



# **Critical review report: Bromazolam**

**Expert Committee on Drug Dependence  
Forty-sixth Meeting  
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## Executive summary

Bromazolam (Chemical Abstracts Service [CAS] registry number: 71368-80-4; CAS name: 8-bromo-1-methyl-6-phenyl-4H-S-triazolo[4,3-*a*][1,4]benzodiazepine) is a triazolobenzodiazepine that was originally developed as a candidate medication but was never approved for use. The first documented detection of bromazolam by government authorities was in Sweden in 2016. Since then, the compound has been detected in products or in biological samples in 17 countries: Australia, Austria, Canada, China, Estonia, Finland, Germany, Iceland, Luxembourg, India, Netherlands (Kingdom of the), New Zealand, the Russian Federation, Sweden, Switzerland, the United Kingdom (Wales) and the USA. Bromazolam is not under international control. It is classified in schedule IV under Canadian law, is controlled under psychoactive drug regulations in Germany and the United Kingdom and is subject to enhanced monitoring by federal drug agencies in Finland and the USA in response to recent increases in reported use.

Little information on the pharmacokinetics of bromazolam is available in the scientific literature. Online forum posts suggest that the primary route of administration is oral (tablets, capsules, solutions and “gummies”); however, in one fatal case, it was detected analytically in two syringes next to the body. Informational websites for users list a dosage range according to intoxicating effects: “light” (0.5–1 mg), “common” (1–2 mg) and “strong” (2–4 mg). The time to onset of effects after oral use is estimated to be 15–45 min, and the duration of action is 5–8 h. After ingestion, bromazolam phase-I metabolism is mediated primarily by several isoforms of the CYP450 enzyme system (CYP2B6, CYP2C19, CYP3A4, CYP3A5 and CYP2C9), whereas phase-II metabolism involves the isoenzymes UGT1A4 and UGT2810. Monohydroxylated metabolites include 4-hydroxylated bromazolam and  $\alpha$ -hydroxy bromazolam, with an additional dehydroxylated metabolite,  $\alpha$ -5-dihydroxy-bromazolam. After glucuronidation,  $\alpha$ -hydroxy glucuronide and *N*-glucuronide are the most abundant phase-II metabolites.

The profile of bromazolam *in vitro* and *in vivo* is consistent with the typical benzodiazepine mechanism of action: positive allosteric modulation of GABAA receptor functioning via binding to a site within the GABAA receptor complex. Bromazolam binds non-selectively to  $\alpha$  subunits of the  $\gamma$ -aminobutyric acid type A:benzodiazepine receptor complex, with measurable binding affinity at receptors containing  $\alpha 1$  ( $K_i = 2.8$  nM),  $\alpha 2$  ( $K_i = 0.69$  nM) and  $\alpha 5$  ( $K_i = 0.62$  nM) subunits. Further, in a [ $^3$ H]flunitrazepam displacement binding assay at GABAA ( $\alpha 1\beta 3\gamma 2$ ) receptors, it showed an affinity ( $K_i$ ) of  $54 (\pm 17)$  nM when GABA was present and  $1750 (\pm 440)$  nM when GABA was absent. Bromazolam also enhanced GABA<sub>A</sub> receptor signalling, with an EC<sub>50</sub> of  $7.62 \pm 0.82$  nM and an E<sub>max</sub> of  $88.0 \pm 9.7\%$ . *In vivo*, bromazolam acted similarly to known benzodiazepines (midazolam and diazepam) in a drug discrimination assay in rats, causing full dose-dependent substitution [ED<sub>50</sub> = 0.54 (confidence limits: 0.26 -; 1.12) mg/kg] in rats trained to discriminate midazolam from its vehicle. Its potency in this procedure was similar to that of diazepam.

Bromazolam has been confirmed analytically in post-mortem blood samples in Canada, Finland and the USA. In the USA, it was detected in over 250 toxicological cases between 2019 and 2022, comprising 236 post-mortem and 14 cases of driving impairment. The rate of detection increased from 1% in the first quarter of 2021 to 37.4% in the second quarter of 2023, and co-detection with fentanyl increased to 75% in the USA and 88% in Canada. The causality of bromazolam in deaths and other adverse effects could not be assigned definitively, as

toxicological results often showed use of more than one substance. Bromazolam-containing tablets have appeared on the illicit market labelled as a legal benzodiazepine (e.g. as falsified alprazolam and diazepam products).

The primary source of information about the psychological effects of bromazolam is self-reports in online forum by people who have used the drug. The reasons given for use include intentional seeking of psychoactive effects and self-medication (for e.g. anxiety, sleep or modulation of a stimulant effect). The reported effects of intentional use include “hypnotic” and “sedative” sensations. Other reports describe muscle relaxation and analgesia; some people have reported amnesia. Online forum posts of self-reported use of bromazolam should be considered anecdotal, as there was no analytical confirmation of sole use of bromazolam.

## 1 Substance identification

### A International Nonproprietary Name (INN)

Not assigned

### B Chemical Abstracts Service (CAS) Registry Number

71368-80-4

### C Other chemical names

8-Bromo-1-methyl-6-phenyl-4H-s-triazolo[4,3-*a*][1,4]benzodiazepine  
8-Bromo-1-methyl-6-phenyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine  
DE(chloro)-bromo-alprazolam  
8-Bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (ACI)  
8-Bromo-1-methyl-6-phenyl-4H-s-triazolo[4,3-*a*][1,4]benzodiazepine

#### Canonical SMILES

BrC=1C=CC2=C(C1)C(=NCC3=NN=C(N32)C)C=4C=CC=CC4

#### InChI

InChI=1S/C17H13BrN4/c1-11-20-21-16-10-19-17(12-5-3-2-4-6-12)14-9-13(18)7-8-15(14)22(11)16/h2-9H,10H2,1H3

#### InChI key

KCEIOBKDDQAYCM-UHFFFAOYSA-N

### D Trade names

Bromazolam is sold under its own name.

### E Street names

Bromazolam is sold as tablets or powders under its own name or as XLI-268 (1).

Novel psychoactive substances (NPS) in the benzodiazepines class can be purchased mainly in the drug online market under various street names such as “legal benzodiazepines”, “designer benzodiazepines” and “research chemicals” (2).

**F Physical appearance**

Bromazolam has been described as a white solid (3) or a crystalline solid (4). Bromazolam has been found in orange or green tablets and as a yellow powder (5).

**G WHO review history**

Bromazolam was reviewed critically at the 45th ECDD meeting, when it was recommended that it be kept under surveillance by the WHO Secretariat

## 2 Chemistry

**A Chemical name**

**IUPAC name:**

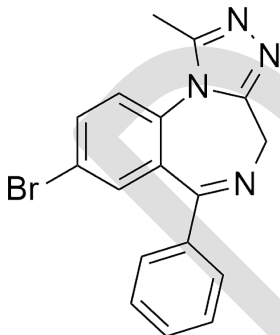
8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

**CA Index name:**

4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-bromo-1-methyl-6-phenyl-(9CI, ACI)

**B Chemical structure**

**Free base:**



**Molecular formula:** C<sub>17</sub>H<sub>13</sub>BrN<sub>4</sub>

**Molecular weight:** 353.22 g/mol

**C Stereoisomers**

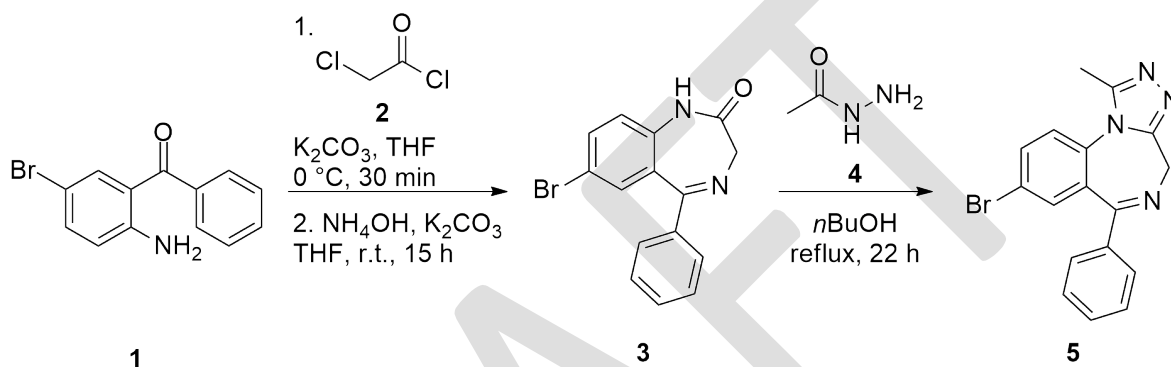
No stereoisomers of bromazolam have been described.

**D Methods and ease of illicit manufacture**

Bromazolam is a triazolo-benzodiazepine and is structurally related to the internationally controlled substance alprazolam, in which the chlorine atom has been replaced with a bromine atom. Bromazolam is also structurally related to

flubromazolam, from which it differs in lack of a fluorine atom on the C2 of the phenyl ring. Bromazolam is also structurally similar to pyrazolam, in which the pyridinyl group has been replaced by a phenyl group (2).

Bromazolam was first synthesized in the 1970s by Hester and von Voigtlander (6). A convenient method of synthesis has been reported in the patent literature (3,7–9). Introduction of a triazole ring into the 1,4 benzodiazepine precursor (3) with hydroxyacetic acid hydrazide (4) gives bromazolam (5) (Hester & von Voigtlander, 1979). The 1,4 benzodiazepine precursor (3) can be prepared by cyclization of 2-amino-5-bromobenzophenone (1) with chloroacetylchloride (2), followed by treatment with ammonia to promote ring closure through imine formation, all in a one-pot procedure (scheme 1) (10).



**Scheme 1. Synthesis of bromazolam.**

No information was available on the routes of synthesis used for the bromazolam products circulating on the market. The synthesis reported in the literature, although simple, requires a chemical synthetic laboratory and qualified personnel.

### **E Chemical properties**

#### *Melting-point*

272.0–275 °C (3,6)

#### *Boiling-point*

No information was found.

#### *Solubility*

Bromazolam is soluble in dimethylformamide (DMF) at a concentration of 30 mg/mL, in dimethyl sulfoxide at a concentration of 20 mg/mL, in ethanol at a concentration of 10 mg/mL, in methanol at a concentration of 1 mg/mL and in a 1:1 mixture of DMF:phosphate-buffered saline (pH 7.2) at a concentration of 0.5 mg/mL (4).

### **F Identification and analysis**

Synthetic bromazolam was characterized by proton and carbon nuclear magnetic resonance ( $^1H$  NMR and  $^{13}C$  NMR), mass spectrometry (MS) and infra-red spectroscopy (IR) (3). Bromazolam is available as a reference material that can be purchased from various commercial suppliers and used in routine analysis for forensic and clinical investigations (4).

Analytical methods for identification of bromazolam in seized sample matrices include IR, <sup>1</sup>H NMR, gas chromatography–MS and liquid chromatography (LC)-MS (11,12).

Bromazolam was analysed in urine with an immunochemical assay (13), in human blood and urine by LC coupled with either high-resolution MS or triple-quadrupole MS (11,12,14).

### 3 Ease of conversion into controlled substances

No information was available in the literature about whether bromazolam can be converted into a controlled substance.

## 4 General pharmacology

### A Routes of administration and dosage

Seizures by law enforcement personnel indicate that bromazolam is typically formulated in tablets or as a powder (5). Oral use (e.g. tablets, capsules or powder formulations in solutions or mixed into food) has been reported in online forums (15–17). Bromazolam-containing chewable candy products (“gummies”) have also been observed (17). While injection is assumed to have been used from the presence of a syringe filled with bromazolam-containing solution next to an overdose victim (5), this route of administration does not appear to be common.

No studies were found of human dosage; however, one informational website has categorized doses according to their intoxicating effects as “light” (0.5–1 mg), “common” (1–2 mg) and “strong” (2–≥ 4 mg). For comparison, the website lists the following doses for diazepam: “light” (2.5–5 mg), “common” (5–15 mg) and “heavy” (15–30 mg) (18). A review of novel psychoactive benzodiazepines gave 1 mg as a “typical recreational dose” (19). The onset of effects is estimated to occur 15–45 min after administration, the duration of action is 5–8 h, and the after-effects last for 1–12 h (20). The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting it.

### B Pharmacokinetics

In the only study available, the pharmacokinetics of bromazolam was studied in pooled human liver S9 fractions, with further analysis of authentic blood and urine samples from two patients (21). The primary metabolic reactions were hydroxylation, glucuronidation and combinations of the two, resulting in eight metabolites. Two prominent monohydroxylated metabolites were formed, tentatively identified as 4-hydroxylated bromazolam and  $\alpha$ -hydroxy bromazolam, as well as one dehydroxylated metabolite,  $\alpha$ -4-dihydroxy-bromazolam. Glucuronidation resulted in  $\alpha$ -hydroxy glucuronide and *N*-glucuronide as the most abundant phase-II metabolites. The parent compound was detected in the urine of both patients, whereas the monohydroxylated metabolites were detected in only one. Recommended screening targets in urine were  $\alpha$ -hydroxy glucuronide and *N*-glucuronide if conjugate cleavage was performed or the parent



compound and the  $\alpha$ -hydroxy metabolite if it was not. Isoenzymes involved in phase I metabolism included CYP2B6, CYP2C19, CYP3A4, CYP3A5 and CYP2C9, whereas phase II metabolism involved the isoenzymes UGT1A4 and UGT2B10.

### **C Pharmacodynamics**

In one study of the in-vitro binding and functional activity of bromazolam at GABA<sub>A</sub> ( $\alpha$ 1 $\beta$ 3 $\gamma$ 2) receptors expressed in human embryonic kidney (HEK) cells (22), bromazolam displaced the tritiated benzodiazepine ligand, [<sup>3</sup>H]flunitrazepam, with an affinity ( $K_i$ ) of 54 ( $\pm$  17) nM when GABA was present in the assay and 1,750 ( $\pm$  440) nM when GABA was absent. Bromazolam also enhanced GABA<sub>A</sub> receptor signaling with an EC<sub>50</sub> of 7.62  $\pm$  0.82 nM and an E<sub>max</sub> of 88.0  $\pm$  9.7%. Diazepam produced similar results in the binding and functional assays.

These results are consistent with those of a single published study on the pharmacodynamics of bromazolam (23). In this study, bromazolam was tested for its binding to  $\alpha$  subunits of the  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) / benzodiazepine receptor complex. Affinity for compounds in HEK cell membranes expressing recombinant GABA<sub>A</sub>/benzodiazepine receptor subtypes ( $\alpha$ 1 $\beta$ 3 $\gamma$ 2,  $\alpha$ 2 $\beta$ 3 $\gamma$ 2,  $\alpha$ 3 $\beta$ 3 $\gamma$ 2,  $\alpha$ 4 $\beta$ 3 $\gamma$ 2,  $\alpha$ 5 $\beta$ 3 $\gamma$ 2 and  $\alpha$ 6 $\beta$ 3 $\gamma$ 2) was measured. Bromazolam was non-selective for the  $\alpha$  subunits, with measurable binding affinity at receptors containing  $\alpha$ 1 ( $K_i$  = 2.8 nM),  $\alpha$ 2 ( $K_i$  = 0.69 nM) and  $\alpha$ 5 ( $K_i$  = 0.62 nM) subunits.

In summary, the profile of bromazolam in these assays is consistent with the typical benzodiazepine mechanism of action: positive allosteric modulation of GABA<sub>A</sub> receptor functioning via binding to a site within the GABA<sub>A</sub> receptor complex (presumably, the benzodiazepine receptor). These in-vitro results are also consistent with the finding that bromazolam acted similarly to known benzodiazepines in vivo in a drug discrimination assay in rats (see section 8A).

## **5 Toxicology**

No studies on the preclinical toxicology of bromazolam were available.

## **6 Adverse reactions in humans**

The presence of measurable concentrations of bromazolam in post-mortem blood samples has been reported in Canada, Finland, and the USA (5,24,25); however, other drugs were also detected in many of the cases, and the extent to which bromazolam contributed to the deaths was not specified. In Germany, two patients with confirmed bromazolam use were found unconscious or minimally responsive (21). Bromazolam has also been reported in blood samples from impaired drivers in the USA (24,26). The reports do not provide details of the physical or behavioural effects of bromazolam use.

People who used bromazolam described its effects as “hypnotic” and “sedative” (15) and referred to its “muscle relaxing” and “pain relieving” properties (17). Other reported effects

include euphoria, increased confidence and empathy (27). Some people who used bromazolam reported amnesia, while others stated that amnesia was less common with bromazolam than with other benzodiazepines (28). Posts on online forums describing self-reported experience of use of bromazolam should be considered anecdotal, as no analytical confirmation of sole use was obtained.

## **7 Dependence potential**

### **A Studies in experimental animals**

No information was found.

### **B Studies in humans**

No information was found.

## **8 Abuse potential**

### **A Studies in experimental animals**

The abuse potential of bromazolam at 0.1–3 mg/kg was evaluated in male rats trained to discriminate the benzodiazepine midazolam in a standard two-lever drug discrimination study (29). Like midazolam and diazepam, bromazolam resulted in full dose-dependent substitution for the 0.3 mg/kg training dose of midazolam, with an ED<sub>50</sub> (± 95% confidence interval [CI]) of 0.54 (0.26 ; 1.12) mg/kg. In comparison, the ED<sub>50</sub> (± 95% CI) was 0.09 (0.06; 0.14) mg/kg for midazolam and 0.66 (0.40 ; 1.12) mg/kg for diazepam. At the dose range tested, bromazolam did not affect response rates. The midazolam-like effects of bromazolam at 3 mg/kg were significantly attenuated by pre-administration of the benzodiazepine receptor antagonist flumazenil at 1 mg/kg. Morphine, tested as a negative control, did not produce a response on the midazolam-associated lever at doses that suppressed the overall response rate.

### **B Studies in humans**

No information was found.

## **9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use**

There is no known therapeutic use for bromazolam.

## **10 Listing on the WHO Model List of Essential Medicines**

Bromazolam is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th WHO Model List of Essential Medicines for Children.

## **11 Marketing authorizations (as a medicinal product)**

Bromazolam has no known marketing authorizations.

## **12 Industrial use**

Bromazolam has no known industrial use.

## **13 Non-medical use, abuse and dependence**

Bromazolam appeared on the European recreational drug market in 2016 in Sweden and in 2019 in the USA (24,30). In addition to intentional use of bromazolam for its benzodiazepine-like psychoactive effects (see section 6), some people have reported self-medication with bromazolam for indications such as anxiety, to aid sleep and to reduce stimulation caused by another drug such as methamphetamine (17,31). Bromazolam has been detected in formulations that contain combinations of benzodiazepines in a single preparation (e.g. tablet, capsule, powder), including preparations falsely labelled as legal prescription drugs (e.g. alprazolam, diazepam, zolpidem) (27,32). The compound has been used in combination with other drugs, including fentanyl, other opioids and methamphetamine (17,24,25,33).

The prevalence of chronic use of and dependence on bromazolam has not been reported. On online forums, several people have reported difficulty in withdrawing from bromazolam after chronic use, and at least one case of withdrawal-associated psychosis and hallucinations was reported after bromazolam was taken repeatedly in combination with phenibut (31,34,35). These reports should be considered anecdotal, as no analytical confirmation of chronic use of bromazolam (or its sole use) was reported.

## **14 Nature and magnitude of public health problems related to misuse, abuse and dependence**

Since 2020, bromazolam has been confirmed analytically in post-mortem samples as well as in samples collected from impaired drivers in Canada, Europe and the USA. It has also been detected in product samples submitted to Welsh laboratories. In Finland, bromazolam was found in a post-mortem blood sample with other benzodiazepines (5). In Germany, bromazolam was present in biological samples from two patients, one of whom was found unconscious and one of whom was “confused and slow to respond” (21). In the USA as of June 2022, bromazolam was confirmed analytically in more than 250 cases, comprising 236 detections in post-mortem blood and 14 in biological samples from impaired drivers (24). While no additional information was available on the clinical course of the cases or on any other drugs present, the average concentration of bromazolam in post-mortem blood samples was 65 ng/mL ( $\pm$  79 standard deviation). In the samples from impaired drivers, the average blood concentration was 61 ng/mL ( $\pm$  47 standard deviation) (24). Between October 2020 and March 2023, 11 cases (seven post-mortem) of analytically confirmed bromazolam were reported by the USA to the Early Warning System Tox-Portal (36).

Bromazolam was designated as contributory (medium) on the causality scale used in the system in all but one case (for which no determination was made). Bromazolam was the only substance detected in half of the cases. In 2022, bromazolam was the sole (or one of only a few) substance(s) detected in over 200 samples analysed by Welsh authorities (27). A substantial number of products were falsely labelled as an approved prescription benzodiazepine (e.g., diazepam, alprazolam, zolpidem).

Bromazolam has also been detected in Scottish prisons (37). Of the 475 samples containing novel benzodiazepines seized between February 2019 and January 2023, bromazolam alone was identified in 38 samples and bromazolam in combination with another novel benzodiazepine was found in an additional 5 samples. Samples included tablets and powder in the early part of the sampling period; however, visitation restriction during the Covid-19 pandemic was associated with increased formulation as infused paper/cards that were sent via the mail.

## 15 Licit production, consumption and international trade

No information was found.

## 16 Illicit manufacture and traffic and related information

The first documented seizure of bromazolam in Europe was in Sweden in 2016 (38), while reports first appeared in the USA in 2019 (24). In the USA, its detection increased from 1% of samples in the first quarter of 2021 to 13% in the second quarter of 2022 and to 37.4% in the second quarter of 2023 (38,39). Samples containing bromazolam submitted to an anonymous testing site (from 2020 to the present) were received from Austria (n=1), China and other Asian countries (n=19), Germany (n=1), India (n=1), Switzerland (n=6), the United Kingdom (n=1) and the USA (n=77) (40). As submission of samples was voluntary, the distribution of sites of origin may not represent the global distribution or trafficking of bromazolam. Other countries in which bromazolam has been detected include Australia (32), Canada (25), Estonia<sup>1</sup>, Honduras<sup>1</sup>, Finland (41), Iceland<sup>1</sup>, Luxembourg<sup>1</sup>, Netherlands (Kingdom of the),<sup>1</sup> New Zealand,<sup>1</sup> the Russian Federation,<sup>1</sup> Sweden (38) and Wales (27).

IONICS reported 118 seizures of bromazolam between 2020 and August 2023, with an increase in incidents beginning in 2022.<sup>1</sup> In the 85 cases where transnational routing information was reported, 60% occurred at international postal facilities and 40%, at airport/carrier/cargo sites. More than half of these seized samples (n=44) originated in the Netherlands. Further, interest in the compound has resulted in substantially increased mention in discussion forums starting in 2021 and several countries (Australia, Canada, and the USA) issued public alerts or notices following increased detection of bromazolam.

Detection of bromazolam with fentanyl has increased dramatically: 75% of bromazolam-positive samples in the USA also contained fentanyl in the months before a trend report was issued in June 2022 (24). Similarly, fentanyl was detected in 88% of 41 post-mortem

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<sup>1</sup> Data provided for this review.

bromazolam-positive samples collected between July 2020 and December 2021 in Canada (25). In these cases, bromazolam was the only benzodiazepine detected in 41% (n=17) of the cases.

## 17 Current international controls and their impact

Bromazolam is not currently under international control.

## 18 Current and past national controls

Bromazolam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany and the United Kingdom. Recently, the Finnish Medicines Agency listed bromazolam as a new substance to be subjected to formal surveillance (41). To prepare a response to WHO queries after last year's critical review of bromazolam, the US Food and Drug Administration published a "Request for comments" concerning the abuse potential of this drug (42). Bromazolam does not appear to be controlled under national regulations in other countries.

## 19 Other medical and scientific matters relevant for a recommendation on scheduling of the substance

Novel psychoactive substances were found in 65 chocolate samples submitted to the National Anti-Drug Laboratory of China for analysis (43). Of these, two contained bromazolam. Information on the source of the chocolate samples or on prevalence was not provided. The presence of bromazolam and other novel psychoactive substances in food may increase the risk of unintentional exposure (including paediatric).

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