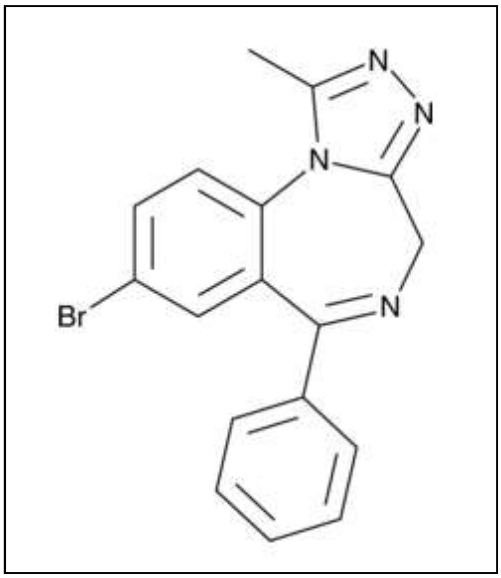


Figure 1: Chemical structure of bromazolam

3.2 Therapeutic value

Whilst there are legitimate medical uses for benzodiazepines, some novel substances in this class (including bromazolam) have no legitimate therapeutic indications. Use of these novel designer benzodiazepines is primarily illicit – either for recreation, self-medication, or are used in place of (or in combination with) other substances to which tolerance/addiction has developed (Brunetti et al 2021; Orsolini et al 2020).

Currently, there is no recognised therapeutic use for bromazolam. It has not undergone preclinical trails, nor is it used as a medicine domestically or internationally (WHO 2022). A literature search found bromazolam to be solely referenced as an illicitly sold, novel, designer benzodiazepine.

The United States patent 4,455,307 describes the use of triazolo-benzodiazepines as antihypertensives, listing bromazolam as one of these compounds (Hester 1984). Some of these compounds underwent clinical trials and are now used therapeutically for various indications, while bromazolam did not. The original patent for bromazolam has now expired.

There are a wide variety of existing benzodiazepines and derivatives available for use as medicines that have similar effects to bromazolam.

3.3 Similarities to other known substances

Structural similarities

Structurally, bromazolam is a triazolo-benzodiazepine. As such, it has structural similarities to other benzodiazepines including those controlled under the Misuse of Drugs Act 1975 and those controlled under the Medicines Act 1981. The general structure of benzodiazepines and triazolo-benzodiazepines is shown in Figure 2. Benzodiazepines consist of a benzene ring fused to a diazepine ring. The triazolo-benzodiazepine subclass is distinguished by an additional triazole group fused to the diazepine ring.

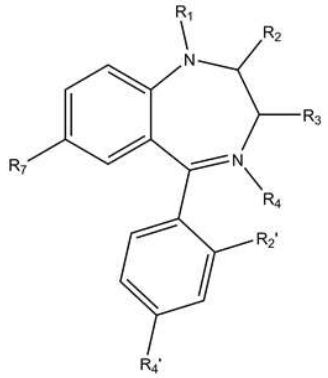
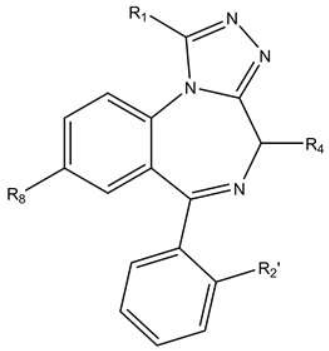
1,4-benzodiazepine	Triazolo-benzodiazepine
	

Figure 2: General structure of benzodiazepines and triazolo-benzodiazepines

When comparing the structure of bromazolam within the triazolo-benzodiazepine group, bromazolam is almost structurally identical to the Class C5 controlled substance alprazolam. In bromazolam, a bromine atom replaces the chlorine atom in alprazolam (CFSRE 2020; Orsolini et al 2020). These structures are shown in Figure 3.

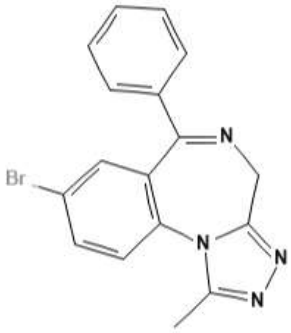
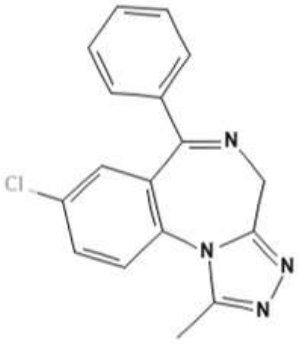
Bromazolam	Alprazolam
	

Figure 3: Structures of bromazolam and alprazolam

Differing structures can retain similar activities when the structural changes are minor or have similar functionality. These structural changes could include replacing benzene rings with similar aromatic rings, or replacing electronegative groups with similar electronegative groups, whilst maintaining molecular size and shape (EMCDDA 2021a). Changing a chlorine atom for a bromine atom is unlikely to significantly affect the activity of the structure, therefore, bromazolam will likely have similar activity to alprazolam.

Pharmacological similarities

User reports, gamma-aminobutyric acid A ($GABA_A$) receptor modelling, and structural similarities of bromazolam suggest that it has similar pharmacological properties to other benzodiazepines, including benzodiazepines scheduled as Class C5 controlled drugs under the Misuse of Drugs Act 1975, and those only controlled under the Medicines Act 1981 (EMCDDA 2021a; Waters et al 2017). For further information on the pharmacology of bromazolam see Section 4.2: General pharmacology.

3.4 Methods and ease of manufacturing

Several patents and papers refer to the synthesis of bromazolam. These patents and papers indicate that the first synthesis occurred in the 1970's by Hester et al (WHO 2022b).

While there are many methods that could be used to synthesise bromazolam, it is likely that the synthesis of bromazolam would follow the same synthesis pathway for alprazolam, the difference being the use of a brominated analogue (eg, 2-amino-5-bromobenzophenone) as the starting material. This pathway could comprise of the following steps.

1. Cyclisation of 2-amino-5-bromobenzophenone with chloroacetylchloride to form a 1,4-benzodiazepine precursor.
2. Introduction of a triazole ring into the 1,4-benzodizepine precursor to form bromazolam (WHO 2022b).

Synthesis would require access to synthetic laboratory equipment and purification equipment such as chromatographs.

For further information on the methods and ease of manufacturing of benzodiazepine, please see the Appendix, Section 11.2: Methods and ease of manufacture.

4 RISK OF HARM

4.1 Likelihood or evidence of abuse in New Zealand

Bromazolam is a triazolo-benzodiazepine which is consumed due to the substance's effects shared with other benzodiazepines (FIMEA 2021). For general information on benzodiazepines in New Zealand please see the Appendix, Section 11.1: Likelihood or evidence of abuse in New Zealand.

Bromazolam has been identified in materials seized by Police and Customs, and in drug checking samples, see Table 1 (NDIB 2022a).

On at least three occasions, samples brought to drug checking services were thought to be alprazolam, but were detected to be bromazolam in the form of counterfeit alprazolam tablets (KnowYourStuffNZ, personal communication, July 2022).

Bromazolam is available at a lower price than other illicitly supplied medicinal benzodiazepines (such as alprazolam) and is often sold in counterfeit tablets. Bromazolam is regularly recorded as being sold on New Zealand-based, dark web marketplaces and social media platforms. The low price point likely makes it attractive to vulnerable populations (NDIB 2022a).

Drug checking services identified bromazolam more frequently in 2022 than in 2021 (Table 1). This may be due to the increased availability of drug testing following the introduction of the Drug and Substance Checking Legislation Act 2021. Nevertheless, these identifications demonstrate that bromazolam is available in the New Zealand community.

New Zealand seizure and drug checking data

Police and Customs have seized bromazolam on at least 16 occasions. ESR has identified bromazolam in these seized materials. This may not represent the true number of seizures

containing bromazolam in New Zealand as, for example, seized replicate alprazolam tablets may not be tested for content (NDIB, personal communication, July 2022).

Table 1: Number of detections of bromazolam per year

Year of detection		2020	2021	2022*	2023*
Type of detection					
Customs and Police seizures	Number	1		13	2
	Amount	13.5g powder		2,089 pills 30.3 g powder	8.87g
Drug checking detections	Number		1	6	2

** provisional data*

4.2 General pharmacology

$GABA_A$ receptor modelling indicates that bromazolam acts similarly to other benzodiazepines (EMCDDA 2021a). For further information on the pharmacology of benzodiazepines, please see the Appendix, Section 11.3: Pharmacology of benzodiazepines.

User reports suggest bromazolam has similar effects to other benzodiazepines including anxiolytic, hypnotic, euphoric, and amnesiac properties (FIMEA 2021; Reddit 2022a; WHO 2022b). Additionally, user reports suggest a slow onset for bromazolam and the potential for loss of consciousness when re-dosing or at high doses (Reddit 2022a). A similarity to alprazolam is noted in user reports, though the extent of similarity is disputed. Some users suggest that bromazolam causes less amnesia and euphoria, and is longer lasting than alprazolam (FIMEA 2021; Reddit 2022c). It is not specified whether longer lasting refers to the duration of action or the after effects (eg, adverse effects/withdrawal).

Routes of administration and dosage

In New Zealand, bromazolam has been detected in both powder and tablet forms, with most detections being of tablet form (KnowYourStuffNZ, personal communication, July 2022; NDIB, personal communication, July 2022). Internationally and domestically, tablets are often presented as counterfeit medicines such as pressed alprazolam bars (CFSRE 2022c; NDIB, personal communication, July 2022).

The primary route of administration for bromazolam appears to be oral, in the form of tablets, capsules, solutions, and “gummies” (FIMEA 2021; Reddit 2022d; WHO 2022b). Bromazolam was detected in syringes next to the body in one fatality, though injection does not appear to be a common route of administration (WHO 2022b).

User report data suggests the common oral dose for bromazolam is in the range of 1–3mg, with a light dose being 0.5–1mg, and a strong dose 3–5mg or more (EMCDDA 2021a; FIMEA 2021; Tripsit 2022). Common recreational doses for novel benzodiazepines appear to be around 1mg. By way of comparison diazepam (a commonly prescribed medicine with proven therapeutic effects) has a user reported common oral dose of 5–15mg, with a light dose being 2.5–5mg and a strong dose of 15–30mg (WHO 2022b). Another medicine used therapeutically, lorazepam has a user reported common oral dose of 1–2mg, with a light dose being 0.5–1mg and a strong dose of 2–4mg (Tripsit 2022). Alprazolam, which has a similar triazolobenzodiazepine structure to bromazolam, has a user reported common oral dose of 0.5–1.5mg, with a light dose being 0.25–0.5mg, and a strong dose of 1.5–2mg (Tripsit 2023).

Pharmacodynamics

Bromazolam has been found to bind non-selectively to the alpha (α) subunits of the $GABA_A$ receptors *in-vitro*, with the following binding affinities: K_i=2.8nM at α-1, K_i=0.69nM at α-2, and K_i=0.62nM at α-5 (Clayton et al 2015; WHO 2022b). This demonstrated potent binding of bromazolam at the α-1 subunit with additional, though less potent, binding potential at the α-2 and α-5 subunits (Clayton et al 2015).

In addition, quantitative structure-activity relationship models suggest bromazolam is likely to bind to the benzodiazepine site on the $GABA_A$ receptor. The predicted binding value for bromazolam was 8.25 (log 1/c), which is similar to values predicted for etizolam of 8.64 (log 1/c). Etizolam is a benzodiazepine which has been implicated widely in illicit use (EMCDDA 2021a; Waters et al 2018).

The specific pharmacology and mechanism of action for bromazolam have not been studied *in-vivo*.

Similarities in pharmacology for bromazolam with other benzodiazepine derivatives are assumed from user reports and extrapolated from structural similarities to therapeutic benzodiazepines with better characterised pharmacology. Significant structural similarity to alprazolam means bromazolam is likely to similarly affect the $GABA_A$ receptors. User reports suggest bromazolam has comparable effects to alprazolam, such as causing drowsiness, amnesic type effects and loss of consciousness (FIMEA 2021; Reddit 2022a).

For further information on the general pharmacology of benzodiazepines, please see the Appendix, Section 11.3: Pharmacology of benzodiazepines.

Pharmacokinetics

Aside from metabolism, the specific pharmacokinetics of bromazolam have not yet been studied.

User report data suggests that the onset of action for an oral dose of bromazolam is 15 – 45 minutes after ingestion, with a duration of action of five to eight hours, and after-effects that can last up to 12 hours (EMCDDA 2021a; FIMEA 2021; Reddit 2022a). Anecdotal user reports suggest that bromazolam may have a longer duration of action than etizolam which has a half-life of five to seven hours (Ministry of Health 2022; Reddit 2022c).

Bromazolam will likely have absorption, distribution, metabolism, and excretion similar to other triazolo-benzodiazepines, such as alprazolam. These similar triazolo-benzodiazepines

are rapidly absorbed and show a high binding affinity to plasma proteins. This is reflected in peak concentrations usually occurring within an hour of ingestion. The 1,4-triazolo ring prevents the oxidative metabolism that non-triazolo, non-imidazole benzodiazepines undergo. This results in the formation of active metabolites with long elimination half-lives. The average elimination half-life of alprazolam in healthy adults has been documented as 9.5 – 12 hours (WHO 2019).

Studies on the metabolism of bromazolam tend to focus on metabolites for use in toxicology screenings. A study on the metabolism of bromazolam *in vivo* and *in vitro* identified hydroxylation, glucuronidation and a combination of these as the predominant metabolic steps in pooled human liver S9 fraction. Bromazolam was detected in human plasma and urine following ingestion. Cytochrome P450 (CYP) and uridine 5'-diphospho-glucuronosyltransferase (UGT) isozymes catalyse the metabolic transformation of bromazolam. CYP3A4 is involved in formation of all phase I metabolites, whilst phase II metabolism involves UGT1A4 and UGT2B10 catalysed N-glucuronidation. Several UGT isoforms catalysed glucuronidation of the hydroxylated-metabolites (Wagmann et al 2021; WHO 2022b.).

4.3 Toxicology

Bromazolam has not undergone preclinical testing, therefore there is no LD_{50} data available.

Anecdotal evidence of bromazolam causing vehicular accidents has been reported in New Zealand (KnowYourStuffNZ, personal communication, July 2022). Data from 14 drug impaired driving cases in the United States, showed sample concentrations of bromazolam between 4.3 and 160ng/mL, with a mean of 61ng/mL and a median of 56ng/mL (CFSRE 2022c). Concentrations of bromazolam found in 236 post-mortem investigations in the United States ranged from 2.1 – 670ng/mL, with a mean of 65ng/mL and a median of 35ng/mL (CFSRE 2022c). Bromazolam overdose may not be the primary cause of death, which may account for the wide range in concentrations in post-mortem samples. By way of example, whilst some deaths may have been directly linked to bromazolam overdose (where you may expect a higher bromazolam level), some deaths may have been due to benzodiazepine withdrawal (where the bromazolam level may have been low).

For more information on the general toxicology of benzodiazepines, please see the Appendix, Section 11.3: Pharmacology of benzodiazepines.

4.4 Risk to public health

Please see the Appendix, Section 11.4: Risks associated with benzodiazepines for general information on benzodiazepines and their risk to public health.

Bromazolam has been found in illicitly manufactured tablets, often under a different substance name such as alprazolam or diazepam. In January 2023, a Welsh drug checking service found that 33% of samples thought to be diazepam, and 36% of samples thought to be alprazolam were in fact bromazolam (WEDINOS 2023). Users of these tablets may be unaware of the true contents which can lead to unintentional harmful consumption of bromazolam (NDIB 2022a). Bromazolam has been identified in counterfeit alprazolam tablets in New Zealand and overseas (CFSRE 2022c; KnowYourStuff, personal

communication, July 2022; NDIB 2022a). There have been anecdotal reports of people in New Zealand experiencing strong effects from the use of bromazolam (NDIB 2022a). User reports also suggest that loss of consciousness is a risk associated with bromazolam (Reddit 2022a).

Information on the toxicology of cases of impaired driving linked to bromazolam can be found in Section 4.3: Toxicology.

Internationally, bromazolam use has resulted in hospitalisations. The primary problem in hospital presentations is the loss of consciousness and respiratory depression. Generally, clinical management is achieved by mechanical ventilation, monitoring and stabilisation of cardiovascular functions (EMCDDA 2021a).

In New Zealand, there has been one analytically confirmed identification of bromazolam in an unidentified substance emergency department case (ESR, personal communication, March 2023).

The detection of bromazolam in United States toxicology samples is increasing as shown in Table 2. The toxicology samples analysed by the Centre for Forensic Science Research and Education (CFSRE) include ante- and post-mortem samples, and samples from driving under the influence of drugs investigations.

Table 2: Bromazolam detections in toxicology samples in the United States by yearly quarter (Q) (CFSRE 2021a, 2021b, 2021c, 2022a, 2022b, 2022d, 2022e, 2023a, 2023b, 2023c).

	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	Q3 2022	Q4 2022	Q1 2023	Q2 2023	Q3 2023
Number of bromazolam detections	17	33	39	60	37	23	39	171	180*	349

*Q2 also includes a small number of positives for drug material rather than toxicology samples

The WHO (based on CFSRE data) reported that bromazolam was detected in 250 United States toxicology cases (236 post-mortem, 14 driving impairment) between 2019 and 2022 (WHO 2022b). More recent data depicted in Table 2 shows higher numbers of bromazolam detections in toxicology samples in 2023 (approximately 700 detections in the first three quarters of 2023).

The percentage of samples which are positive for bromazolam in CFSRE toxicology samples (in the United States) is also increasing. In the first quarter of 2021 the percentage of samples containing novel psychoactive substances positive for bromazolam was 1%, this increased to 13% by the second quarter of 2022, and to 37.4% by the second quarter of 2023 (CFSRE 2022c, WHO 2023a). In the fourth quarter of 2022, bromazolam was the most detected benzodiazepine novel psychoactive substance (CFSRE 2022e).

As other substances were frequently co-detected alongside bromazolam it is not possible to definitively determine the causality of bromazolam in these deaths (WHO 2022b). Between October 2020 and February 2022, ten cases (including post-mortems) were reported to the

United Nations Office on Drugs and Crime (UNODC) Early Warning System Tox-portal. In five of those cases bromazolam was the only substance detected. Similarly in 2022, in over 200 toxicology samples analysed in Wales, bromazolam was the sole (or one of only a few) substance(s) detected (WHO 2022).

In the United States, bromazolam is commonly detected alongside fentanyl suggesting concomitant use. Co-detection with fentanyl increased from approximately 20% at the end of June 2021, to 75% at the end of June 2022 in bromazolam positive samples (CFSRE 2022c). Use of benzodiazepines may increase the rewarding and reinforcing effects of opioids, possibly by amplifying the mu-opioid receptor agonist effects of opioids. This may explain why co-use of benzodiazepines and opioids in opioid dependent patients is widespread (EMCDDA 2021a).

The increased prevalence of bromazolam in New Zealand could impact vulnerable and marginalised populations. These populations are already more susceptible to poor mental health outcomes, and alcohol and other drug use.

4.5 Potential to cause death

Bromazolam has been identified in at least 236 post-mortem investigations in the United States. Bromazolam is often co-administered with other substances – this leads to identification alongside other substances, such as opioids (including fentanyl) (CFSRE 2022c). General information on the risk of death from benzodiazepines can be found in the Appendix, see Section 11.4: Risks associated with benzodiazepines.

A review of reported data found one confirmed death where bromazolam was the only novel psychoactive substance (NPS) or benzodiazepine present (NDIB 2022a). Additionally, bromazolam has been implicated in combination with other substances in other deaths by toxicology samples and forensic casework. The rate at which bromazolam is being identified has increased since April 2020 (see Section 4.4: Risk to public health). Bromazolam is likely under-represented in literature regarding toxicology findings due to a lack of specificity of testing and publication of reporting internationally (NDIB 2022a).

In New Zealand, there has been one detection of bromazolam in connection to a coronial case (ESR, personal communication, March 2023).

4.6 Potential for physical or psychological dependence

Bromazolam is likely to have similar dependence potential to other benzodiazepines. For general information on the dependence potential of benzodiazepines, please see the Appendix, Section 11.4: Risks associated with benzodiazepines. The physical and psychological dependence potential of bromazolam is likely similar to alprazolam. Despite tapering bromazolam use, some anecdotal reports include seizures as a withdrawal symptom (Reddit 2022b). At least one case has been reported of withdrawal-associated psychosis and hallucinations requiring hospitalisation for medically supervised withdrawal after repeated use of bromazolam in combination with phenibut (WHO 2022b).

5 CLASSIFICATION

5.1 New Zealand classification and regulation

The Ministry considers that bromazolam is captured as a benzodiazepine derivative and is therefore classified as a prescription medicine under the Medicines Regulations 1984. Bromazolam is currently subject to a TCDO, and for the duration of the TCDO bromazolam is also treated as a Class C1 controlled drug under the Misuse of Drugs Act 1975.

5.2 International classification and regulation

Bromazolam was recommended to be added to Schedule IV of the Convention on Psychotropic Substances (1971) by the World Health Organization Expert Committee on Drug Dependence in December 2023 (WHO 2023b).

Australia

Bromazolam is regulated under the entry for 'benzodiazepine derivatives except when separately specified' listed in Schedule 4 of the Poisons Standard 2022. Bromazolam is not explicitly listed as a controlled drug under the legislation (Australian Government 2022).

United Kingdom

Bromazolam is a named Class C substance under the Misuse of Drugs Act 1971 and is listed in Schedule 1 of the Misuse of Drugs Regulations 2001 (Gov.uk 2022).

United States

Bromazolam is not currently federally controlled in the United States (Federalregister.gov 2022). However, some states including Oregon have regulated bromazolam as a Schedule I Controlled Substance through a benzodiazepine group entry (State of Oregon 2020). Virginia has also named bromazolam as a controlled substance under Schedule I of the Drug Control Act 1970 (Virginia Law 2022).

Canada

Bromazolam is regulated under the entry for 'benzodiazepines, their salts and derivatives' in Schedule IV of the Controlled Substances Act 1996 (Government of Canada 2022; Health Canada, personal communication, August 2022). Bromazolam is not explicitly listed as a controlled drug under the legislation (Government of Canada 2022).

Germany

Bromazolam is controlled as part of the group entry for benzodiazepines under the Neue-psychoactive-Stoffe-Gesetz 2016 in Germany (Gesetze im Internet 2023).

Sweden

Bromazolam is listed under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code 1992 (Sveriges Riksdag 2022).

Finland

The Finnish Medicines Agency (FIMEA) assessed that bromazolam should be included in the Annex IV for the Government Decree on narcotic substances, preparations, and plants 2008 (FIMEA 2021).

5.3 UN classification

Bromazolam was assessed by the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) in December 2023. The ECDD recommended that bromazolam be added to Schedule IV of the Convention on Psychotropic Substances (1971) by the World Health Organization Expert Committee on Drug Dependence in December 2023 (WHO 2023b).

6 OTHER RELEVANT INFORMATION

6.1 Anticipated future trends

Based on trends in the United States (see Section 4.4: Risk to public health), the proportion of bromazolam detections in toxicology cases is likely to increase in future, suggesting an increasing presence of bromazolam in the community. It is likely that this will continue until the supply of bromazolam is restricted. In April 2021 there was an increase in online mentions of bromazolam by new users who had not previously mentioned the drug (National Drug Early Warning System 2021). This may indicate a greater awareness of bromazolam. NDIB reports that there is currently increasing harm from bromazolam in New Zealand (NDIB 2022a).

7 CLASSIFICATION OPTIONS

Option 1 – Maintain status quo

Bromazolam would not be scheduled under the Misuse of Drugs Act 1975, and solely remain a prescription medicine under the Medicines Act 1981. The maximum period of supply per prescription would remain at three months. By way of comparison substances classified as a Class C controlled drug under the Misuse of Drugs Act 1975 also have a maximum period of supply of three months per prescription, usually dispensed monthly. Note that whilst it is a prescription medicine, bromazolam is not used therapeutically, and commercial preparations are not available, and therefore is unlikely be prescribed.

Anyone caught in possession of a prescription medicine (without a prescription) for personal use faces three months imprisonment and/or a $500 fine. Anyone (other than those exempted under the Medicines Act 1981) convicted of selling or supplying a prescription medicine faces up to six months imprisonment or a fine not exceeding $20,000.

Option 2 – Schedule as a Class A controlled drug under the Misuse of Drugs Act 1975

Substances posing a very high risk of harm to individuals or society that are highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse.

The penalties for Schedule 1 (Class A) controlled drugs are listed below in Table 3. For a full breakdown on the controls, please see the EACD guidelines.

Option 3 – Schedule as a Class B controlled drug under the Misuse of Drugs Act 1975

Substances posing a high risk of harm to individuals or society that can be highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse.

The penalties for Schedule 2 (Class B) controlled drugs are listed below in Table 3. For a full breakdown of the differences in control between these parts of Schedule 2, please see the EACD guidelines.

Option 4 – Schedule as a Class C controlled drug under the Misuse of Drugs Act 1975

Substances posing a moderate risk of harm to individuals or society and a moderate to high risk of abuse and dependency or are easily convertible into drugs that are similarly addictive and liable to abuse.

The penalties for Schedule 3 (Class C) controlled drugs are listed below in Table 3. For a full breakdown of the differences in control between these parts of Schedule 3, please see the EACD guidelines.

Table 3: Comparison of regulatory requirements and penalties under the Misuse of Drugs Act 1975

Class	Requirements	Penalties
A	Ministerial approval required for supplying, administering, prescribing, or granting licences to deal in, import or export Class A controlled drugs – except for cocaine and derivatives. All Class A controlled drugs must be kept in a controlled drugs safe.	Maximum penalty of life imprisonment for the importation, manufacture, or supply (subject to presumption of supply). Up to 14 years imprisonment for conspiracy to commit an offence. Up to 6 months imprisonment or $1,000 fine or both for possession.
B1	Ministerial approval required for supplying, administering, prescribing, or granting licenses to deal in, import or export Class B1 controlled drugs – except for morphine or opium and derivatives. Must be kept in a controlled drugs safe.	All Class B drugs hold the same maximum penalties for offences involving these drugs. Up to 14 years imprisonment for importation, manufacture, or supply (subject to presumption of supply). Up to 10 years imprisonment for conspiracy to commit an offence. Up to 3 months imprisonment or $500 fine or both for possession.
B2	Ministerial approval required for prescribing, dispensing, and administration. No Ministerial approval required for granting licences to deal in, import or export Class B2 controlled drugs. Must be kept in a controlled drugs safe.	
B3	No Ministerial approval required for supplying, administering, prescribing or	

	granting licenses to deal in, import or export Class B3 controlled drugs. Must be kept in a controlled drugs safe.	
C1	A person who wishes to import, manufacture, and supply or administer a Class C1 controlled drug must apply for a written approval of the Minister for issuance of a licence to do so. Class C1 drugs are required to be stored in a safe.	All Class C drugs hold the same maximum penalties for offences involving these drugs. The penalty for anyone caught in possession of a class C controlled drug for personal use without a prescription is the same as that for a prescription medicine (3 months imprisonment and/or a $500 fine). The penalties for anyone involved in the importation, manufacture and supply of Class C drugs is up to 8 years imprisonment, or, summarily, 1 year jail and/or a $1,000 fine. (similar or slightly harsher than for a prescription medicine). The penalty for conspiracy to commit an offence involving Class C drugs is up to 7 years imprisonment, and up to 3 months imprisonment or a $500 fine or both for possession.
C2-5	A person who wishes to import, manufacture, and supply or administer a Class C2-5 controlled drug must obtain a licence to do so but doesn't need the written approval from the Minister. Class C2-4 drugs are required to be stored in a safe. Class C5 drugs are not required to be stored in a safe.	

8 PRESUMPTION FOR SUPPLY

8.1 Options for presumption of supply

Option 1: Status quo

Option 1 is to set no presumption of supply. The default amount of **56g** will apply.

This would be approximately **28,000 doses,** assuming an average dose of 2mg.

This option, being no presumption of supply (and therefore a default of **56g),** would align with the presumption of supply set for the other benzodiazepines that are scheduled under the Misuse of Drugs Act 1975.

Option 2: Proposed presumption of supply

Option 2 is to set a presumption for supply at **50mg** for **25 doses** of bromazolam, assuming an average dose of 2mg.

Alternatively, a presumption of supply could be set for **100 doses** of bromazolam. This would be **200mg**, assuming an average dose of 2mg.

9 FUTURE ACTIONS

If the Committee recommends that bromazolam be scheduled under the Misuse of Drugs Act 1975, the Secretariat will draft a letter from the Committee to the Minister of Health to progress the advice. The Secretariat may undertake targeted consultation with industry to

ensure the impact on any legitimate use of bromazolam is reasonable and minimised. If the status quo is kept, no further action is required.

10 REFERENCES

Afzal A, Kiyatkin EA. 2019. Interactions of benzodiazepines with heroin: respiratory depression, temperature effects, and behavior. *Neuropharmacology* 158: 107677. DOI: 10.1016/j.neuropharm.2019.107677.

Australian Government. 2022. Poisons Standard June 2022. URL: https://www.legislation.gov.au/Details/F2022L00730/Html/Text#_Toc93920870 (accessed 16 August 2022).

Brunetti P, Giorgetti R, Tagliabracci A, et al. 2021. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. *Pharmaceuticals 2021.* 14(560*).* DOI: 10.3390/ph14060560.

BPAC. 2021. Withdrawing patients from long-term use of benzodiazepines or zopiclone. URL: https://bpac.org.nz/2021/benzo.aspx (accessed 23 August 2022).

Cayman Chemical. 2022. Bromazolam. URL: https://www.caymanchem.com/product/22665/bromazolam (accessed 14 July 2022).

CFSRE. 2020. Center for Forensic Science Research and Education NMS Labs: Bromazolam. URL: https://www.cfsre.org/images/monographs/Bromazolam_050120_NMSLabs_Report.pdf (accessed 15 August 2022).

CFSRE. 2021a. Center for Forensic Science Research and Education Trend Report – Q2 2021: NPS benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2021-Q2_NPS-Benzodiazepines_Trend-Report.pdf (accessed 21 July 2022).

CFSRE. 2021b. Center for Forensic Science Research and Education Trend Report – Q3 2021: NPS benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2021-Q3_NPS-Benzodiazepines_Trend-Report.pdf (accessed 21 July 2022).

CFSRE. 2021c. Center for Forensic Science Research and Education Trend Report – Q4 2021: NPS benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2021-Q4-NPS-Benzodiazepines-Trend-Report.pdf (accessed 21 July 2022).

CFSRE. 2022a. Center for Forensic Science Research and Education Trend Report – Q1 2022: NPS benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2022-Q1-NPS-Benzodiazepines-Trend-Report.pdf (accessed 7 July 2022).

CFSRE. 2022b. Center for Forensic Science Research and Education Trend Report – Q2 2022: NPS benzodiazepines in the United States. URL:

https://www.cfsre.org/images/trendreports/2022-Q2-NPS-Benzodiazepines-Trend-Report.pdf (accessed 7 July 2022).

CFSRE. 2022c. Center for Forensic Science Research and Education Public alert: Bromazolam Prevalence Surging Across the United States Driven In Part by Increasing Detections Alongside Fentanyl. URL: https://www.cfsre.org/nps-discovery/public-alerts/bromazolam-prevalence-surging-across-the-united-states-driven-in-part-by-increasing-detections-alongside-fentanyl (accessed 12 August 2022).

CFSRE. 2022d. Center for Forensic Science Research and Education Trend Report: NPS Benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2022-Q3-NPS-Benzodiazepines-Trend-Report.pdf (accessed 8 March 2023).

CFSRE. 2022e. Center for Forensic Science Research and Education Trend Report: NPS Benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2022-Q4-NPS-Benzodiazepines-Trend-Report.pdf (accessed 8 March 2023).

CFSRE. 2023a. Center for Forensic Science Research and Education Trend Report: NPS Benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2023-Q1-NPS-Benzodiazepines-Trend-Report.pdf (accessed 8 March 2023).

CFSRE. 2023b. Center for Forensic Science Research and Education Trend Report: NPS Benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2023-Q2-NPS-Benzodiazepines-Trend-Report.pdf (accessed 8 March 2023).

CFSRE. 2023c. Center for Forensic Science Research and Education Trend Report: NPS Benzodiazepines in the United States. URL: https://www.cfsre.org/images/trendreports/2023-Q3-NPS-Benzodiazepines-Trend-Report.pdf (accessed 8 March 2023).Clayton T, Poe MM, Rallapalli S. 2015. A Review of the Updated Pharmacophore for the Alpha 5 GABA(A) Benzodiazepine Receptor Model. *International Journal of Medicinal Chemistry.* DOI: 10.1155/2015/430248.

EMCDDA. 2021a. European Monitoring Centre for Drugs and Drug Addiction: New Benzodiazepines in Europe – a review. DOI: 10.2810/725973. (accessed 7 July 2022).

EMCDDA. 2005. European Monitoring Centre for Drugs and Drug Addiction: Differences in patterns of drug use between women and men. URL: https://www.emcdda.europa.eu/attachements.cfm/att_34281_EN_TDS_gender.pdf (accessed 6 September 2022).

Federalregister.gov. 2022. International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; ADB-BUTINACA; Adinazolam; Bromazolam; Protonitazene (Propoxynitazene); Etazene (Etodesnitazene); Etonitazepyne (N-Pyrrolidino etonitazene); 2-Methyl-AP-237; Alpha-PiHP; 3-Methylmethcathinone (3-MMC); Zopiclone; Request for Comments. URL: https://www.federalregister.gov/documents/2022/08/03/2022-16572/international-drug-

scheduling-convention-on-psychotropic-substances-single-convention-on-narcotic (accessed 16 August 2022).

FIMEA. 2021. Finnish Medicines Agency: FIMEA/2021/006148 Assessment form: Bromazolam. URL: https://ec.europa.eu/growth/tools-databases/tris/index.cfm/fr/search/?trisaction=search.detail&year=2021&num=726&iLang=EN (accessed 14 July 2022).

Gesetze im Internet. 2023. Neue-psychoaktive-Stoffe-Gesetz (NpSG). URL: https://www.gesetze-im-internet.de/npsg/NpSG.pdf (accessed 7 March 2023).

Gov.uk. 2022. Guidance: List of most commonly encountered drugs currently controlled under the misuse of drugs legislation. Updated 8 August 2022. URL: https://www.gov.uk/government/publications/controlled-drugs-list--2/list-of-most-commonly-encountered-drugs-currently-controlled-under-the-misuse-of-drugs-legislation (accessed 16 August 2022).

Government of Canada. 2022. Controlled Drugs and Substances Act. URL: https://laws-lois.justice.gc.ca/eng/acts/c-38.8/FullText.html (assessed 17 August 2022).

Hester JB. 1984. Antihypertensive used of Triazolobenzodiazepines.United States Patent No. 4,455,307. URL:https://patentimages.storage.googleapis.com/c5/93/83/295c487712bcc0/US4455307.pdf (accessed 21 July 2022).

Milani SA, Raji MA, Che L, et al. 2021. Trends in the Use of Benzodiazepines, Z-Hypnotics, and Serotonergic Drugs Among US Women and Men Before and During the COVID-19 Pandemic. *JAMA Network Open*. 4(10): e2131012. DOI: 0.1001/jamanetworkopen.2021.31012.

Ministry of Health. 2022. *Etizolam: Report to the Expert Advisory Committee on Drugs*.

NDIB. 2022a. TCDO request for Bromazolam. URL:https://www.health.govt.nz/system/files/documents/pages/tcdo-request-form-bromazolam.docx.

National Drug Early Warning System (USA). 2021. Bromazolam – Online mentions. URL: https://ndews.org/?wysija-page=1&controller=email&action=view&email_id=136&wysijap=subscriptions (accessed 22 August 2022).

NZ Drug Foundation. 2022. *State of the Nation 2022*. URL: https://www.drugfoundation.org.nz/policy-and-advocacy/state-of-the-nation-2022/ (accessed 15 July 2022).

Orsolini L, Corkery JM, Chiappini S, et al. 2020. 'New/Designer Benzodiazepines': A Analysis of the Literature and Psychonauts' Trip Reports. *Current Neuropharmacology*. 18(9): 809-837. DOI: 10.2174/1570159X18666200110121333.

Reddit. 2022a. *Bromazolam Experience Report*. URL: https://www.reddit.com/r/researchchemicals/comments/q2qfc6/bromazolam_experience_report/ (accessed 16 August 2022).

Reddit. 2022b. B*romazolam is the benzo I've been searching for all my life*. URL: https://www.reddit.com/r/researchchemicals/comments/stzrij/bromazolam_is_the_benzo_ive_been_searching_for/ (accessed 16 August 2022).

Reddit. 2022c. *bromazolam review – it's legit*. URL: https://www.reddit.com/r/researchchemicals/comments/uqiy78/bromazolam_review_its_legit/ (accessed 16 August 2022).

Reddit. 2022d. *Better Way to Ingest Bromazolam Solution*. URL: https://www.reddit.com/r/researchchemicals/comments/lonalz/better_way_to_ingest_bromazolam_solution/ (accessed 22 August 2022).

Reddit. 2022e. *Bromazolam is the shit*. URL: https://www.reddit.com/r/researchchemicals/comments/rmcgvs/bromazolam_is_the_shit/ (accessed 22 August 2022).

State of Oregon. 2020. Notice of proposed rulemaking including statement of need & fiscal impact. URL: https://www.oregon.gov/pharmacy/Documents/NoticeFilingTrackedChanges_Clonazolam.pdf (accessed 11 July 2022).

Sveriges Riksdag. 2022. Ordinance (1992:1554) on the Control of Drugs. URL: https://riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/forordning-19921554-om-kontroll-av-narkotika_sfs-1992-1554 (accessed 11 July 2022).

Tripsit. 2022. *Tripsit Factsheets: Bromazolam*. URL: https://drugs.tripsit.me/bromazolam (accessed 15 August 2022).

Tripsit. 2023. *Tripsit Benzodiazepine Dosage Converter*. URL: https://benzo.tripsit.me/ (accessed 20 October 2023).

Van der Waals FW, Mohrs J, Foets M. 1993. Sex differences among recipients of benzodiazepines in Dutch general practice. *BMJ.* 307(6900):363-6. DOI: 10.1136/bmj.307.6900.363. Louisiana State Legislature. 2022. Composition of schedules. URL: https://legis.la.gov/Legis/Law.aspx?d=98877 (accessed 13 July 2022).

Virginia Law. 2022. Code of Virginia. URL: https://law.lis.virginia.gov/vacode/title54.1/chapter34/section54.1-3446/ (accessed 13 July 2022).

Waters LJ, Manchester KR, Maskell PD, et al. 2018. The use of a quantitative structure-activity relationship (QSAR) model to predict GABA-A receptor binding of newly emerging benzodiazepines. *Science and Justice*. 58(3):219-225. DOI: 10.1016/j.scijus.2017.12.004.

Wagmann L, Manier SK, Felske C, et al. 2021. Flubromazolam-Derived Designer Benzodiazepines: Toxicokinetics and Analytical Toxicology of Clobromazolam and Bromazolam. *Journal of Analytical Toxicology*. 45 (9):1014-1027. DOI: 10.1093/jat/bkaa161.

WHO. 2023a. Critical Review Report: Bromazolam

WHO. 2023b. Annex 1. 46th WHO ECDD summary assessments, rationale and recommendations, 16–19 October 2023. URL: https://cdn.who.int/media/docs/default-source/46th-ecdd/unsg_letter_46th-ecdd-annex.pdf?sfvrsn=db605662_5. (accessed 12 January 2024)

WHO. 2022a. 45th WHO ECDD summary assessments, findings and recommendations, 10-13 October 2022. URL: https://cdn.who.int/media/docs/default-source/controlled-substances/45th-ecdd/45th-ecdd-annex1-summary-assessments.pdf?sfvrsn=9f81c6e1_3 (accessed 8 March 2023).

WHO. 2022b. Critical Review Report: Bromazolam.

WHO. 2019. Critical Review Report: Flualprazolam.

11 Appendix – General information on benzodiazepines

11.1 Likelihood or evidence of abuse in New Zealand

In 2018, benzodiazepines were the third most frequent drug type implicated in drug-related deaths in New Zealand. Drug-related deaths included drug toxicity, suicide, and secondary contribution where death was caused by another form of injury (eg, drowning or a vehicle accident). There were 43 deaths where benzodiazepines were the primary contributor and eight where benzodiazepines were a secondary contributor. In 2017, 30 accidental poisonings causing death were attributed to benzodiazepines. An additional 810 people were discharged from publicly funded hospitals following use of benzodiazepines (for accidental or intentional poisoning). In the years 2017/2018, in New Zealand, women were overrepresented in hospitalisations for benzodiazepine or opioid overdoses (66%) (NZ Drug Foundation 2022). This differs to typical gender use patterns seen for illicit drugs domestically and internationally, where young men are over-represented (EMCDDA 2005; NZ Drug Foundation 2022). New Zealand hospitalisation data does not distinguish between licit and illicit use, the over-representation of women in hospital data may reflect use of benzodiazepines obtained through licit means. Internationally, women are more likely to be prescribed benzodiazepines than men (Milani et al 2021; Van der Waals et al 1933). Māori are generally over-represented in all drug-related deaths, with rates nearly three times that of non-Māori (NZ Drug Foundation 2022).

11.2 Methods and ease of manufacture

Designer benzodiazepines were likely first synthesised to circumvent the regulations and legal sanctions placed on existing benzodiazepines (Brunetti et al 2021). Production likely occurs in countries where the novel benzodiazepines are not yet regulated. Commonly, designer benzodiazepines have been found to be synthesised in chemical and pharmaceutical laboratories in China and shipped internationally as bulk powder (either pure or mixed with bulking agents). Upon arrival in their destination country, they may be further processed prior to illicit distribution (EMCDDA 2021a). In addition to bulk powder, designer benzodiazepines may be sold in tablet form (after addition of bulking agents or binders). Increasingly, designer benzodiazepines are manufactured into counterfeit versions of commonly prescribed benzodiazepines such as alprazolam or diazepam for the illicit market (EMCDDA 2021b; WHO 2022b).

11.3 Pharmacology of benzodiazepines

General pharmacology

Benzodiazepines exhibit central nervous system (CNS) depressive effects, and can cause sedation, loss of consciousness, memory loss and disinhibition. Benzodiazepines have anxiolytic, anti-convulsant, muscle relaxant, hypnotic, and sedative effects. Some benzodiazepines also demonstrate euphoric effects (EMCDDA 2021a).

Routes of administration and dosage

Benzodiazepines appear in various dosage forms including powders, tablets, liquids, and blotters (CFSRE 2022c).

Pharmacodynamics

Benzodiazepines target $GABA_A$ receptors which are abundant in the CNS and can be found in the post and presynaptic membranes (EMCDDA 2021a). Generally, the pharmacological effect of benzodiazepines is due to positive allosteric modulation of those $GABA_A$ receptors which have a benzodiazepine binding site (FIMEA 2021). Benzodiazepines bind at the interface of an α and γ subunit on the $GABA_A$ receptor. Positive allosteric modulation of the $GABA_A$ receptor increases the frequency of $GABA_A$ activated channel-opening, thereby increasing channel conductance and leading to enhanced chloride permeability at the post-synaptic neuron. This results in hyperpolarisation and therefore inhibition of neurotransmission. The enhanced effect of GABA results in CNS depressant effects (EMCDDA 2021a; FIMEA 2021). Receptors with a γ-2 subunit are more sensitive to benzodiazepines than receptors with a γ-1 subunit. Overall receptor affinity depends on the α subunit, with the α-1 subunit said to be linked to addictive properties. The specific effects depend on the $GABA_A$ receptor location. Sixteen different $GABA_A$ receptors with seven subunit families are described in humans. The CNS effects observed include anxiolytic, anticonvulsant, muscle relaxant, hypnotic and sedative properties. Interaction with peripheral benzodiazepine receptors (such as, binding to the translocator protein) can result in anxiolytic effects without sedation (EMCDDA 2021a).

In animal studies, triazolo-benzodiazepines (eg, alprazolam, bromazolam) have been shown to have a strong CNS depressant activity, often greater by an order of magnitude than equivalent non-triazolo benzodiazepines (eg, diazepam), with low concomitant toxicity (Hester et al 1971).

Toxicology

Triazolo-benzodiazepines generally have low toxicity, but benzodiazepines have increased toxicological risks when used in combination with other CNS depressants (Hester et al 1971; Tripsit 2022). Combining benzodiazepines with alcohol increases the risk of vomit aspiration while unconscious. Internationally, fatal overdoses often result from the use of benzodiazepines in combination with opioids. Benzodiazepines can potentiate the effects of opioids, and in combination can lead to life threatening respiratory depression (Afzal and Kiyatkin 2019).

11.4 Risks associated with benzodiazepines

Risk to public health

Benzodiazepines and their derivatives are CNS depressants which are especially dangerous when used in combination with opioids, alcohol, cannabis, and other CNS depressants. User reports suggest that benzodiazepine users often switch between different benzodiazepines depending on availability (Reddit 2022e).

Due to their pharmacological action, the ability to drive or operate machinery can be greatly impaired when under the influence of benzodiazepines through changes to reaction times and compromised attention. Sedative effects can include drowsiness and dizziness (EMCDDA 2021a).

Social risks connected to long-term benzodiazepine use include development of lethargy, lack of motivation, depression, and dependence. These can consequently influence an

individuals' education, career, and relationships. Sedative hypnotic medicines are also used to commit drug facilitated crimes (such as robbery or sexual assaults) (EMCDDA 2021a).

Designer benzodiazepine use and abuse is most common in young individuals with a previous history of substance abuse and mental illness (Brunetti et al 2021; WHO 2019).

Risk of death

Drug-related deaths from benzodiazepines usually involve concomitant drug use. Benzodiazepine fatalities are commonly linked with other depressants such as alcohol and opioids (CFSRE 2020; EMCDDA 2021a). The primary presentation in these cases is the loss of consciousness and respiratory depression. Mortality for benzodiazepine users when used alone is relatively low, despite unconsciousness and respiratory depression being common (EMCDDA 2021a).

Risk of death is also related to impairment whilst driving due to compromised attention, memory storage and reaction times, and possible sedative effects which may lead to drowsiness, dizziness, or confusion. These effects may be aggravated by use of alcohol or other CNS depressants (EMCDDA 2021a).

Potential for physical or psychological dependence

Benzodiazepines and their derivatives have a risk of dependence due to being highly addictive substances with severe and potentially life-threatening withdrawal symptoms that may lead to hospitalisation (EMCDDA 2021a).

Cessation of regular use of benzodiazepines can result in withdrawal (both psychological and physical) and is associated with an increased seizure risk.