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Critical Review Report:

3,4-Methylenedioxy-*N*-benzylcathinone

(Benzylone, BMDP)

Expert Committee on Drug Dependence

Forty-fourth Meeting

Geneva, 11-15 October 2021

Contents

Executive Summary

3,4-Methylenedioxy-*N*-benzylcathinone (benzylone; BMDP; IUPAC name: 1-(2*H*-1,3-benzodioxol-5-yl)-2-(benzylamino)propan-1-one) is a ring-substituted synthetic cathinone. Benzylone is most likely to appear on the streets in the form of a racemate.

Benzylone has not been previously pre-reviewed or critically reviewed by the WHO.

There is no specific information available about the routes of synthesis employed for the benzylone products circulating on the drug market but straightforward methods for its preparation exist without requiring access to precursors that are controlled internationally. It is technically feasible to convert benzylone into 3,4-methylenedioxyamphetamine (MDA, tenamfetamine; IUPAC name: 1-(2*H*-1,3-benzodioxol-5-yl)propan-2-amine) which is listed in Schedule I of the UN Convention on Psychotropic Substances 1971.

The number of systematic studies available at this time is limited but in vitro studies suggest that benzylone is able to inhibit the uptake of dopamine and norepinephrine albeit at lower potency than cocaine, methamphetamine, and methcathinone. Whether benzylone acts as a substrate at these transporters is unknown. In terms of potency, the ability to inhibit the uptake of serotonin appears to be negligible. The results from locomotor activity studies indicated that significant effects were only modest increases or decreases (at random) suggesting that these effects were not dose-dependent across the tested doses. Based on the currently available information it appears that benzylone might not be a significant psychomotor stimulant. Information obtained from Internet forums on the effects of benzylone appear to be very limited. Benzylone was reported to be inactive by some forum members. One report suggested this substance to be active following nasal insufflation whereas another report suggested the effects to be considered mild following oral administrations of high doses. However, the assessment of such reports is challenging not least because people who are using these substances might not have been able to confirm the actual substance or the amount used.

Information on acute or chronic preclinical toxicology studies, adverse reactions in humans, and dependence potential in humans or animals involving benzylone could not be identified.

In rats, benzylone failed to fully substitute for the discriminative stimulus effects of MDMA. When methamphetamine was used as the training drug there was a tendency for benzylone to be perceived as methamphetamine-like, but this trend was not significant and only occurred at doses that significantly impaired responding. These currently available findings suggest that benzylone is unlikely to display abuse liability in contrast to other synthetic cathinones under international control.

Information about therapeutic use could not be identified and benzylone is also not listed in the WHO Model Lists of Essential Medicines. Benzylone is not known to have any marketing authorizations and Information about any agricultural, industrial or cosmetic uses could not be

identified. Benzylone is used as reference material and for scientific research. Some Internet retailers advertise it for sale as a 'research chemical'.

Epidemiological evidence concerning the use of benzylone could not be identified and its use is likely to be limited to recreational substance users rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other substances and users may be unaware of the exact dose or compound being ingested (by whatever route).

Epidemiological data on harms associated with benzylone could not be identified. Six postmortem cases were identified that involved poly-substance use where benzylone and other substances have been detected. Information available from the EMCDDA and drug testing services in Switzerland and the USA revealed the detection of benzylone in some products acquired as/sold as MDMA and ketamine. In one case, benzylone was detected in an e-liquid used for vaping together with six synthetic cannabinoid receptor agonists. These findings suggest the possibility that some people using such products might get exposed to benzylone unintentionally.

The detection of benzylone was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) in December 2010. Also in 2010, the United Nations Office on Drugs and Crime (UNODC) received notifications from four UN Member States. As of 15 July 2021, a total of 17 countries of the EU Early Warning System Network and the United Kingdom have reported physical detections of benzylone to the EMCDDA.

Since it was formally notified, the EMCDDA has received reports of 173 seizures of benzylone. Between 2011 and 2018 a total of 33 seizures were reported, 89 in 2019, and 51 in 2020 (data for 2020 not final). The majority of seizures occurred in 2019 (52%). In seizures reported to the EMCDDA, benzylone was mostly found as a powder (86 % of all cases). Much less frequently reported were tablets (9% of cases) and herbal material (3%).

Overall, approximately 25 kg of powders containing benzylone were reported to the EMCDDA. Between 2011 and 2018 approximately 2.7 kg was reported, 21.8 kg in 2019, and just under 0.5 kg in 2020 (data for 2020 are not final). Most of the powder seized was in 2019 (87%). Finally, the EMCDDA has received reports of approximately 1,657 tablets containing benzylone, all of which were seized in 2020. In one collected sample, benzylone was found in a blue tablet also containing eutylone, which had been purchased as MDMA. In seizures of powders, benzylone was found in bags labeled as RTI-11, 3-MMC, 3F-phenmetrazine, 5-DBFPV and diclazepam.

Since 2010, UNODC's Early Warning Advisory received a limited number of notifications from UN Member States though the number rose to 19 countries in 2019 and then dropped back to two in 2020. The U.S. National Forensic Laboratory Information System (NFLIS) reported the detection of benzylone for the first time in 2019. The number of reports involving benzylone represented 0.17, 0.15, and 0.13% of all reports captured under the phenethylamine classification (2019–midyear 2020). When included in the list of top 10 most frequently reported synthetic cathinones, 8% of NFLIS-Drug reports were represented by benzylone. Between Jan 2020–March 2021, a total number of 468 benzylone detections were reported by NFLIS, which represented 4.34% of the top five

selected synthetic cathinones. This suggests that the number of drug reports involving benzylone was comparatively low.

Benzylone is not controlled under the 1961, 1971 or 1988 United Nations Conventions but is controlled in some UN Member States.

1. Substance identification

A. International Nonproprietary Name (INN)

Information could not be identified

B. Chemical Abstract Service (CAS) Registry Number

1387636-19-2 (base)
1823274-68-5 (HCl salt)

C. Other Chemical Names

3,4-Methylenedioxy-*N*-benzylcathinone
N-Benzyl-3,4-methylenedioxycathinone
Methylenedioxybenzedrone [sic]
1-(3,4-Methylenedioxyphenyl)-2-(benzylamino)-1-propanone
1-(1,3-Benzodioxol-5-yl)-2-(benzylamino)propan-1-one
1-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-1-propanone
2-Benzylamino-1-(3,4-methylenedioxyphenyl)propan-1-one
1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one
N-Benzylmethylone [sic]
N-Benzylnormethylone

D. Trade Names

Information could not be identified

E. Street Names

Chemical names mentioned above may be encountered as street names. Other code names include BMDP, benzylone, bk-MDBZ, and 3,4-MDBC.

F. Physical Appearance

The hydrochloride salt of benzylone has been described as crystalline solid (Cayman Chemical 2016). In its pure form, benzylone hydrochloride is expected to be odorless and white similar to many other ring-substituted synthetic cathinones. Benzylone hydrochloride has also been described as a white powder (SWDRUG 2019).

G. WHO Review History

Benzylone has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

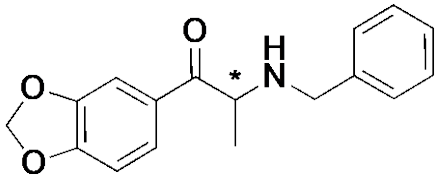
2. Chemistry

A. Chemical Name

IUPAC Name: 1-(2*H*-1,3-Benzodioxol-5-yl)-2-(benzylamino)propan-1-one
CA Index Name: 1-(1,3-Benzodioxol-5-yl)-2-[(phenylmethyl)amino]-1-propanone

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral center

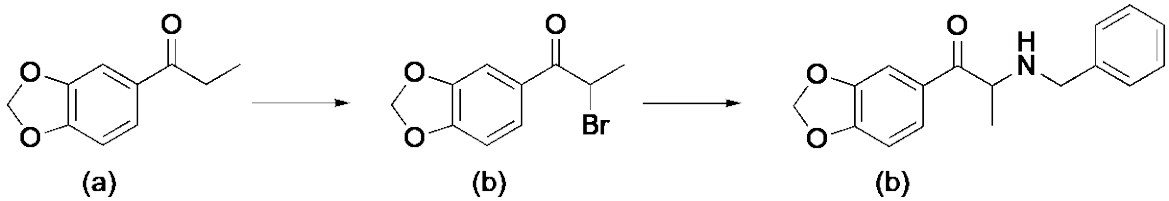
Molecular Formula: $C_{17}H_{17}NO_3$
Molecular Weight: 283.33 g/mol

C. Stereoisomers

The presence of a chiral center at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-benzylone and (*R*)-benzylone. However, on the streets benzylone is most likely available as the racemic mixture though the appearance of individual stereoisomers cannot be excluded.

D. *Methods and Ease of Illicit Manufacturing*

Information on the specific routes of synthesis employed for benzylone products circulating on the market could not be identified. However, the chemistry to produce ring-substituted synthetic cathinones is well established and straightforward. One common approach could involve the bromination of the 3,4-methylenedioxypropiophenone precursor (a) to yield the alpha-brominated intermediate (b). This is then followed by amination with phenylmethanamine to give benzylone (c) similar to procedures employed for related cathinones under investigation by pharmaceutical companies already in the 1960s (e.g. Köppe, Ludwig and Zeile 1967).



E. Chemical Properties

Melting point
Information could not be identified

Boiling point
Information could not be identified

Solubility
Benzylone hydrochloride was reported to be soluble in ethanol (~3 mg/mL) and DMSO and DMF (5 mg/mL) but only sparingly soluble in aqueous buffers. If dissolved in DMF first, the solubility of benzylone hydrochloride was given as approximately 0.13 mg/mL in a 1:7 solution of DMF:phosphate buffered saline (pH 7.2) (Cayman Chemical 2016). A seized sample of benzylone hydrochloride was described as being partially soluble in water and dichloromethane and soluble in methanol (Slovenian National Forensic Laboratory 2017).

F. Identification and Analysis

Identification, especially when available in larger quantities than normally encountered in forensic toxicological work, is straightforward. Analytical data disseminated in scientific publications include those recorded from photodiode array detection (Nagashima et al. 2011); electron ionization mass spectrometry (Elie, Elie and Baron 2013; Fornal, Stachniuk and Wojtyla 2013; Nagashima et al. 2011); electrospray ionization single and tandem mass spectrometry (Adamowicz and Tokarczyk 2016; 2019; Ameline et al. 2019a; Fornal 2013; 2014; Fornal, Stachniuk and Wojtyla 2013; Lau, Concheiro and Cooper 2020; Yap and Drummer 2016; Zuba and Adamowicz 2018); direct analysis in real time (DART) ionization mass spectrometry (Fowble, Shepard and Musah 2018; Musah et al. 2014); nuclear magnetic resonance spectroscopy et al. 2011); Fourier transform infrared spectroscopy (Fornal, Stachniuk and Wojtyla 2013) and gas chromatography (Sisco, Burns and Moorthy 2021). The analysis of biological samples requires the use of sensitive analytical methods, e.g. gas- or liquid chromatography coupled to (tandem) mass spectrometry approaches (high and low resolution). Analytical information available in the public domain includes chromatographic, mass spectral and spectroscopic data (Cayman Chemical 2012; Krotulski, Fogarty and Logan 2019; Slovenian National Forensic Laboratory 2017; SWDRUG 2019). Certified reference material is commercially available for analytical method development and validation. Results from presumptive color tests have also been disseminated in the public domain (DrugsData.org 2021a; b; c).

3. Ease of Convertibility Into Controlled Substances

Specific information on the conversion of benzylone to substances under international control could not be identified. However, subjecting benzylone to conditions resulting in *N*-debenzylation and reduction of the ketone group could give

access to 3,4-methylenedioxyamphetamine (MDA, tenamfetamine; IUPAC name: 1-(2*H*-1,3-benzodioxol-5-yl)propan-2-amine) which is listed in Schedule I of the UN Convention on Psychotropic Substances 1971.

4. General Pharmacology

A. Routes of administration and dosage

Data from clinical studies on benzylone could not be identified and information obtained from Internet discussion forums appears to be limited as far as dosages and routes of administrations were concerned. There have been suggestions that benzylone might be inactive (Reddit 2020a; b; c; 2021). However, in one case, a 70–100 mg nasal administration was suggested to induce a 'decent rush' (Reddit 2020c) whereas another report suggested effects to be 'very light and short lived'. The route of administration was not described but the explored dosage was 500 mg commencing with 200 mg and followed by two 150 mg doses with no 'increase in results' (Bluelight 2018). Another report describing several trials involving oral administrations of 550 mg and doses above 1.4 g suggested some mild effects including 'wiggle eyes, chills, stretching, sweaty palms, mild grind' and although some comparisons were made with methylone (3,4-methylenedioxymethcathinone; 1-(2*H*-1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one), the psychoactive effects associated with these doses were not considered favorable (Bluelight 2019). The assessment of such reports is challenging not least because people who are using these substances might not be able to confirm the actual substance or the amount used. Given the difficulties of collecting accurate self-reported data, these reports should be interpreted with caution.

B. Pharmacokinetics

Data obtained from clinical studies could not be identified. One self-report following oral administration of 1 g what was believed to be benzylone suggested a short duration of 2 hours giving a "methylone rush" (Bluelight 2019) though other reports suggested benzylone to be inactive (see above). Exposure of benzylone to pooled human liver microsomes led to the detection of the three metabolites 2-(benzylamino)-1-(3,4-dihydroxyphenyl)propan-1-one, 1-(2*H*-1,3-benzodioxol-5-yl)-2-(benzylamino)propan-1-ol, and 2-amino-1-(2*H*-1,3-benzodioxol-5-yl)propan-1-one, therefore reflecting desmethylenation, reduction of the keto group, and *N*-debenzylation. It is conceivable that the *N*-debenzylated metabolite (3,4-methylenedioxycathinone, bk-MDA) is biologically active (Dal Cason, Young and Glennon 1997; Luethi et al. 2019; Rickli et al. 2015; Smith, Blough and Banks 2017) though it is currently unknown whether the concentrations - if formed in vivo -would be sufficient to induce bioactive effects.

C. Pharmacodynamics

Results from in vitro assays involving binding affinity to monoamine transporters and inhibition of uptake are summarized in Table 1 (Janowsky 2019). The binding affinities determined for benzylone in HEK293 cells expressing human recombinant monoamine transporters were found to be very low with K_i values close to 2.5 µM at the dopamine (DAT) and norepinephrine (NET) transporter and the binding affinity at the serotonin transporter (SERT) was even lower with K_i = 11.5 µM (Table 1). Cocaine, methamphetamine and methcathinone were tested for comparison. At DAT, the binding affinity of cocaine was 3-times higher whereas methamphetamine and methcathinone showed a 2-fold and 2.5-fold drop in potency. At SERT, the binding affinity of cocaine was 20-times higher whereas methamphetamine and methcathinone showed a 15-fold and 25-fold drop in potency. At NET, the binding affinity of cocaine was somewhat comparable whereas methamphetamine was equipotent and methcathinone showed a 2-fold drop in potency. Uptake inhibition of radiolabeled neurotransmitters was also determined (Table 1) and it was found that benzylone showed submicromolar K_i values at DAT (K_i = 764 nM) and NET (K_i = 469 nM). At DAT and NET, cocaine, methamphetamine and methcathinone inhibited uptake at higher potencies. Cocaine was also more potent than benzylone at SERT and methamphetamine and methcathinone were significantly potent than benzylone (Table 1).

Table 1. Binding data and effects of benzylone on uptake using HEK-hDAT, HEK-hSERT and HEK-hNET cells (modified from Janowsky 2019)

HEK-hDAT	Benzylone	Cocaine	Methamphetamine	Methcathinone
[^{125}I]RTI-55 binding; IC_{50} (nM)	2,300	–	–	–
[^{125}I]RTI-55 binding; K_i (nM)	2,240	710	4,610	5,500
[^{3}H]DA uptake; IC_{50} (nM)	764	376	61.7	186
HEK-hSERT	**Benzylone**	**Cocaine**	**Methamphetamine**	**Methcathinone**
[^{125}I]RTI-55 binding; IC_{50} (nM)	11,900	–	–	–
[^{125}I]RTI-55 binding; K_i (nM)	11,500	580	174,000	285,000
[^{3}H]5-HT uptake; IC_{50} (nM)	7,500	265	9,200	45,000
HEK-hNET	**Benzylone**	**Cocaine**	**Methamphetamine**	**Methcathinone**
[^{125}I]RTI-55 binding; IC_{50} (nM)	2,480	–	–	–
[^{125}I]RTI-55 binding; K_i (nM)	2,460	1,960	2,580	5,560
[^{3}H]NE uptake; IC_{50} (nM)	469	301	24.3	36.5

DA: dopamine; 5-HT: serotonin; NE: norepinephrine.

In comparison, uptake experiments involving benzylone have also been carried out as part of the U.S. National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH-PDSP) (Iversen et al. 2013). At SERT, no inhibition was observed below 10 µM whereas the K_i values at NET and DAT were recorded at 1,629 nM and 637 nM. In

comparison, uptake inhibition values for cocaine were reported as follows under the experimental conditions: NET (K_i = 1,275 nM); DAT (K_i = 249 nM); SERT (K_i = 818 nM) (Iversen et al. 2013).

Benzylone was also screened against 49 targets as part of the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH-PDSP) and the results of binding affinities below K_i = 10 µM are summarized in Table 2 (Iversen et al. 2013). Mephedrone (4-methylmethcathinone; 2-(methylamino)-1-(4-methylphenyl)propan-1-one) results have been included for comparison. For benzylone, the only submicromolar K_i values were determined for sigma$_1$ receptors and NET (980 nM) and DAT (40 nM). In this study, the radioligands used for NET and DAT binding were [^{3}H]nisoxetine and [^{3}H]WIN-35428 ([^{3}H]citalopram for SERT) whereas [^{125}I]RTI-55 was employed for all three transporters (see above, Table 1) (Janowsky 2019).

Table 2. Binding affinities to receptor and transporters (K_i, nM) (National Institute of Mental Health's Psychoactive Drug Screening Program) (Iversen, Gibbons, Treble, Setola, Huang and Roth 2013) [a]

Compound	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{2B}$	α_{2B}	α_{2C}	D_4	σ_1	σ_2	NET	DAT	DOR	KOR
Benzylone	1,140	–	1,660	3,775	3,775	1,969	155	2,841	980	40	4,300	3,030
Mephedrone	–	1,630	739	–	4,476	–	–	–	–	–	–	–

[a] Results only for K_i < 10 µM. NET: norepinephrine transporter; DAT: dopamine transporter; DOR: delta opioid receptor; KOR: kappa opioid receptor.

5. Toxicology

Information on acute or chronic preclinical toxicology studies involving benzylone could not be identified.

6. Adverse Reactions in Humans

Information about benzylone-induced adverse reactions in humans could not be identified. Correspondence received by the ECDD secretariat from the U.S. Office of National Drug Control Policy (ONDCP) claimed that " at least 9 post mortem overdose event has involved BMDP, specifically, in the United States since 2012" (citing "private correspondence between ONDCP and key partners in state public health departments, March 15–22, 2021") but any further data were not available. As summarized in Table 3, the detection of benzylone together with other substances has been reported in postmortem cases involving poly-substance use. The involvement of benzylone as the causative agent can be considered unlikely. The UNODC Early Warning Advisory - Tox-Portal database lists one case from Australia featuring the detection of etizolam and benzylone in femoral blood obtained from a postmortem case. The relative/probable contribution for both substances was listed as "contributory (medium)" (UNODC 2021a).

One country of the EU Early Warning System Network reported one serious adverse event to the EMCDDA in which exposure to benzylone was analytically confirmed from a biological sample involving a fatal case that occurred in 2019 but further details were not available (EMCDDA 2021).

Table 3. Detections of benzylone and other substances in postmortem cases (Krotulski, pers. commun.; Krotulski, Papsun and Logan 2020; Krotulski et al. 2020) suggesting poly-substance use.

Case no.	Date submitted	Demographics [a]	Case history	Findings [b]
1	June 2019	50 / M / FL	Suspected overdose; history of intravenous drug use; found deceased faced down on floor of bathroom; unknown powder found on floor near decedent	Benzylone, etizolam, morphine, naloxone, hydrocodone, THC
2	August 2019	22 / M / PA	Not available	Benzylone, methamphetamine, xylazine, 4-ANPP, quinine, fentanyl, etizolam
3	August 2019	24 / M / NY	Suspected overdose; history of "heroin" overdose	Benzylone, fentanyl, morphine, naloxone, THC
4	August 2020	28 / M / FL	Suspected overdose; history of cocaine and "heroin" use	Benzylone, eutylone, cocaine, lidocaine, fentanyl, etizolam, aripiprazole, ethanol
5	Not available	Not available	Not available	Benzylone, eutylone

[a] Order of age, gender, location. M: male; FL: Florida; PA: Pennsylvania

[b] 4-ANPP: 4-anilino-*N*-phenethyl piperidine (*N*-phenyl-1-(2-phenylethyl)piperidin-4-amine)

7. Dependence Potential

A. Animal Studies

Information could not be identified.

B. Human Studies

Information could not be identified.

8. Abuse Potential

A. Animal Studies

Time-course (6 h) locomotor activity tests in mice were undertaken to compare the effects of benzylone and methamphetamine (Table 4) (Gatch 2020c). The results from this investigation suggested that benzylone had little effect even at high doses. Modest stimulant effects at 50 mg/kg occurred within 10 minutes following injection and lasted 30 min. Depressant effects were also noted following administration of 2.5 and 100 mg/kg. Significant effects were modest increases or decreases (at random) suggesting that these effects were not dose-dependent across the tested doses. The benzylone ED_{50} value (117.07 µmol/kg) was determined based upon a linear regression against log10 doses from 25–50 mg/kg benzylone.

Table 4. Locomotor activity test results [a] (Gatch 2020c)

Compound	ED_{50} values [mg/kg (µmol/kg)]	95% Confidence Interval [mg/kg (µmol/kg)]
(*S*)-(+)-Methamphetamine HCl	0.62 (3.34)	0.19–2.06 (1.02–11.09)
Benzylone HCl	37.44 (117.07)	12.99–107.88 (40.60–337.33)

[a] Separate groups of 8 non-habituated male Swiss-Webster mice (Hsd:ND4, aged 2–3 months) were used. Benzylone HCl was injected via the intraperitoneal route at concentrations of 1, 2.5, 5, 10, 25, 50 or 100 mg/kg. Horizontal activity (interruption of photocell beams) was measured for 6 h within 10-min periods. Testing was conducted with one mouse per activity chamber. The period 0–30 min was selected for analysis of dose-response data (maximal effects for benzylone). Stimulant effects occurred within 10 minutes following injection and lasted 30 minutes.

Drug discrimination studies:

When testing benzylone for substitution for the discriminative stimulus effects of MDMA, no significant substitution occurred. Using a two-lever discrimination task (10 male Sprague-Daley rats; MDMA training dose 1.5 mg/kg) under a fixed-ratio (FR10) schedule of reinforcement, benzylone (test doses ranging from 5 to 50 mg/kg) produced increases in MDMA lever responding with a maximum MDMA-appropriate responding of 33 ± 33% at 50 mg/kg and the response rate of benzylone decreased to 34% of vehicle control following 50 mg/kg administration (full substitution requires ≥80% MDMA-appropriate responding). Unusual effects following any dose of benzylone were not observed (Gatch 2020a).

Tests for substitution of methamphetamine (training dose 1 mg/kg) showed that benzylone (test doses ranging from 10 to 50 mg/kg) produced increases in methamphetamine-lever responding with a maximum methamphetamine-appropriate responding of 67 ± 20% at 50 mg/kg. Response rate of benzylone increased to 139% of vehicle control following 10 mg/kg and decreased to 26% of vehicle control following 50 mg/kg benzylone. A decreased muscle tone was observed in 8 of 10 rats following 50 mg/kg and 5/10 rats failed to complete the

first fixed ratio following 50 mg/kg benzylone (Gatch 2020b). These findings suggests that there was a tendency for benzylone to be perceived as methamphetamine-like, but this trend was not significant and only occurred at doses that significantly impaired responding. In other words, effects occurred in parallel with significant decreases in response rates. Overall, these data suggest that benzylone is unlikely to display abuse liability.

B. Human Studies

Information could not be identified.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Information about therapeutic use could not be identified.

10. Listing on the WHO Model List of Essential Medicines

Benzylone is not listed on the 21st WHO Essential Medicines List (EML) or the 7th WHO Essential Medicines List for Children (EMLc) updated in June 2019.

11. Marketing Authorizations (as a Medicinal Product)

Information on marketing authorization of benzylone as a medicinal product could not be identified.

12. Industrial Use

Information about recorded industrial use could not be identified.

13. Non-Medical Use, Abuse and Dependence

Epidemiological evidence concerning the use of benzylone could not be identified and its use is likely to be limited to recreational substance users rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and people using this substance may be unaware of the exact dose or compound being ingested (by whatever route). Benzylone is also available in its own right and is advertised for sale by some Internet retailers. Currently information available (Sections 4 and 8) suggest that benzylone is unlikely to show abuse liability and that it might not show any significant psychostimulant properties comparable to other synthetic cathinones under international control.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Epidemiological data on harms associated with benzylone could not be identified. The information available on six postmortem cases (Section 6) involved poly-substance use and included the detection of benzylone among other substances. Information available from

the EMCDDA and drug testing services in Switzerland and the USA suggest the detection of benzylone in products acquired as/sold as MDMA and ketamine (DrugsData.org 2021a; b; c; EMCDDA 2021), which suggest that people using certain types of recreational drugs might get exposed to benzylone unintentionally. EMCDDA also reported that an e-liquid used for vaping found on a poisoned patient was determined to contain the synthetic cannabinoid receptor agonist (SCRA) MDMB-4en-PINACA (methyl 3,3-dimethyl-2-{[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino}butanoate) along with five other SCRAs and benzylone. The case occurred in July 2020 (De Morais et al. 2020).

15. Licit Production, Consumption and International Trade

Benzylone is used as reference material for scientific research. It is not known to have any agricultural, industrial or cosmetic uses. Some Internet retailers advertise it for sale as a 'research chemical'.

16. Illicit Manufacture and Traffic and Related Information

The detection of benzylone was reported first to the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) in December 2010 based on a sample collected in October 2010 (EMCDDA 2011; 2021). As of 15 July 2021, a total of 17 countries of the EU Early Warning System Network and the United Kingdom have reported physical detections of benzylone to the EMCDDA (EMCDDA 2021).

Since it was formally notified, the EMCDDA has received reports of 173 seizures of benzylone. Between 2011 and 2018 a total of 33 seizures were reported, 89 in 2019, and 51 in 2020 (data for 2020 not final). The majority of seizures occurred in 2019 (52%) (EMCDDA 2021).

In seizures reported to the EMCDDA, benzylone was mostly found as a powder (86 % of all cases). Much less frequently reported were tablets (9% of cases) and herbal material (3%) (EMCDDA 2021).

Overall, approximately 25 kg of powders containing benzylone were reported to the EMCDDA. Between 2011 and 2018 approximately 2.7 kg was reported, 21.8 kg in 2019, and just under 0.5 kg in 2020 (data for 2020 is not final). Most of the powder seized was in 2019 (87%) (EMCDDA 2021).

Finally, the EMCDDA has received reports of approximately 1,657 tablets containing benzylone, all of which were seized in 2020. In one collected sample, benzylone was found in a blue tablet also containing eutylone, which had been purchased as MDMA. In seizures of powders, benzylone was found in bags labeled as RTI-11, 3-MMC, 3F-phenmetrazine, 5-DBFPV and diclazepam (EMCDDA 2021).

The number of countries that reported benzylone detections to the United Nations Office on Drugs and Crime (UNODC) varied in the period since 2010: 2010 (4); 2011 (4); 2012 (4);

2013 (2); 2014 (2); 2015 (0); 2016 (0); 2017 (1); 2018 (8); 2019 (19); 2020 (2); 2021 (2) (UNODC 2021c). In 2019, results reported from the NPS Monitoring Programme of China (June 2018–June 2019) showed that benzylone was featured in 17 identifications in this time period. Eutylone was counted 15 times and *N*-ethylnorpentylone (1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) was identified 58 times. From a list of top 10 synthetic cathinones, benzylone ranked at position 6 (UNODC 2020). In the follow-up UNODC report on synthetic drugs in East and Southeast Asia published in 2021, eutylone was still featured but not benzylone (UNODC 2021b). The Brazilian Federal Police reported the detection of benzylone first in 2018 (Anonymous 2018).

The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA has registered a relatively low number of reports involving the detection of benzylone that appeared to emerge first in 2019 (Table 5). According to the currently available collection of mid-year and annual reports, benzylone reports submitted to NFLIS decreased in 2020.

Table 5. Number of reports (and percentage of reports under the phenethylamine classification) received by the U.S. National Forensic Laboratory Information System (NFLIS) related to detections of benzylone in law enforcement operations.

Year [a]	Benzylone (%)	Eutylone [b] (%)	MDMA [c] (%)	Meth [d] (%)	Reference
2018 (AR)	NR [e]	260 (0.06)	6,616 (1.56)	386,272 (91)	(DEA 2019b)
2019 (MY)	390 (0.17)	2,800 (1.23)	3,558 (1.56)	209, 439 (92.03)	(DEA 2020f)
2019 (AR)	681 (0.15)	5,787 (1.28)	7,238 (1.60)	417,867 (92.43)	(DEA 2020e)
2020 (MY)	246 (0.13)	5,118 (2.64)	2,672 (1.38)	177,794 (91.69)	(DEA 2021c)

[a] MY: mid-year report (January to June); AR: annual report (January to December)

[b] Eutylone: 1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one (*N*-ethylnorbutylone)

[c] MDMA: 3,4-methylenedioxymethamphetamine

[d] Meth: methamphetamine

[e] NR: not reported

A summary of snapshot drug reports received by NFLIS-Drug is presented in Table 6 where benzylone was featured as one of the top five synthetic cathinones where the number (and percentage) of benzylone reports dropped in the Jan–March 2021 period (81 reports, 3.40%) compared to 2020.

In the 2020 National Drug Threat assessment document published by the U.S. Drug Enforcement Administration (DEA) in March 2021, it was stated that 9,575 reports of synthetic cathinones were submitted to NFLIS-Drug in 2019, which represented a 28 percent

decrease compared to 2018 (13,226 reports). Eutylone was the most reported synthetic cathinone (58%) compared to 8% for benzylone (DEA 2021a). Based on the snapshot data shown in Table 6, the mean proportion of benzylone submissions dropped to 4.34% considering the period between January 2020 and March 2021 whereas the mean eutylone report numbers increased to 78.42% in the same period. The snapshot data only contained the number of reports counted for the top five synthetic cathinones.

Table 6. U.S. National Forensic Laboratory Information System (NFLIS) snapshot reports – top five drugs in the category "selected synthetic cathinones"

Period	Benzylone (%)	Eutylone (%)	Total	Reference
Jan–March 2020 [a]	91 (4.90)	1,221 (65.86)	1,854	(DEA 2020d)
April–June 2020 [b]	135 (4.79)	2,116 (75.04)	2,820	(DEA 2020c)
October–December 2020 [c]	161 (4.87)	2,745 (82.96)	3,309	(DEA 2020b)
Jan–March 2021 [d]	81 (3.40)	2,381 (84.76)	2,809	(DEA 2021b)
Total	468 (4.34)	8463 (78.42)	10,792	–

[a] Drug reports received by NFLIS-Drug submitted to a NFLIS participating laboratory on or after January 1, 2019. The three other synthetic cathinones were: *N*-Ethylpentylone [sic] (185); alpha-PiHP (4-methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one) (86), and *N*-butylpentylone [sic] (1-(2*H*-1,3-benzodioxol-5-yl)-2-(butylamino)pentan-1-one) (56).

[b] Drug reports received by NFLIS-Drug submitted to a NFLIS participating laboratory on or after 01 April 2019. The three other synthetic cathinones were: *N*-Ethylpentylone [sic] (135); butylpentylone [sic] (99); alpha-PiHP (83).

[c] Drug reports received by NFLIS-Drug submitted between 01 October 2020 and 31 December 2020. The three other synthetic cathinones were: *N*-Ethylpentylone [sic] (90); alpha-PHP (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one) (48); alpha-PiHP (32).

[d] Drug reports received by NFLIS-Drug between January 1, 2021, and March 31, 2021. The three other synthetic cathinones were: *N*-Ethylpentylone [sic] (54); 3,4-methylenedioxy PV8 (1-(2*H*-1,3-benzodioxol-5-yl)-2-(1-pyrrolidinyl)-1-heptanone) (45); "fluoro-methyl-alpha-PVP" [sic] – isomer not specified (17).

In the DEA Emerging Threat Reports covering drug reports collected from the DEA's laboratory system, benzylone was not included in the 2018 annual report which presented 327 detections of synthetic cathinones (21 compounds listed). Sixty-two percent of identifications (204/327) were represented by *N*-ethylpentylone and eutylone was also not listed (DEA 2018). In the 2019 report, benzylone was reported for the first time in this period with 12/184 (6.5%; 19 cathinones listed) identifications. In comparison, eutylone was identified 67/184 times (36%) (DEA 2019a). The 2020 annual report listed 13 synthetic cathinones (200 identifications in total) with benzylone being identified 5 times (2.5%) compared to 154 eutylone detections (77%) (DEA 2020a).

17. Current International Controls and Their Impact

Benzylone is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

Detections of benzylone may be under-reported if this substance is not routinely screened for in all laboratories receiving samples for analysis.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Data were obtained from 98 Member States (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 20 countries had information on BMDP (Table 1).

Table 1. Numbers of countries providing information on BMDP

Region	Number of countries without information	Number of countries with information on substance
African	5	0
Eastern Mediterranean	8	0
European	16	14
Region of the Americas	9	3
South-East Asia	4	0
Western Pacific	8	3
Total (70)	50	20

APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

No countries reported any approved human medical products, therapeutic indications, scientific use or industrial use relating to BMDP.

EPIDEMIOLOGY OF NON-MEDICAL USE

Five countries (4 European, 1 Region of the Americas) described seizures and reports from health professionals as evidence of non-medical use of BMDP in their country (use outside of the medical, industrial or scientific context).

Routes of administration and formulations

The most commonly reported routes of BMDP administration was oral and smoking (Table 2).

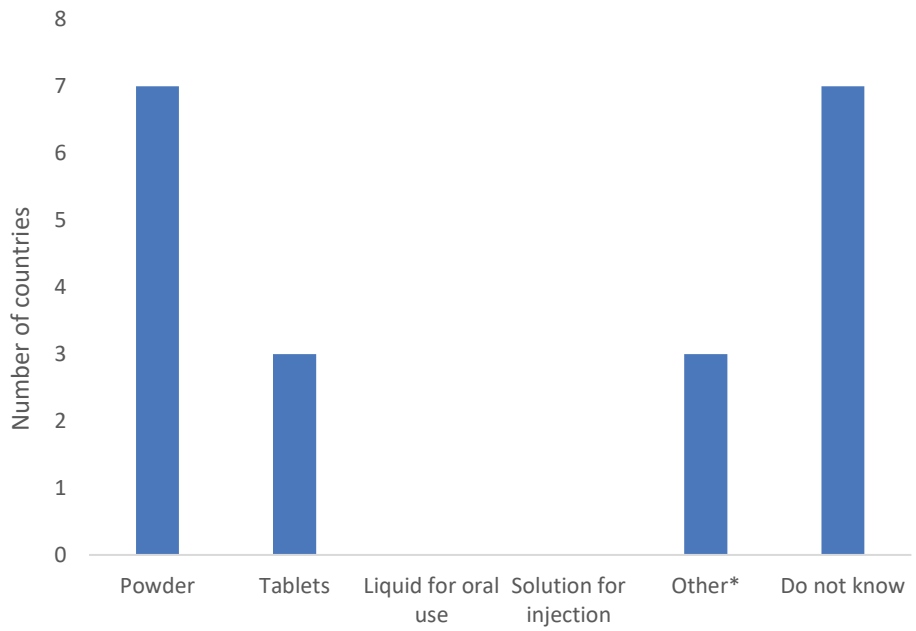
Table 2. Reported routes of BMDP administration

Route of administration	Number of countries
Oral	2
Smoking	2
Inhalation	1
Sniffing	1
Injection	1
Other*	1
Do not know	12

* Rectal use

The most commonly reported formulation of BMDP was powder (Figure 1).

Figure 1. Formulations of BMDP



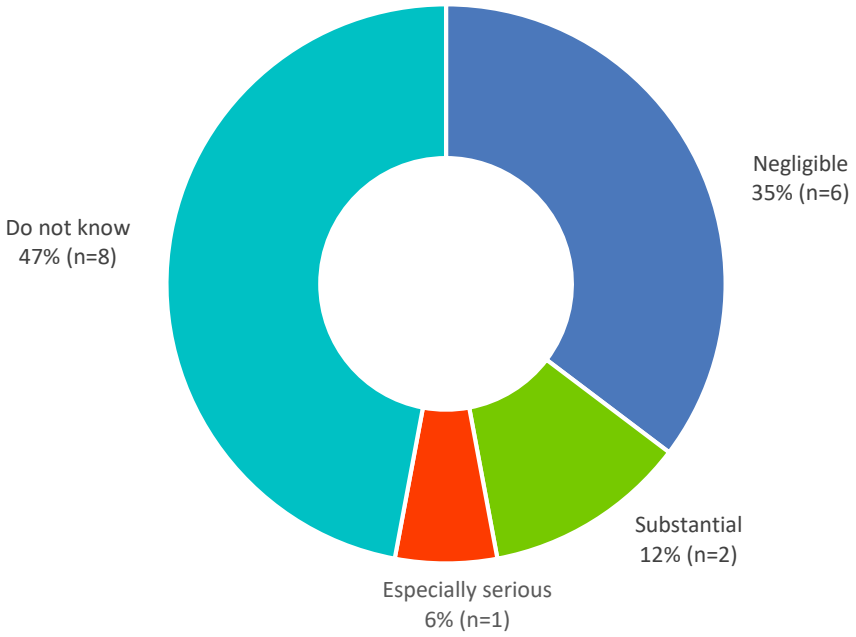
* Three countries described other BMDP formulations: "capsule and crystalline from" (n=1),

crystal powder (n=1), and "rock, capsule, drug patch, plant or vegetable matter" (n=1).

Perceived negative health impact

Three countries (1 Region of the Americas, 1 European, 1 Western Pacific) reported the level of negative health impact due to BMDP's non-medical consumption was "substantial" or "especially serious" (Figure 2). These countries did not specify the nature of these health impacts.

Figure 2. Countries reporting negative health impact of the non-medical consumption of BMDP



Emergency Department visits

No countries were aware of emergency room/department visits related to BMDP.

Deaths

No countries reported any deaths where BMDP was the only substance involved. One country (European) reported a death in 2019 where BMDP and another substance(s) were involved.

Drug Dependence

No countries reported they were aware of people presenting to drug dependence treatment in their country due to use of BMDP.

CURRENT DRUG CONTROL

Eleven countries (7 European, 2 Western Pacific, 2 Region of the Americas) responded BMDP is currently controlled under national legislation to regulate its availability. Table 3 shows reported activities involving BMDP.

Table 3. Reported activities involving BMDP for purposes other than medical, scientific or industrial use.

Activity	Number of countries
Trafficking	5
Internet sales (other or location of sellers and website unknown)	4
Smuggling (from other countries)	3
Internet sales (from abroad to buyers in respondent's country)	3
Internet sales (seller or website located in respondent's country)	2
Manufacture of the substance by chemical synthesis	1
Direct sales	1
Do not know	10

Seizures

Four countries (2 Region of Americas, 1 European, 1 Western Pacific) reported seizures of BMDP in 2021. Seizure numbers ranged from 2 to 105 (Table 4).

Seven countries (5 European, 2 Region of Americas) reported seizures of BMDP in 2020. Seizure numbers ranged from 1 to 587, and seizure quantities ranged from 0.26 to 3244 grams.

Nine countries (5 European, 2 Region of the Americas, 2 Western Pacific) reported seizures of BMDP in 2019. Seizure numbers ranged from 1 to 780, and seizure quantities ranged from 1 grams to 1022 grams.

Table 4. Reported seizures of BMDP

Year	Number of countries reporting seizures	Number of seizures
2021	4	123
2020	7	659
2019	9	859

Eighteen countries (13 European, 3 Western Pacific, 2 Region of the Americas) reported having the forensic laboratory capacity to analyze BMDP.