World Health Organization

Critical review report:

3-Methylmethcathinone (3-MMC)

Expert Committee on Drug Dependence

Forty-fifth Meeting

Geneva, 10–14 October 2022

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Executive summary

3-Methylmethcathinone (3-MMC) (IUPAC name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one) is a synthetic cathinone and a regioisomer of the internationally controlled 4-methylmethcathinone (4-MMC, mephedrone, Schedule II, 1971). The first emergence of 3-MMC was recorded in Europe in 2012. 3-MMC is most likely to be sold on the street in the form of a racemate. Evidence also indicates that 3-MMC re-emerged in Europe during 2020.

No specific information was available about the routes used to synthesize the 3-MMC products circulating on the drug market, but there are straightforward methods for its preparation that do not require access to internationally controlled precursors. It is not feasible to convert 3-MMC into another substance currently listed in the United Nations Conventions of 1961, 1971 and 1988. As 2-MMC and 4-MMC are 3-MMC regioisomers, analytical difficulties may arise during routine case work.

3-MMC was critically reviewed in 2016, but it was decided to request another critical review, to be considered at a subsequent meeting, pending the availability of more information.

3-MMC is typically administered by nasal insufflation (snorting), orally and by intravenous injection. Other routes have been reported occasionally, such as rectal administration and inhalation or smoking. High-risk use by injection has been described by people who consume drugs in the context of sexual activity ("chemsex" and "slamsex"), who include men who have sex with men.

3-MMC induces psychostimulant effects, the duration depending on the route of administration. Some information suggests that the effects of 3-MMC may be short-lived and less intense than those reported for 4-MMC (mephedrone). Assessment of such reports is, however, difficult, because people who use these substances may have been unable to confirm the actual substance or the amount used.

Information from in-vitro studies suggests that 3-MMC inhibits the uptake of dopamine, norepinephrine and serotonin and that it induces a monoamine transporter-mediated release of monoamines with 10-fold selectivity for catecholamines over serotonin, resulting in a DAT:SERT ratio of 10 (synaptosomal preparations).

Detection of 3-MMC in biological fluids collected from cases of adverse effects (including deaths) confirmed that this drug is circulating on the market and is used recreationally.

The Early Warning Advisory Tox-Portal of the United Nations Office of Drugs and Crime (UNODC) lists 27 cases in which detection of 3-MMC in blood and/or urine samples was documented between June 2016 and May 2022. Twenty-one cases were clinical admissions, one involved driving under the influence of drugs (DUID), two were post-mortem investigations, and two were unspecified. Seven cases included detection of additional substances, although detailed information was not reported.

A risk assessment by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) comprised 14 cases of acute poisoning (most non-fatal) with confirmed exposure to 3-MMC. In 7 cases, exposure to other substances was reported, including central nervous system depressants and central nervous system stimulants, and four of the cases were considered life-threatening. The EMCDDA also received reports on 192 cases of suspected exposure to 3-MMC from five Member States, although analytical confirmation was not available at the time.

Over 400 detections of 3-MMC (including DUID and non-fatal intoxications) have been described in the scientific literature since 2013. In the majority of cases, detections of other substances were also described, and some cases were reported or reviewed more than once. Over 100 of the cases were reported to involve ingestion of 3-MMC alone or self-reported ingestion with no analytical confirmation. In most cases, the reported clinical features were consistent with sympathomimetic toxicity, including tachycardia, agitation, aggression, hypertension, hallucinations and increased creatine phosphokinase levels (rhabdomyolysis and/or kidney failure).

The EMCDDA also received notifications of 27 deaths with confirmed exposure to 3-MMC. In at least eight cases, 3-MMC was reported to be the cause of or to have contributed to the death. Some of these cases might have also been reported in the scientific literature. Co-exposure to other substances was common.

Since 2013, 34 deaths in which 3-MMC was detected were identified in the scientific literature. Poly-drug use was identified in the majority of cases (including psychostimulants and central nervous system depressants such as alcohol and γ-hydroxybutyric acid [GHB]), and some cases were reported more than once; some may also have been reported to the EMCDDA. In eight cases, either no other substance was detected, or the authors established that accidental intoxication with 3-MMC was the cause of death. Three other fatal cases involved suicide (two by hanging). Some of the deaths were related to acute 3-MMC intoxication in the context of chemsex practices. The descriptions included acute circulatory and respiratory failure, deteriorating neurological conditions (cerebral oedema consistent with a global anoxic brain injury) and cardiac complications.

No studies of dependence potential were identified. Some people believed to have taken 3-MMC reported binge use. Information received by EMCDDA suggests that some people who reported use of 3-MMC experienced withdrawal symptoms.

Studies in adult male Sprague-Dawley rats showed that 3-MMC and methamphetamine induce locomotor activity. 3-MMC increased activity between 5–30 min and 95–100 min whereas methamphetamine administration increased locomotor activity between 5 and 120 min. In the elevated plus maze test, a single Intraperitoneal injection of 3-MMC led to increased time spent in the open arm (3 mg/kg), consistent with anxiolytic activity of the drug. After administration for 7 days (3 mg/kg), the time spent in the open arms was shorter than with saline or methamphetamine, indicating increased anxiety-like behaviour. No significant difference was seen between acute and chronic administration of methamphetamine (1 mg/kg). 3-MMC at 3 and 10 mg/kg induced “conditioned place preference” after 8 days of training. The scores recorded on day 9 after the 10 mg/kg dose of 3-MMC were comparable to those recorded for methamphetamine at 1 mg/kg.

The catecholamine-selective effects on monoamine transporters together with the effects on animals suggest that the profile of 3-MMC is comparable to those of other psychostimulants under international control, such as 4-MMC (mephedrone) and other amphetamine-type stimulants, which also include abuse liability.

No epidemiological evidence on the use of 3-MMC was found in household surveys, although some information is available from targeted surveys of specific populations, such as recreational substance users and men who have sex with men who report drug consumption in the context of sexual activity.

The health concerns associated with chemsex or slamsex practices involving 3-MMC are due not only to poisoning from overdosing via the intravenous route and infections associated with the injection sites and extravasation but also to co-administration with other drugs to enhance the experience. In addition, such practices increase the risk of sexually transmitted diseases, as the sexual behaviour of such users may increase their risks of transmission of HIV and hepatitis C virus.

The EMCDDA reported a decrease in the number of seizures in Europe between 2016 and 2018 that coincided with its control in China in October 2015. In 2020, however, 3-MMC began to re-emerge and continued to be imported, distributed and used in parts of Europe during 2021. Currently, 3-MMC is imported into Europe in bulk quantities, mainly from India. The EMCDDA also reported that at least three illicit sites, including some that directly produce 3-MMC, have been identified in Europe, most recently in 2020. Approximately 350 kg of *N*-acetyl-3-MMC (a so-called “designer precursor”, which can readily be converted into 3-MMC) were seized in one European country in 2019 (imported from India).

Information from drug testing services in the USA suggests the detection of 3-MMC in some products acquired or sold as other substances, including MDMA. This implies that people who use certain

recreational substances may be exposed to 3-MMC unintentionally, either alone or in combination with other substances, which might increase the risk of harm (e.g., potential exacerbation of a psychostimulant toxidrome).

1. Substance identification

A. International nonproprietary name

No information was found.

B. Chemical Abstracts Service registry number

1246911-86-3 (base)
2291027-30-8 (*R*)-enantiomer (base)
2107851-15-8 (*S*)-enantiomer (base)
1246816-62-5 (HCl)
1329834-37-8 (*N*-CD_3) (HCl)
1330267-42-9 (*N*-CD_3) (base)
2416463-56-2 (2,2,2-trifluoroacetate (1:1))

C. Other chemical names

1-(3-Methylphenyl)-2-(methylamino)propane-1-one
1-(3-Methylphenyl)-2-(methylamino)-1-propanone
2-(Methylamino)-1-(*m*-tolyl)propan-1-one
3-Methylmethcathinone
3-Methyl-methcathinone
3-Methyl-*N*-methylcathinone
Metaphedrone
3-MMC
3-MeMMC
3-Mephedrone
3-Methylephedrone
Mepedrone
3-Me-M-CAT
3-Methyl MC

D. Trade names

3-MMC

E. Street names

Some of the chemical names listed above are also used as street names, and "3-MMC" and "metaphedrone" appear to be used commonly. The term "sladoled" (ice cream) has been used in Slovenia *(1)*. 3-MMC has also been reported in a product called "MCH", and products labelled "Product Imitation: Red Dirt" and "Ruby Sand Additive, 0.5 Gram – Product Imitation'" were reported to contain 3,4-dimethylmethcathinone and 3-MMC, respectively *(2).* 3-MMC has been traded as "Synthacaïne" or "Synthacaine", "Charly Sheen" and "Crystal'" *(3)*. It should be noted, however, that the compositions of branded products are likely to change over time. Other names include "Miauw 2.0 "and "The 3".

F. Physical appearance

In its pure form, 3-MMC hydrochloride is expected to be odourless and white, like many other ring-substituted synthetic cathinones. Synthesized 3-MMC hydrochloride has been described as a white powder *(4),* a white solid (*5)* and a grey solid *(6).* A sample obtained from a material reference collection was described as a white powder *(7)* and a crystalline solid *(8).* According to the EMCDDA *(3)*, the majority of seized and collected 3-MMC samples were in powder form.

Powders were reported to range from “white rocks” to “white/off-white powders” (mostly pure); in some cases, 3-MMC was yellow and orange (usually with other substances).

G. *WHO* review history

3-MMC was critically reviewed at the 38th meeting of the WHO ECDD, in November 2016 *(9)*. It was decided to request a further critical review when more information became available and to consider it at a subsequent meeting of the Expert Committee *(10).*

2. Chemistry

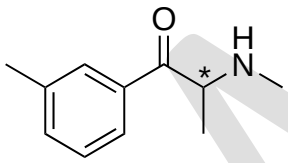
A. Chemical Name

IUPAC name: 2-(Methylamino)-1-(3-methylphenyl)propan-1-one

Chemical Abstracts index name: 2-(Methylamino)-1-(3-methylphenyl)-1-propanone

B. Chemical structure

Free base:



Note: * refers to a chiral centre

Molecular formula: $C_{11}H_{15}NO$

Molecular weight: 177.25 g/mol

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair (*S*)-3-MMC and (*R*)-3-MMC. 3-MMC is most likely to be available as the racemic mixture, although the appearance of individual stereoisomers cannot be excluded.

D. Methods and ease of illicit manufacture

No information was found on the routes of synthesis for 3-MMC products circulating on the market; however, the chemistry of production of ring-substituted synthetic cathinones is well established and straightforward. No precursors that are currently controlled are required. Although several methods are available, one of the most common is based on so-called α-bromination of a ketone intermediate followed by amination. These types of reactions are easy to perform and lend themselves to both small and large-scale manufacture *(4, 11, 12)*. Other synthetic routes could be applied to 3-MMC *(3)*.

According to the EMCDDA *(13)*, at least 2100 kg of α-bromoketone intermediates were seized in Europe, most being 2-bromo-4-chloropropiophenone used in the synthesis of 4-chlorormethcathinone, and 2-bromo-4-methylpropiophenone, used in the synthesis of 4-MMC

(mephedrone). Given the practicality of this synthesis procedure, it is likely to have been adopted for large-scale manufacture of 3-MMC.

Of particular note is that the EMCDDA reported seizure of 350 kg *N*-acetyl-3-MMC in one European Union Member State *(3)*. in the context of new psychoactive substances (NPS), such modifications may be referred to as "masked derivatives", "masked precursors" or "designer precursors", which indicate that they can be converted back into 3-MMC in one simple chemical step. These types of protecting group are widely used in synthesis procedures. Another alternative was used in the amination step, whereby *N*-benzyl-*N*-methylamine was reacted with the brominated intermediate, and the resulting intermediate was converted to 3-MMC with 1-chloroethyl chloroformate *(5, 6).* The *N*-benzyl-3-MMC intermediate could serve as another potential "masked precursor" for 3-MMC, although other types of protection groups can also be used.

E. Chemical properties

Melting-point

188–190 °C (HCl) *(4)*
206.5 °C (HCl) *(7)*
193.2 °C (HCl) *(14)*
190–192 °C (HCl) *(5)*
193–195 °C (HCl) *(6)*

Boiling-point

No information was found.

Solubility

3-MMC hydrochloride was reported to be soluble in phosphate-buffered saline (pH 7.2; ~10 mg/mL), ethanol (~5 mg/mL), dimethyl sulfoxide (~2.5 mg/mL) and dimethylformamide (~1 mg/mL) *(15)*. The hydrochloride salt is also considered to be water-soluble and can be dissolved for oral use and injection *(3)*. The water solubility of the hydrochloride salt was reported to be 2.0 mg/mL *(14)*.

F. Identification and analysis

Identification is straightforward, especially when larger quantities of the substance are available than are usually the case in forensic toxicology. Analytical difficulties may arise, for example, in differentiation of the 2- and 4-methylphenyl regioisomers 2-MMC and 4-MMC (mephedrone, listed in Schedule II of 1971 *(16)*). Adequate separation techniques are required to reduce potential misidentification, especially in samples (e.g., biological) containing only small quantities. 3-MMC and its isomers are, however, available as certified reference materials, and the results of various analytical methods have been described extensively in the scientific literature (Annex 2). Analysis of biological samples requires sensitive methods, e.g., gas or liquid chromatography coupled to (tandem) mass spectrometry approaches (high and low resolution). Some analytical data, including chromatographic, mass spectral and spectroscopic data, are available in the public domain *(e.g., 7, 17, 18)*.

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

No clinical studies on 3-MMC were found; however, the available information suggests that 3-MMC is typically administered by nasal insufflation (snorting), orally and by intravenous injection. Other routes have been reported occasionally, such as rectal administration and inhalation or smoking *(1, 3, 19, 20, 21)* (sections 6 and 14). Some people who used 3-MMC expressed a preference for nasal insufflation over oral administration *(1)*.

In a study of 3-MMC intoxications in the Netherlands, two distinct patient groups were identified: younger patients who used 3-MMC by ingestion or snorting and older patients who used 3-MMC by injection. The authors found that younger patients were more likely to use 3-MMC in a social, nonsexual context, whereas older patients ("mostly middle-aged men") were more likely to prefer use by injection in the context of sexual activity ("slamsex") *(21)* (see also section 14).

Some information on the doses used by different routes of administration is in the public domain. For oral administration, a "light" dose was suggested to be 25–75 mg; "common", 75–150 mg; and "strong", 150–≥ 300 mg *(22)*, but higher doses have also been reported *(23)*. In cases involving acute intoxication, doses in the range ~0.5–2 g were reported, and some people reported taking several doses in succession on consecutive days *(19).*

In a survey of people who used 3-MMC, 26.2% took > 1.5 g of 3-MMC during a single evening (n = 168), and over half of the respondents consumed > 0.5 g of 3-MMC during a single evening *(1)*. Binge use of 3-MMC was identified in a follow-up investigation of interviews with NPS users: when 3-MMC was used for several days, the amount consumed ultimately exceeded the amount originally planned *(24).* In a retrospective analysis of intoxications involving 3-MMC, the median self-reported dose per session was estimated to be 1000 mg (range, 0.3–6000 mg) *(21).*

"Typical" dosages depend on factors such as the route of administration, individual tolerance, use of other drugs and the desired effects. Assessment of such reports is difficult, as people who use these substances might not be able to confirm the actual substance or the amount used. Given the difficulty of collecting accurate self-reported data, these reports should be interpreted with caution.

In a patent application for 3-MMC-assisted psychotherapy, four examples were included in which a range of doses was used, depending on the therapeutic context: 1: three sessions with 200 mg given orally (treatment of post-traumatic stress disorder); 2: six sessions with 150 mg (plus 100 mg) over 6 months (couples therapy); 3: three sessions with 300 mg for relationship distress; and 4: twice weekly administration of 200–400 mg 3-MMC on 2 consecutive days for 8 weeks (post-traumatic stress disorder and generalized anxiety disorder) *(25)*.

In another patent application, in which 3-MMC was proposed for treatment of menstrual cycle-induced disorders and symptoms, a number of trials were conducted which typically involved oral administration of 3-MMC at doses of 12.5–50 mg per trial *(26).*

B. Pharmacokinetics

No clinical studies were identified.

A study was reported in 3-month-old male pigs given a single intravenous dose of 0.33 mg/kg followed by oral administration of 3 mg/kg *(14)*. A short half-life was observed (0.8 h) after both routes. The apparent volume of distribution after injection was 8 L/kg (28–34 kg body

weight), while bioavailability after oral administration was only 7% , which may have been due to an extensive first-pass effect. The maximal concentration after oral administration was detected after 0.08 h, suggesting rapid absorption; rapid elimination was also observed.

The duration of effects depends on factors such as the route and frequency of administration, individual tolerance, use of other drugs and the desired effects. The profile after oral administration has been reported by people who have used the drug as follows: total duration: 4–6 h; onset: 10–30 min; "come up": 30–60 min; peak: 2–3 h; "offset": 1–1.5 h; and "afterglow": 2–4 h. The profile after nasal insufflation was: total duration: 2.5–4.5 h; onset: 5–10 min; "come up": 10–20 min; peak: 1–1.5 h; "offset": 1–2 h; and "afterglow": 1–1.5 h *(27)*. These profiles agree to some extent with other reports (e.g., 23, 28–30). The effects of 3-MMC were perceived as short-lived by some users *(21)*.

No studies were found of the metabolism of 3-MMC, although some metabolites were identified in biological samples. In a fatal case, 3-MMC was detected with nor-3-MMC, dihydro-3-MMC, nor-dihydro-3-MMC, hydroxytolyl-3-MMC, 3-carboxy-3-MMC and 3-carboxy-dihydro-3-MMC (Rojek et al. cited in *31*). Detection of 3-MMC, dihydro-3-MMC and nor-dihydro-3-MMC was described in pubic hair samples *(32),* and detection of nor-3-MMC and hydroxylated 3-MMC was reported in femoral blood in an investigation of a fatal case *(20)*, suggesting that the metabolism of 3-MMC may be similar to that of 4-MMC (mephedrone) (e.g., *33*). Nor-3-MMC and dihydro-3-MMC metabolites were tentatively detected in cases of non-fatal intoxication with 3-MMC *(34)*.

C. Pharmacodynamics

In-vitro assays of monoamine uptake mediated by human dopamine (hDAT), norepinephrine (hNET) and serotonin transporters (hSERT), stably expressed in HEK293 cells, showed that 3-MMC inhibited the uptake of radiolabelled neurotransmitters (Table 1). The DAT:SERT ratios calculated from these results were 3.7, 10.4, 53.6 and 31.5, which suggests selectivity for DAT over SERT. It has been suggested that substances with high DAT:SERT ratios have higher abuse liability than those with low ratios *(35)*. Further in-vitro studies confirmed that 3-MMC has some affinity to monoamine transporters and receptors (Table 2). 3-MMC did not activate serotonin subtype receptors at a meaningful concentration, and activation of the mouse trace amine-associated receptor 1 was negligible *(36)* (Table 2).

Table 1. Mean IC_{50} values for inhibition of monoamines at human dopamine (hDAT), norepinephrine (hNET) and serotonin transporters (hSERT), stably expressed in HEK293 cells

hDAT IC_{50} [µM]	hNET IC_{50} [µM]	hSERT IC_{50} [µM]	Reference no.
2.6	0.27	9.5	*37*
0.43	0.08	4.5	*38*
2.5	5.2	134	*39*
4.1 [a]	3.1 [a]	129 [a]	*39*

[a] 3-MMC sample obtained from an Internet retailer

Table 2. Monoamine transporter and receptor binding affinities

Monoamine transporter	K_i (µM)[a] *(37)*	EC_{50} (µM) *(37)*	K_i (µM)[b] *(38)*

NET	5.6	–	2.85
DAT	3.2	–	6.33
SERT	> 22	–	7.9
D_2	> 12	–	–
α_{1A}	7.9	–	–
α_{1A}	1.1	–	–
5-HT_{1A}	4.8	–	–
5-HT_{2A}	3.4	> 20	–
5-HT_{2B}	–	> 20	–
5-HT_{2C}	3.6	–	–
$TAAR1_{human}$ [c]	–	> 30	–
$TAAR1_{rat}$ [c]	5.7	> 10	–
$TAAR1_{mouse}$ [c]	11	3.8 (E_{max} = 25%)[d]	–

[a] Radioligands used: *N*-methyl-[^{3}H]-nisoxetine and indatraline (NET), [^{3}H]citalopram and indatraline (SERT), [^{3}H]WIN35,428 and indatraline (DAT), [^{3}H]8- hydroxy-2-(di-n-propylamine)tetralin and indatraline (5-HT_{1A}R), [^{3}H]ketanserin and spiperone (5-HT_{2A}R), [^{3}H]mesulgerine and mianserin (5-HT_{2C}R), [^{3}H]prazosin and risperidone (α_1R), [^{3}H]rauwolscine and phentolamine (α_2R), [^{3}H]spiperone and spiperone (D_2R) and [^{3}H]RO5166017 and RO5166017 (TAAR1R)

[b] Radioligand used: [^{125}I]RTI-55

[c] Simmler et al. *(36)*

[d] Reference substances for comparisons of affinity values and functional potency and efficacy: phenethylamine, *p*-tyramine and tryptamine.

3-MMC was also shown to act as substrate-type releaser, inducing transporter-mediated release of monoamines. In rat brain synaptosomal preparations, the EC_{50} values of DAT- and SERT-mediated release were 70.6 and 292 nM (DAT:SERT = 4.1) *(5)* (NET: 94% induced by 10 µM) and 28 and 268 nM (DAT:SERT = 9.6). The EC_{50} value for NET-mediated release was 27 nM *(6)*. In comparison, the DAT:SERT ratio for 4-MMC (mephedrone) under the same conditions was 2.4, indicating that 3-MMC was more potent at DAT and less potent at SERT than 4-MMC *(6)*. In HEK293 cells that stably express human DAT, NET and SERT, monoamine release was induced by one high dose of 3-MMC (100 µM); release was observed for all three transporters (DAT: ~160% relative to mazindol; SERT: ~155% relative to citalopram; NET: ~155% relative to nisoxetine) *(37)*.

The results of an in-vitro assay of neuronal activity have been reported *(39)*. Exposure to 3-MMC and a number of other cathinones led to changes in spontaneous neuronal activity in rat primary cortical cultures grown on microelectrode arrays. The test drugs inhibited the mean spike rate, mean burst rate and mean network burst rate after acute exposure. The IC_{50} values obtained for 3-MMC after acute (30 min), prolonged (4.5 h) and recovery (after washout of the exposure 24 h after the start of the 5-h exposure) were 65, 87 and 710 µM (mean spike rate); 79, 109 and > 1000 µM (mean burst rate) and 67, 116 and >1000 µM (mean network burst rate). 4-MMC was less potent. The extent to which such observations indicate neurotoxicity in humans remains to be determined *(39)*. Increased acute inhibition of neuronal activity was also reported at higher temperatures *(40).*

Some people who use 3-MMC might find its effects less intense than those of 4-MMC (mephedrone) (e.g., *1, 3*), but most of the information currently available suggests that 3-MMC has a typical psychostimulant profile.

In a study of the impact of 3-MMC on weight gain in pigs (one intravenous and five consecutive oral administrations), significant reductions in weight gain and food intake were observed, which confirmed its appetite-suppressant effect. Triglyceride levels were also reduced *(14)*.

Repeated intraperitoneal injections of 3-MMC (3 mg/kg) for 7 days to adult male Sprague-Dawley rats weighing 280–300 g increased the number of c-Fos-labelled neurons in the nucleus accumbens, the ventral tegmental area and the anterior cingulate cortex, which indicates increased expression of c-Fos, comparable to that of methamphetamine at 1 mg/kg intraperitoneally *(41).* Electrophysiology experiments were conducted in which whole-cell patch-clamp recordings were made from nucleus accumbens slices 24 h after the last exposure to record spontaneous excitatory and inhibitory postsynaptic currents. Both methamphetamine and 3-MMC decreased the amplitude of inhibitory postsynaptic currents, while the frequency remained unchanged. Neither drug changed the frequency or amplitude of spontaneous excitatory postsynaptic currents, suggesting that chronic exposure to both test drugs inhibited only inhibitory neurotransmission *(41)*.

5. Toxicology

Administration of 3-MMC (intravenously at 0.3 mg/kg and a single daily oral dose of 3 mg/kg to six healthy pigs (Landrace; 28–34 kg, 3 months old) caused abnormal alterations to clinical chemistry and haematological parameters. Histopathological examination of two treated and two untreated animals showed mild diffuse hepatocellular vacuolation. In two treated animals, the authors observed mild multifocal collapse of alveolar walls and mild multifocal mononuclear infiltration of the alveolar and interlobular septa (interstitium). Mild hyperplasia of bronchiolar-associated tissue was observed in one control pig. No abnormal histopathological changes were observed in any other tissue sample investigated *(14).*

3-MMC did not induce gene mutations in a *Salmonella* microsomal assay, although it caused single and double-strand breaks of DNA in a human-derived buccal cell line (TR146) in single-cell gel electrophoresis. Significant induction of micronuclei was noted as a consequence of structural and chromosomal aberrations at 100 and 150 µM. No oxidative damage to DNA was observed *(42).*

Isolated primary Wistar rat hepatocytes were exposed to 3-MMC for 24 h at 37 °C (31 nM–10 mM) to study various toxicological outcomes, and cytochrome P450 inhibition was studied in CYP2E1, CYP2D6 and CYP3A4 and general CYP inhibition at 1 mM *(43).* Cell viability was assessed in three assays (leakage of lactic dehydrogenase, neutral red uptake and tetrazolium dye (MTT) reduction) with potencies (EC_{50}) of 3.13, 1.36 and 1.68 mM. The authors stated that when CYP2D6 was inhibited (MTT test), significantly higher 3-MMC concentrations were necessary to induce similar levels of cell death (EC_{50} = 2.08 mM); when cells were pre-treated with metyrapone (CYP2E1 inhibitor), the EC_{50} decreased to 1.40 mM at 3-MMC concentrations up to ~1.20 mM, indicating less metabolic CYP2E1 inhibition at low concentrations. Inhibition of CYP2E1 increased cell death at higher 3-MMC concentrations, whereas inhibition of CYP3A4 did not influence 3-MMC toxicity. General inhibition of CYP450 increased cell death only from ~1.03 mM 3-MMC. Production of oxygen and nitrogen reactive species increased significantly at concentrations of 10, 100 and 500 µM but not at 1 µM. Mitochondrial membrane potential was not affected by 3-MMC, although cellular ATP levels decreased significantly at concentrations ≥ 100 µM. Pro-apoptotic caspase-3, -8 and -9 activities increased significantly at 10 µM. Evaluation of nuclear morphology suggested induction of apoptosis

at 1 µM, the highest late apoptotic levels occurring at 10 µM and 100 µM. At the highest concentrations, necrosis was found to predominate at 500 µM. 3-MMC was also reported to increase acidic vesicular organelles, compatible with autophagy, particularly at 100 µM.

Studies of cytotoxicity in hSERT-, hDAT- and hNET-transfected HEK 293 cells (ToxiLight bioassay kit) after drug treatment for 1 h at room temperature showed no effects on adenylate kinase release as a result of cell membrane integrity loss *(37).* Tests of the viability of HEK 293 cells and primary rat cortical cultures in the neutral red assay with a 4.5-h exposure to the drug at 1–1000 µM (37 °C) showed no signs of cytotoxicity at concentrations > 1000 µM *(39)*. In a follow-up study to mimic hyperthermic conditions (41 °C), no reduced cell viability was observed in rat cortical cells after prolonged exposure (4.5 h) and washout (recovery; 19 h after exposure, i.e., 24 h after the start of exposure) at concentrations of 1–1000 µM *(40).*

C2C12 myoblasts were exposed to 3-MMC for 1 or 24 h in various cytotoxicity assays. Incubation with 3-MMC affected cell membrane integrity (24 h exposure, IC_{50} > 2 mM) and ATP content (IC_{50} = 1.08 mM) but not mitochondrial oxygen consumption. Mitochondrial superoxide production increased significantly at 500, 1000 and 2000 µM. Overall, although 3-MMC was found to deplete the cellular ATP pool and impair cell membrane integrity in C2C12 myoblasts, the concentrations reached were considered greater than those that would be expected after ingestion of typical doses *(44)*.

6. Adverse reactions in humans

Cases of 3-MMC intoxication in humans (fatal and non-fatal)

The UNODC Early Warning Advisory Tox-Portal lists 27 cases in which 3-MMC was detected in blood and/or urine samples. Twenty-six cases were submitted from France and one from the United Kingdom. Nineteen cases were in people aged 25–44, four in people aged 45–64 and three in people aged 15–24. Twenty-five cases were in males and two in females. The cases in France occurred between June 2016 and May 2022 (20 since 2020). The case reported from the United Kingdom occurred in March 2018 *(45)*.

Twenty-one cases were clinical admissions, one involved DUID, two were post-mortem investigations, and two were unspecified. No specific information was available on the cases; however, blood concentrations were provided in six cases (6.8–110 µg/L). In one post-mortem case (peripheral blood concentration, 8.1 µg/L), 3-MMC was reported as "present but contributory (low)". In the other post-mortem result, reported from the United Kingdom, 3-MMC was reported as detected (no concentration) with another cathinone, 4-methyl-*N*-ethylpentedrone ((2-(ethylamino)-1-(4-methylphenyl)pentan-1-one)). The femoral blood concentration was reported to be 0.93 mg/L. No more details were available, and a causal relationship "could not be established". Seven cases involved detection of additional substances *(45).*

The EMCDDA risk assessment of 3-MMC included a total of 14 acute poisonings with confirmed exposure to 3-MMC (most considered to be non-fatal) reported from France (6), the Netherlands (6), Germany (1) and Spain (1). Exposure to other substances was reported in seven cases, including central nervous system depressants and central nervous system stimulants. It was not known whether the remaining seven cases represented mono-intoxications. It was reported that four of the cases were considered life-threatening (required admission to intensive care or involved a life-threatening condition such as respiratory arrest or coma). The EMCDDA also received reports on 192 cases of suspected exposure to 3-MMC from five Member States, although no analytical confirmation was available at the time *(45).*

Twenty-seven deaths with confirmed exposure to 3-MMC were reported from Sweden (nine), the Netherlands (eight), France (six), Spain (three) and Slovenia (one). The information indicated that 21 of these cases occurred between 2013 and 2021: seven in 2013, three in 2016, five in 2019, five in 2020 and one in 2021. In the 13 cases in which information was available, 12 were in males and 1 in a female. Age was reported for seven men aged 22–46 (mean, 29; median, 27). In at least eight cases, 3-MMC was reported to be the cause of or to have contributed to the death. Eighteen of the cases were reported as either mixed poisonings or with other substances identified in biological samples; no information on the remaining nine cases was available. Other substances were identified in biological samples (seven cases), and other substances were involved in six cases. Mixed intoxications with no information on substances were reported for the five remaining cases. Individuals were found dead in three cases, and the deaths were related to sexual practices (chemsex, intentional sex under the influence of psychoactive drugs, mostly among men who have sex with men) *(3)*. Some of these cases have also been published in the scientific literature (see below).

Scientific literature: non-fatal cases

Over 400 detections of 3-MMC (including DUID and non-fatal intoxications) have been described in the scientific literature since 2013. In the majority of cases, other substances have been detected, and some cases were reported or reviewed more than once. Over 100 of the cases were reported to involve ingestion of 3-MMC alone (and self-reported ingestion without analytical confirmation). In most cases, the reported clinical features were consistent with sympathomimetic toxicity, including tachycardia, agitation, aggression, hypertension, hallucinations and increased creatine phosphokinase levels (rhabdomyolysis and/or kidney failure).

Between August 2012 and March 2014, 50 of 786 cases of suspected NPS intoxications in Sweden were found to involve 3-MMC *(19)*. Exposure to 3-MMC was confirmed in 49 blood (serum) and 35 urine samples obtained from 50 (38 male and 12 female) patients. In 34 cases (68%), both blood and urine samples were available, and 3-MMC could be detected in both matrices. The age range of the 3-MMC-positive patients was 17–49 years (median, 24; mean, 25.5 years). The 3-MMC concentrations were between 0.002 and 1.49 µg/mL in serum (median, 0.091 µg/mL) and between 0.007 and 290 µg/mL in urine (median: 3.05 µg/mL). Mono-intoxication was found in only four cases (8%). Thus, 27 NPS other than 3-MMC were detected in this subgroup, although two deaths occurred with 3-MMC alone *(19)* (see below).

The main clinical features reported in patients who tested positive for 3-MMC included tachycardia (≥ 100/min) and hypertension (systolic blood pressure, ≥ 140 mm Hg), which were documented in 24 (48%) and 19 (38%) cases, respectively. Furthermore, severe hypertension (systolic blood pressure, ≥ 160 mm Hg) and severe tachycardia (≥ 140/min) were observed separately in five cases each. Other features included hyperthermia (> 39 °C, 6%), seizures (8%), diaphoresis (12%), dilated pupils (24%) and agitation (44%). In 16 patients (32%), a reduced level of consciousness (Glasgow coma scale < 15) was observed, although it was considered that causes other than a direct effect of 3-MMC were present in all cases, including circulatory arrest (2%), postictal state (6%), ethanol (14%), central nervous system-depressing substances (20%) and co-exposure to benzodiazepines (22%). Significant chest pain was not documented in any of the cases *(19).*

In Slovenia, seven patients were treated for poisoning with 3-MMC in 2013 and 2014. The most common clinical features reported were tachycardia, hypertension and psychological effects such as disturbed perception of surroundings, confusion and restlessness. Treatment was symptomatic, mainly with diazepam. Ingestion of ethanol (three cases) and amphetamines (two cases) was also mentioned *(28).*

A 34-year old man was involved in a traffic accident and then found sleeping in his car *(46)*. The observed clinical features included glassy and narrow pupils, reddened eyes, disorientation, "washed-out" pronunciation, impaired balance, coordination and fine motor skills, delayed reaction time and deficient concentration. He was treated with methadone. A blood sample taken 8 h later revealed the methadone (127 ng/mL), its metabolite thylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (6.0 ng/mL), lorazepam (25.4 ng/mL) and 3-MMC (35.6 ng/mL) in serum *(47).*

A review of blood concentrations in 95 cases in which 3-MMC was detected between 2013 and mid-2015 (5200 samples overall) in Poland *(29)* showed that most cases positive for 3-MMC were cases of DUID (66) and traffic accidents (4). The remaining six cases involved intoxication, including fatal poisoning (5), drug possession (9) and 10 others (violence, theft, rape and kidnapping). In 76 of the 95 cases, 3-MMC was not the only substance detected. 3-MMC concentrations ranged from traces (< 1 ng/mL) up to 1.6 µg/mL (mean concentration, 51.3 ng/mL; median, 18.5 ng/mL). The concentrations grouped by type of incident were 1–171 ng/mL (driving DUID), < 1–29 ng/mL (traffic accidents), 2–408 ng/mL (drug possession), < 1–1600 ng/mL (intoxication) and < 1–61 ng/mL (others, including violence, theft, rape and kidnapping). One example was provided in which 3-MMC was detected in the blood of a male patient (21 ng/mL) with benzoylecgonine (58 ng/mL), although no further information was presented. In 19 DUID cases, 3-MMC was the only substance detected. Interestingly, clinical features were found in only six cases, which included uncoordinated movements, tachycardia (100 bpm), aggression, agitation, stuttering, fatigue, verbosity and gaiety. In one non-fatal case in a male subject (no details available), the authors reported blood concentrations of 21 ng/mL 3-MMC and 58 ng/mL benzoylecgonine *(29)*.

In a review of the detection of 3-MMC in biofluids in the cases in Poland described above, Adamowicz et al. *(48)* reported that, in the period 2012–2014, 112 of 1058 samples were found to contain NPS. Of these, 50 contained 3-MMC, with blood concentrations between 1 and 1600 ng/mL (mean, 96; median, 13). As described previously, the observed effects included uncoordinated movements, aggression, agitation, stuttering, verbosity and gaiety. Other drugs were commonly present.

In France, five patients were hospitalized after ingestion of NPS. 3-MMC was stated to have been involved in three cases. The clinical features were reported to include hallucinations (n = 3), agitation (n = 3), tachycardia (n = 3), arterial hypertension (n = 3) and a poison severity score (PSS) of 1 or 2. Symptomatic treatment included sedation in four cases, but all resolved favourably. 3-MMC was detected in three cases: (i) a woman aged 23 years: PSS, 2; 304 µg/L 3-MMC in plasma; methadone, citalopram and possibly 1-(benzofuran-5-yl)-*N*-methylpropan-2-amine (5-MAPB) also detected; (ii) a 36-year-old man, ~7 µg/L 3-MMC in plasma, 2370 µg/L in urine; and (iii) a 19-year-old man, 220 µg/L 3-MMC in whole blood, not detected in urine *(34).*

In a follow-up publication from France of six intoxications with 3-MMC *(49),* additional information was provided for some of the cases. A woman aged 22 years who showed confusion, somnolence, myosis, Glasgow Coma Scale = 10 and PSS = 2, was found to have 300 µg/L 3-MMC, 20 µg/L 5-MAPB and 100 µg/L methadone in plasma. In a 35-year-old man, intravenous use resulted in agitation, hypertension, chest pain and tachycardia, PSS = 2 and detection of 7 µg/L 3-MMC in plasma and 2370 µg/L in urine. A 29-year-old man experienced hallucinations and tachycardia (PSS = 2), with detection of 220 µg/L 3-MMC in whole blood and an estimated concentration of 2 µg/L 5F-AKB48 in plasma. A 23-year-old man experienced seizures, with a Glasgow Coma Scale = 3. His plasma contained 3-MMC (1600 µg/L), 4-methylethcathinone (890 µg/L) and methoxetamine (1180 µg/L) and his urine 3-MMC (141 000 µg/L), 4-methylethcathinone (61 000 µg/L) and methoxetamine (39 000 µg/L). A 37-year-old man with a PSS = 2 showed agitation, mydriasis and tachycardia. His plasma contained 3-MMC (60 µg/L), 4-methylethcathinone (240 µg/L), methoxetamine (10 µg/L) and MDMA (110 µg/L), and his urine contained 3-MMC (13 000 µg/L), 4-methylethcathinone (85 000 µg/L), methoxetamine (930 µg/L), MDMA (5,600 µg/L) and MDA (320 µg/L). A 30-year-old man presented with coma, myosis,

bradypnoea, Glasgow Coma Scale = 3–5 and PSS = 3. Plasma contained 3-MMC (150 µg/L) and GHB (200 000 µg/L), while urine contained 3-MMC (41 600 µg/L) and GHB (685 000 µg/L) *(49)*.

In Germany in 2014, a 26-yearold woman who was DUID ("conspicuous way of driving") was reported to have pupil abnormalities (slow reaction to light), gazing and appeared to be depressed. The blood concentration of 3-MMC in a blood sample taken 1 h and 10 min after the incident was 39.9 ng/mL. No other substances were detected *(46).*

A retrospective single-centre study was conducted between January 2010 and January 2016 of 81 patients being treated for acute cathinone intoxication and complications of cathinone use *(50)*. In 10 cases reported between 2014 and 2015, 3-MMC was the sole substance.; additional substances were ingested in three other cases. The reported clinical features included hypertension, tachycardia and increased creatine phosphokinase levels.

A series of cases of intoxication in Poland involved predominantly 4-chloromethcathinone. One DUID case also included detection of amphetamine (15 ng/mL), 3-MMC (450 ng/mL) and THC-COOH (8 ng/mL), in addition to 4-chlorormethcathinone (25.4 ng/mL). The case involved a male of unknown age who was reported to have had slurred speech and red eyes and face. No further information was available *(51)*.

Two non-fatal cases were described in France. One involved a 33-year-old man who was found wandering the streets 24 h after killing his wife and his 2-year-old daughter in an outburst of violence. A blood sample was collected immediately, and chest hair was collected 1 month later. 3-MMC was detected in blood at a concentration of 3 ng/mL; THC (0.5 ng/mL) and THC-COOH (14 ng/mL) were also detected. Hair analysis revealed 3-MMC (14 pg/mg), methoxamine (260 pg/mg), ethylphenidate (41 pg/mg), THC (2229 pg/mg), cocaine (193 pg/mg), pholcodine (239 pg/mg) and zopiclone (416 pg/mg). In the second case, a 31-year-old man was found unconscious, with partial body paralysis and obstruction of one or more coronary arteries. The man was known to engage in drug consumption in the context of sexual activity (chemsex). Blood analysis revealed 3-MMC (392 ng/mL), 4-methylethcathinone (4.5 ng/mL), GHB (234 mg/L), nordiazepam (199 ng/mL), oxazepam (26 ng/mL) and bromazepam (149 ng/mL) *(52)*.

In a review of presentations to emergency departments in Europe between January 2014 and December 2017 for seizures associated with recreational substance use, 1013 of 23 947 cases involved seizures. Of 25 cases involving 3-MMC ingestion, four presented with seizures. The authors concluded that ingestion of 3-MMC was significantly associated with the likelihood of seizures. It was not stated whether 3-MMC was the only substance ingested *(53).*

Several non-fatal intoxications have been reported in France with detection of 3-MMC and other substances, especially GHB, in the context of drug consumption, including by injection, and sexual activity (chemsex and slamsex) *(54–56).* 3-MMC was reported to be one of the most common substances associated with slamsex in France *(57, 58)* (see also section 14).

A 40-year-old man being treated for HIV and a history of substance use, including intravenous use predominantly of GHB and cocaine, and psychiatric treatment, was admitted to intensive care for a reduced state of consciousness (Glasgow Coma Scale = 3), bradypnoea with episodes of apnoea and bilateral miosis. Urine analysis revealed 3-MMC, 4-methylethcathinone and cocaine metabolites. Serum analyses established a GHB concentration of 301 mg/L. No further details were reported *(55)*.

A 35-year-old man was admitted to hospital after having ingested two glasses of alcohol and 3-MMC intranasally. He presented with hallucinations, vomiting and then lost consciousness (blood pressure, 194/91 mm Hg; heart rate, 81 bpm, with no chest pain). Hyperthermia was not noted, and blood sugar was 1.10 g/L. An electrocardiogram showed elevated ST segment in the anterior territory. On admission, the following laboratory values were found: creatinine phosphokinase, 671 IU/L (normal,

0–195 IU/L); myoglobin, 105.8 µg/L (normal, < 90 µg/L); and troponin T-HS, 9.5 ng/L (normal, < 34.2 ng/L). Transthoracic echocardiography showed a normal left ventricular ejection fraction, with no disruption of segmental kinetics or pericardial effusion. The patient was discharged with a prescription for a cardiac examination. Urine screening was negative for amphetamines, cocaine, opiates, methadone and natural cannabinoids but positive for ethanol (0.2 g/L). 3-MMC was detected in urine but was not quantified *(56).*

A 31-year-old man who confirmed injection of 3-MMC and consumption of GHB but with no known medical history was admitted to hospital with severely impaired consciousness. The Glasgow Coma Scale score was 3, and he exhibited hypothermia (< 35 °C). His pupils reacted normally to light and were of regular width. No other clinical observations were made, and his electrocardiogram was unremarkable. Apart from polynuclear neutrophilic leukocytosis (12 G/L), the results of standard clinical laboratory tests were also unremarkable. The patient was intubated and mechanically ventilated and recovered after several hours. Analysis of biofluids confirmed the presence of 3-MMC (177 ng/mL and 22 000 ng/mL in blood and urine, respectively) and GHB (131 mg/L and 2000 mg/L in blood and urine, respectively) *(54)*.

A review of toxicological analyses carried out in Poland between 2013 and 2019 included 57 cases (39 fatal and 18 non-fatal) involving use of synthetic cathinones *(2).* 3-MMC was identified in six non-fatal cases, predominantly DUID, between 2013 and 2014 (Table 3). The concentrations of 3-MMC in the DUID cases ranged from 12 to 344 ng/mL (mean, 226 ng/mL; median, 267 ng/mL).

Table 3. **Case reports of non-fatal intoxications associated with 3-MMC in Poland**

Sex/age	Comments	3-MMC in blood (ng/mL)
M/41	Man holding a hostage	311
M/unknown	Roadside check; taken a powder labelled “MCH”	12
M/20	Driver; dilated pupils and weak pupillary light reflex noted	293
M/29	Driver; regular pulse, normal pupils and normal pupillary light reflex noted	240
M/25	Driver; regular pulse and rowdy mood noted	344
M/34	Driver; regular pulse, normal pupils, normal pupillary light reflex, positive Romberg test and positive finger–nose test	155

Reviewed by Pieprzyca et al. *(2)*. No other drugs were detected.

A 60-year-old man was admitted to hospital with acute kidney injury considered to represent a combination of rhabdomyolysis and pre-renal injury due to existing stage-III chronic kidney disease and 3-MMC use. The patient reported consumption of 3-MMC, but confirmation by biofluid analysis was not reported *(59).*

In the Netherlands, where increased popularity and use of 3-MMC were observed among certain sectors of the population (e.g., “clubbers”), 3-MMC poisonings reported to the Dutch Poisons Information Centre were reviewed *(21).* A telephone service was provided for health-care professionals responding to poisoning cases, so that information obtained from patients on their substance use was based of self-reports and confirmation by analysis of biofluids was usually not available. A total of 184 poisonings involving 3-MMC (with and without relevant concomitant exposure to other substances) were reported between January 2013 and June 2021. Of these, 84 acute poisonings involved self-reported use of 3-MMC only. The reported sympathomimetic effects included agitation (n = 16, 19%), hypertension (n = 17, 20%) and tachycardia (n = 29, 35%). In most

patients, initial PSS (information provided during consultations at the Dutch Poisons Information Centre) was minor (n = 37, 44%) to moderate (n = 39, 46%). Severe poisoning (repeated convulsions [n = 1], ventricular fibrillation followed by cardiac arrest [n = 1] and hypertension [systolic blood pressure > 180 mm Hg; n = 3] was observed in five patients during initial consultations. Eight of 16 patients who reported use of 3-MMC only between January 2016 and June 2019 were followed up in a prospective study. The sympathomimetic symptoms included tachycardia, hypertension, chest pain, agitation and perspiration. In one case, the presence of 3-MMC was confirmed in blood at 172 ng/mL after self-reported injection of a solution containing 4500 mg 3-MMC. The PSS was severe, and the clinical features reported were mydriasis, dry mouth, throat and nose, perspiration, tachypnoea (40/min), hypertension (210/142 mm Hg), electrocardiographic abnormalities (prolonged QRS, 110 ms and prolonged QTc, 474 ms), tachycardia (123 bpm), chest pain, anxiety and agitation *(21).* In one case, 3- and 4-MMC could not be differentiated (2-MMC was not mentioned). One of the cases was followed up outside the prospective cohort study, and blood was found to be positive for 3-MMC and caffeine (no concentrations given). After ingestion of an unknown amount of suspected 3-MMC powder, the patient reported tachycardia (120 bpm), agitation, hyperthermia (38.3 °C), ventricular fibrillation and cardiac arrest in the ambulance. The poisoning was considered severe. The authors stated that the effects of 3-MMC poisoning appear to be short-lived (≤ 24 h), although severe adverse effects and complications of injection can prolong hospitalization *(21).*

In a qualitative study of the prevalence of visual disturbances after substance use ("visual snow"), 1 of 24 participants identified 3-MMC as a trigger. No more information on substance use was available, and it was not possible to determine whether other substances were involved in the episode thought to have triggered this condition *(60).*

Since 2013, 34 deaths in which 3-MMC was detected have been identified in the scientific literature (Table 4). Poly-drug use was found in the majority of cases (including psychostimulants and central nervous system depressants such as alcohol and GHB). Some cases were reported more than once, and some may also have been reported to the EMCDDA. In eight cases, either no other substance was detected or the authors established accidental intoxication with 3-MMC as the cause of death. Three other fatal 3-MMC poisonings involved suicides (two by hanging). Some of these deaths were related to acute 3-MMC intoxication in the context of chemsex practices. Overall, the descriptions included acute circulatory and respiratory failure, deteriorating neurological condition (cerebral oedema consistent with global anoxic brain injury) and cardiac complications.

Table 4. **Cases of fatal intoxication with detection of 3-MMC and other substances**

Year published	Sex/age (years)[a]	Comments	Reference no.
2014	M/20	Estimated ingestion of about 500 mg 3-MMC and 400 mg 5-APB with 250 mL vodka (40% v/v). Clinical features included hyperthermia, tachycardia, hypertension, bradycardia and seizures; patient died about 4 h after substance use. Cause of death: acute cardiovascular collapse after mixed intoxication with NPS and alcohol. Post-mortem blood concentrations of 1600 ng/mL 3-MMC and 5600 ng/mL 5-APB. Serum alcohol concentration was 1.4 g/L in an ante-mortem sample collected 1 h after admission to the hospital.	*61*
2014	U/U	No specific information reported. Detection of AH-7921 (0.35 µg/g, femoral blood), 3-MMC and buprenorphine (matrix and concentrations not reported).	*62*

2014	U/U	No specific information reported. Deceased was treated in intensive care. Detection of AH-7921 in hair (0.35 µg/g) and femoral blood and 3-MMC (matrix and concentration not reported).	*62*
2014	M/23	No specific information reported; deceased bought the substances on the Internet. Peripheral blood contained AH-7921 (0.43 mg/L), codeine (1.4 µmol/L), 2-FMA (0.041 µmol/L), paracetamol (124 µmol/L) and 3-MMC (0.012 µmol/L). This may be the same case reported by Karinen et al. *(63)*.	*62*
2014	M/20s	Prescribed 400 mg acetaminophen and 30 mg codeine after a minor accident. Ingested powders labelled "3-MMC" and "4-FMA." The decedent fell asleep and died shortly thereafter. Apart from oedematous lungs (weight, 2080 g), no other findings were made at autopsy. Peripheral whole blood analysis showed AH-7921 (0.43 mg/L), codeine (0.42 mg/L), codeine-6-glucuronide (0.77 mg/L), acetaminophen (19 mg/L), 2-FMA (0.0069 mg/L) and 3-MMC (0.0021 mg/L). The cause of death was reported to be intoxication with AH-7921 and other psychoactive substances.	*63*
2014	M/25	Found unresponsive in his room. Autopsy revealed acute bronchitis, pneumonia, brain and lung oedema (weight of lungs, 1256 g) and pulmonary congestion. Drugs detected in femoral blood: AH-7921 (0.35 µg/g) and 3-MMC (no concentration given). Cause of death ruled to be intoxication and the manner of death to be accidental.	*64*
2015	U/U	Ingestion of amphetamine with 3-MMC. Brought to hospital in circulatory arrest. No further information reported.	*19*
2015	M/25	Man with a history of alcohol and amphetamine use and chronic hepatitis C infection was found unresponsive and reported to have taken 3-MMC the previous evening. Was unconscious and wheezing, tachypnoic and cyanotic; systolic blood pressure was 75 mm Hg, and he was tachycardic. A seizure that occurred during transport was treated with diazepam. In hospital, the patient was unconscious (body temperature, 39 °C) and hypotensive (80/40 mm Hg), tachycardic (140/min) and with a respiratory rate of 36/min. During oxygen supplementation, his oxygen saturation was 96%; he also had metabolic acidosis. After treatment with naloxone and flumazenil, his condition remained unchanged; he was intubated and placed on a ventilator. He remained hyperthermic despite sedation, external cooling and administration of cold fluids, and his body temperature peaked at 40.9 °C 20 h after admission. His neurological condition deteriorated, and further examination showed generalized cerebral oedema consistent with a global anoxic brain injury. Patient died 6 days after admission. Blood and urine samples were collected in hospital on the second day, and 3-MMC was found at 2 ng/mL in serum and 85 ng/mL in urine. Other substances detected in urine at low concentrations were buprenorphine, conjugated ethanol metabolites (ethyl glucuronide and ethyl sulfate) and diazepam (probably treatment-related). No other substances were reported.	*19*
2015	U/U	3-MMC was detected in post-mortem blood at a concentration of 4.4 mg/L (no further details reported).	Rojek et al. cited in *31*
2016	M/U	Patient ingested 3-MMC and collapsed; taken to hospital and died the following day. 3-MMC concentration, < 1 ng/mL; MDMA, 33 ng/mL. The authors suggested that the long delay between ingestion and death, the	*29*

		emergency procedures performed and the short half-life of 3-MMC might explain the low concentration.	
2016	U/U	3-MMC (22 ng/mL) and 5-APB (146 ng/mL) detected. A medicinal product containing potassium chloride was found near the cadaver (concentration in stomach, 3.4 mg/g). No further details were provided.	*29*
2016	M/U	Had used 3-MMC and 25I-NBOMe. Blood concentrations were 11 and 3 ng/mL. Reported to have taken "legal highs". The cause of death was ruled as acute respiratory failure caused by pneumonia, which occurred during septic shock, followed by multiple organ failure.	*29*
2016	M/U	Individual found dead. 3-MMC (3 ng/mL) detected in conjunction with tramadol at a therapeutic concentration (563 ng/mL). No further details were reported.	*29*
2016	M/30s	Died after consumption of a white powder (no further information provided). Blood contained 3-MMC (78.8 ng/mL), 4-methylethcathinone (124 ng/mL), paracetamol (0.12 µg/mL), paroxetine (0.12 µg/mL), sildenafil (76.4 ng/mL) and ethanol (0.18 g/L). 3-MMC was also detected in cardiac blood, urine, bile and vitreous humour. The authors concluded that death was due to acute intoxication involving 3-MMC.	*65*
2016	M/30s	Died after consumption of a white powder (no further information provided). 3-MMC was detected at 249 ng/mL in peripheral blood and in cardiac blood, urine, bile and vitreous humour. Detection of other substances was not reported. The authors concluded that death was due to acute intoxication involving 3-MMC.	*65*
2016	M/69	While attending a party, the patient vomited and developed cardiopulmonary arrest. 3-MMC and "poppers" (alkyl nitrites) were found at the scene. Peripheral blood analysis showed the presence of 3-MMC (0.33 mg/L), pseudoephedrine (0.03 mg/L) and GHB (576 mg/L). These drugs were also detected in hair, gastric content, bile, urine and cardiac blood.	*31*
2016	U/U	In a fatal case in 2013 due to hanging, 3-MMC was detected (1.1 mg/L) in post-mortem femoral blood, with venlafaxine (1.62 mg/L) and *O*-desmethylvenlafaxine (2.77 mg/L).	Elliott, cited in reference *9*
2017	M/32	Found dead at home after ingesting white powder intranasally (also known history of GHB consumption). He suffered from headache and warm sensations, lay down and was found dead in the morning. Autopsy revealed no obvious cause of death. Toxicological analysis showed the presence of 3-MMC in various tissues (ng/mL): peripheral blood (249); cardiac blood (609), vitreous humour (2988), bile (1291) and urine (29 694). Cause of death: intoxication; manner of death: accidental. This case may be one of those reported previously *(65).* No other substances were reported. Analysis of the powdered samples confirmed the presence of 3-MMC.	*66*
2017	U/U	Patient required cardiopulmonary resuscitation by paramedics for cardiac arrest after ingestion of 3-MMC, which was successful; however, cerebral oedema and brain death subsequently ensued. 3-MMC was detected in the patient's urine (no further information reported). Detection of other substances was not reported.	*50*
2019	M/38	Found dead at home with no evidence of violence or traumatic lesions. Femoral blood analysis showed 3-MMC (613 ng/mL), amphetamine (938	*52*

		ng/mL) and GHB (154 mg/L). Hair analysis showed 3-MMC (17 100 pg/mg) and amphetamine (14 800 pg/mg). The same case was briefly summarized by Ameline et al. *(30).*	
2019	M/50	Found deceased by hanging in a "swinger's" nightclub; known to participate in chemsex practices. 3-MMC detected in cardiac blood (462 ng/mL), with methoxamine (70 ng/mL), nordiazepam (< 10 ng/mL) and bromazepam (< 10 ng/mL). The same case was summarized by Ameline et al. *(30)*.	*52*
2019	F/19	Subject was found dead in the woods after a quarrel with her boyfriend by telephone, when she suggested committing suicide and appeared agitated and confused. 3-MMC was determined in blood (800 ng/mL), vitreous humour (150 ng/mL). and total stomach contents (5.5 mg). Forensic pathologist excluded any cause of death other than poisoning. Detection of other substances was not reported.	*67*
2020	M/49	Committed suicide by hanging. 3-MMC detected in femoral blood (49 ng/mL), cardiac blood (53 ng/mL), urine (310 ng/mL), stomach contents (74 ng/mL) and bile (205 ng/mL). Traces of diazepam and nordiazepam were also detected. Analysis of pubic hair showed 12 pg/mg MDMA, 4 pg/mg 3-MMC and 28 pg/mg buphedrone. The authors suggested that the 3-MMC concentrations might have been underestimated because of the chemical instability of the drug.	*68*
2020	U/U	Three unpublished cases of fatal intoxications involving 3-MMC (no information provided) at the university hospital in Lille, France.	*69*
2021	F/34	Found dead, apparently under the influence of drugs. Before death, she was agitated, shivering and nervous, and her speech was slurred; she had a history of drug and alcohol dependence. The concentrations of 3-MMC were 391 ng/mL in blood and 64 ng/mL in urine., and those of alcohol were 0.3 mg/mL in blood and 0.6 mg/mL in urine. The cause of death was stated as acute circulatory and respiratory failure after intoxication. Detection of other substances was not reported.	*2*
2021	M/U	Found dead, with needles, a syringe with a depressed plunger, small plastic bags labelled "ruby sand additive 0.5 gram – product imitation", small empty resealable bags with traces of colourless liquid and empty mineral water bottles. Man had a history of using "legal highs", amphetamine and cannabis in the form of smoking mixtures, powders and tablets; he was also allegedly taking steroids. The biofluid concentrations of 3-MMC were 5310 ng/mL in blood (concentration range: 391–5310 ng/mL; mean: 2691 ng/mL; median: 2531 ng/mL) and 1361 ng/mL in urine, and that of amphetamine was 1990 ng/mL in urine. The cause of death was recorded as acute circulatory and respiratory failure after intoxication.	*2*
2021	F/28	Died after taking about 0.4 g 3-MMC crystals dissolved in water, had sex with partner and then had convulsions, nose bleed and loss of consciousness. Had treatment of migraine with hydroxyzine, ketoprofen and other custom-made medicines. Biofluid concentrations of 3-MMC were 3352 ng/mL in blood and 748 ng/mL in vitreous humour; those of caffeine were 300 ng/mL in blood and 100 ng/mL in vitreous humour; and that of codeine was 6 ng/mL in vitreous humour. The cause of death was acute circulatory and respiratory failure after intoxication.	*2*

2021	M/52	The corpse was found without hands and wrists due to "activity of animals". Blood contained 1710 ng/mL 3-MMC, 20 ng/mL diazepam and 6 ng/mL nordiazepam. Cause of death was recorded as acute circulatory and respiratory failure after intoxication in a person with AIDS and pneumonia.	*2*
2022	M/59	Subject found dead at home in a corridor, naked, wearing a black hood and a collar around his neck with a dog leash attached. He had piercings on the testicles and nipples. Several electrodes were posed along the penis and connected to a stimulator and battery. An empty 1-mL syringe was found in a rectal vein on the right of the buttock, which had contained 3-MMC. The femoral blood and urine concentrations of 3-MMC were 1437 and 16 733 ng/mL, respectively. Detection of other xenobiotics was not reported. The cause of death was ruled to be acute 3-MMC poisoning in the context of chemsex.	*20*
2022	55/U	Death stated to be directly related to consumption of 3-MMC during chemsex (no details provided). The concentration of 3-MMC in blood was reported to be 5480 µg/L, and "poppers" were also reported (39% in methaemoglobin).	*70*
2022	54/U	The death was stated to be directly related to consumption of 3-MMC during chemsex (no details provided). The concentration of 3-MMC in blood was reported to be 12 µg/L, and mexedrone was also detected.	*70*
2022	M/55	A man who had sex with men was found dead after a chemsex party with 32 stab wounds. His medical history included cardiovascular disorders treated with amlodipine, valsartan and hydrochlorothiazide. He occasionally took benzodiazepines. Femoral blood contained MXP (606 µg/L) and traces of lidocaine. Urine contained 3-MMC (238 µg/L), MXP (1066 µg/L), lidocaine (traces), valsartan (traces) and oxazepam (750 µg/L); hair contained 3-MMC (< 0.25 ng/mg) and diphenidine (0.25 ng/mg). Two syringes were found to contain 3-MMC and MXP, and one syringe contained diphenidine. The cause of death was ruled as homicide due to stabbing.	*71*

[a] U, unknown or not reported

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

In studies of locomotor activity in adult male Sprague-Dawley rats (280–300 g), 3-MMC (3 mg/kg intraperitoneally) and methamphetamine (1 mg/kg intraperitoneally) increased the

total distance travelled. When compared with saline, 3-MMC increased activity by 5–30 min and 95–100 min, whereas methamphetamine increased locomotor activity by 5–120 min *(41)*.

In the elevated plus maze test, a single intraperitoneal administration of 3-MMC at a dose of 1, 3, 5 or 10 mg/kg increased the time spent in the open arm at 3 mg/kg, consistent with anxiolytic behaviour. After chronic administration (7 days; 3 mg/kg), the time spent in the open arms was shorter than with saline and methamphetamine, which the authors interpreted as increased anxiety-like behaviour. Acute and chronic administration of methamphetamine (1 mg/kg) showed no significant effect *(41)*.

3-MMC (3 and 10 mg/kg; intraperitoneally) induced conditioned place preference in adult male Sprague-Dawley rats (280–300 g; 8 days of training and tests on day 9), and the conditioned place preference score recorded for the 10-mg/kg dose of 3-MMC was comparable to that of methamphetamine at 1 mg/kg. 3-MMC at 1 mg/kg had no effect *(41)*.

B. Studies in humans

No information was found.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

No information was found on established uses; however, some patent applications include use of 3-MMC in psychotherapeutic interventions *(25)*. 3-MMC has also been proposed for enhancing the acute emotional effects of LSD, psilocybin and other psychedelics *(72)*. Another patent application suggests its use in the treatment of menstrual cycle-induced disorders and symptoms *(26).* No current clinical trials were identified on therapeutic use of 3-MMC.

10. Listing on the WHO Model Lists of Essential Medicines

3-MMC is not listed on the 22nd WHO Essential Medicines List or the 8th WHO Essential Medicines List for Children.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No recorded industrial use was identified.

13. Non-medical use, abuse and dependence

No epidemiological evidence on use of 3-MMC in household surveys was found; however, some information is available from targeted surveys of specific populations, such as users of recreational substances and men who have sex with men who use substances in the context of chemsex or slamsex and from cases of fatal and non-fatal intoxication involving 3-MMC (section 6).

Blood and urine samples were collected from people prosecuted for use of illicit and/or designer drugs in a study in Hungary. Thus, 2744 suspected substance users were sampled in Budapest

between July 2012 and June 2013, and 774 people were sampled in south-east Hungary during 2012 and 2013 *(73)*. Nineteen positive samples (0.97%) were identified in Budapest and 24 positive samples (5.07%) in south-east Hungary. All cases were detected in combination with other substances, including pentedrone, benzodiazepines, amphetamine and THC *(73).*

Over 5 months in Slovenia in 2014, 249 people who currently or previously reported NPS use completed an online survey. The study also included preliminary results obtained from in-depth interviews about drug markets conducted with 26 people who used NPS *(1)*. The results showed that 169 (67.9%) respondents had tried 3-MMC, whereas 35 (14.1%) had used it > 40 times, which was the highest share of frequent users of all NPS. More than one fourth (26.8%) confirmed use for more than 1 year, and one third confirmed use in the past month (n = 168). Over 28% of 3-MMC users had used it once or twice, whereas 20.7% (n = 169) stated that they had used it 40 times or more. The author stated that 3-MMC is used in nightlife settings, open public places and chemsex parties *(1)*.

In a qualitative follow-up study in Slovenia between December 2013 and October 2014, 19 interviews were conducted with 25 individuals on their experiences of NPS use *(24)*. 3-MMC was reported to be the most common drug of choice. Participants reported a wide range of frequencies of use, with some reporting use every weekend and others stating use once every fortnight or every few months; others reported use only on special occasions. Binge use of 3-MMC for several days was reported, with the amount consumed exceeding the amount originally planned. Younger people reported ready access to 3-MMC, whereas older people reported that it was easier to obtain conventional drugs. One participant reported having experienced withdrawal symptoms while trying to abstain from 3-MMC after more than 1 year of daily use. The reported symptoms included sleep paralysis, “brain zaps”, anxiety, insomnia and depression *(24)*.

In a retrospective analysis of 81 cases of intoxications with confirmed use of synthetic cathinones between January 2010 and January 2016 in southern Germany, 13 cases occurring in 2014 and 2015 involved detection of 3-MMC, either alone or in combination with other substances. The clinical features included hypertension and elevated creatine phosphokinase concentration *(50)*.

An Internet-based survey of German-speaking people who reported use of “bath salts” was conducted between June 2016 and January 2017. Of 96 respondents, 48 (50%) were familiar with 3-MMC, and 10 (10%) considered it to be their favourite cathinone; 50 (52%) cited methylenedioxypyrovalerone as their favourite *(74)*.

Two cases of substance dependence with confirmed exposure to 3-MMC were reported by one Member State to the EMCDDA in 2021. In one case, the patient reported injecting 3-MMC (slamming) and was hospitalized for withdrawal from 3-MMC and 4-fluoromethylphenidate. In the second case, 3-MeO-PCP and 2F-DCK were also detected in biological samples, and the patient confirmed experimenting with a range of NPS, frequently obtained from the Internet. The same Member State also informed the EMCDDA about three cases of substance dependence with suspected exposure to 3-MMC. In one case, a person was hospitalized for withdrawal from 3-MMC. The patient reported having switched from cocaine to 3-MMC because of the lower price of 3-MMC. The two other cases involved use of 3-MMC in in the context of chemsex and slamsex; in one case, the individual was hospitalized for withdrawal symptoms related to GBL use *(3)*.

Some evidence suggests that 3-MMC circulates at music festivals. In New Zealand, 47 submissions amounting to 305 samples of substances seized between December 2018 and March 2019 were analysed. Five capsules (average dose, 74 mg) containing 3-MMC were found *(75)*. In the United Kingdom, 377 samples considered to resemble MDMA-containing products were collected from music festivals in 2021. Synthetic cathinones were detected in 73 samples (19.4%), and 3-MMC was detected in 16 of 73 (21.9%) *(76)*.

In an analysis of the occurrence of 3-MMC in forensic drug samples, consumer drug samples and exposures reported to poisons centres between 2013 and 2017 in the Netherlands, increasing detections of 3-MMC were reported *(77)*.

According to reports received by the EMCDDA, the drug testing service, Welsh Emerging Drugs and Identification of Novel Substances, received 29 samples containing 3-MMC submitted between December 2014 and September 2021. In the majority of cases, 3-MMC was sold as another substance: 4-fluoroamphetamine (1), 3-fluorophenmetrazine (1), ketamine (1), cocaine (2), 2C-B (2), MDMA (6) or mephedrone (9). The effects reported by people who believed they had taken 3-MMC were in agreement with those reported for other synthetic cathinones and included agitation, increased energy, euphoria, chest pains, paranoia, confusion, visual hallucinations and irregular heartbeat *(3)*. One sample received in March was confirmed to contain this substance *(78)*. Drug testing services in Austria, the Netherlands, Switzerland and the USA reported detection of 3-MMC in at least 40 cases. The products were sometimes sold as 3-MMC *(79)*.

In a study of the detection of NPS in influent wastewater samples collected bimonthly between October 2017 and June 2018 and October 2019 and February 2020 in Australia, 3-MMC was detected once in one territory *(80)*. In a snapshot analysis of influent wastewater collected from 14 sites in eight countries during the New Year period of 2019–2020, 3-MMC was detected in three countries (Italy, the Netherlands and Spain) *(81)*. In an extended study, 144 influent wastewater samples were collected from 25 sites in 10 countries during the 2020−2021 New Year period. 3-MMC (together with eutylone) was detected most frequently and at the highest mass loads. Although methcathinone was detected in every country, this might have been due to oxidation of ephedrine or pseudoephedrine. 3-MMC was detected in three European countries and New Zealand *(82)*. 3-MMC is available in its own right and is advertised for sale by some Internet retailers.

See also Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

According to the EMCDDA, four Member States (Denmark, France, Hungary and Sweden) and Norway reported 45 cases of suspected DUID with confirmed exposure to 3-MMC, including four traffic accidents *(3)*. As described in section 6, 3-MMC has been detected in cases of DUID, in some cases with evidence of impairment. 3-MMC was commonly detected with other substances *(2, 46, 47, 51, 83, 84)*.

In a retrospective study of the numbers of self-reported 3-MMC poisonings to the Dutch Poisons Information Centre between 2013 and June 2021, the annual number increased from 1 in 2013 to 63 in 2020. The majority (n = 158, 86%) were reported after 2018, with 70 poisonings reported during the first half of 2021, which suggests increased use of 3-MMC in the Netherlands. 3-MMC was placed under national control in the country in October 2021 *(21)*.

According to the EMCDDA and the published literature cited below, the circumstances under which substances (including 3-MMC) are consumed should be considered to identify new patterns and settings. Those attracting increasing attention in the context of 3-MMC use are chemsex and slamsex. Most such cases have been reported by researchers in France (see also section 6). The health concern is not only poisoning due to overdosing via the intravenous route and infections associated with injection sites and extravasation but also co-administration of other drugs to enhance the user's experience. In addition, the risk of sexually transmitted diseases is increased, as the people who use substances such as 3-MMC in these contexts may engage in sexual behaviour that increases the risks

for transmission of HIV and hepatitis C virus. Furthermore, chemsex has been associated with a high risk of nonconsensual sex, anal and rectal trauma and penile abrasion *(85)*. Polydrug use has been reported to be common (including combinations with GHB and GBL), and 3-MMC is one of the commonly used synthetic cathinones in this context (see also section 6) *(3, 20, 54–56, 58, 69–71, 85, 86)*.

Information from drug testing services in Europe and the USA suggests that 3-MMC is present in products acquired or sold as other substances, including MDMA *(79)*. This suggests that people who use certain types of recreational drugs may be exposed unintentionally to 3-MMC, either alone or in combination with other substances, which might add additional risks of harm (e.g., potential exacerbation of a psychostimulant toxidrome).

Between 1 January 2012 and 28 September 2021, nine European Union Member States reported 672 samples containing 3-MMC to the EMCDDA: Spain (3), Belgium (3), Czechia (4), Portugal (8), Austria (20), Poland (40), Slovenia (52), France (99) and the Netherlands (443). Of these samples, 14 were collected in 2012, 35 in 2014, 28 in 2015, 25 in 2016, 72 in 2017, 101 in 2018, 133 in 2019, 166 in 2020 and 98 in 2021 (until October). The samples of 3-MMC were mostly in powder form (577), but tablets (36), capsules (28) and samples in liquid form (16) were also reported. Most of the samples (590) were collected by drug testing services but also by the Polish National Medicinal Institute (29) and by the Slovenian National Laboratory of Health, Environment and Food (23). In 628 cases (94%), 3-MMC was the only substance detected. It has been detected in combination with other substances an average of six times a year since 2015. In 2016, 3-MMC was detected in combination with other substances in 16 collected samples. Almost all contained “methylethcathinone” without specification of the isomer *(3)*.

See also Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

3-MMC is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use. Some Internet retailers advertise it for sale as a “research chemical”.

16. Illicit manufacture and traffic and related information

According to the EMCDDA *(3)*, a total of 9038 seizures were reported by 25 countries in Europe representing 2820 kg of the material in all its physical forms between 1 January 2012 and 8 October 2021, with 1930 kg between 2012 and 2019 and 747 kg (27% of all material seized) in 2020. In 2021, 138 kg were seized. Most of the seizures reported (n = 8343; 92%) were of powders, amounting to 2630 kg. Seizure of other forms was also reported: blotters (7), herbal material (16), liquids (33), other or unknown physical forms (79) and tablets and capsules (560 cases). As reported by the EMCDDA *(3)*, in a case reported by the Netherlands in 2019, approximately 350 kg of *N*-acetyl-3-MMC imported from India was seized, with 154 kg of 3-MMC at a “dealer/producer” site. *N*-Acetyl-3-MMC is an uncontrolled chemical that can readily be converted into 3-MMC (section 2D).

Information from law enforcement authorities suggests that at least 55 illicit cathinone laboratories have been dismantled in Europe since 2011. About 50% were seized between 2019 and 2021, indicating increasing interest in producing cathinones in Europe. Three sites were reported to be involved in the production of 3-MMC. One was seized in Slovakia (2013), and two were seized in the Netherlands (2017 and 2020). The laboratory in Slovakia was considered an operational site, whereas the Dutch sites were considered to be storage and packaging units. According to Europol, a number

of abandoned clandestine laboratories for the production of 3-MMC were seized in Slovakia in 2018. One site exploded due to “incompetent handling”, resulting in “environmental damage” *(3)*.

In a study in Italy, 479 drug samples suspected to contain NPS were found in 212 seized postal parcels collected between May and October 2020. Synthetic cathinones were found in 117 items (24.4%), 89 of which were attributed to 3-MMC, which was the predominant cathinone (76%) *(87)*. An analysis of samples seized in the Tuscany area (Italy) between 2006 and 2016 indicated that 3-MMC use emerged in Italy in 2015 *(88)*.

The numbers of countries that have reported detections of 3-MMC to the UNODC Early Warning Advisory on NPS database since its first detection were: three in 2012, 32 in 2013, 21 in 2014, 22 in 2015, 26 in 2016, 20 in 2017, 21 in 2018, 30 in 2019, 31 in 2020, 14 in 2021 and 2 so far in 2022. In some instances, several entries from the same country have been counted for the same year *(89)*.

3-MMC was first reported to the US National Forensic Laboratory Information System in 2012, and three reports were listed in 2021 (90).

See also Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

3-MMC is currently not controlled under the 1961, 1971 or 1988 United Nations conventions.

18. Current and past national controls

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

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

None.

References

1. Sande M, Characteristics of the use of 3-MMC and other new psychoactive drugs in Slovenia, and the perceived problems experienced by users. Int J Drug Policy. 2016;27:65–73 (doi: 10.1016/j.drugpo.2015.03.005).
2. Pieprzyca E, Skowronek R, Czekaj P. Toxicological analysis of intoxications with synthetic cathinones. J Anal Toxicol. 2022;46(7):705–11 (doi: 10.1093/jat/bkab102).
3. Report on the risk assessment of 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended). Risk assessments. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2022 (https://www.emcdda.europa.eu/system/files/publications/14507/Report on the risk assessment of 3-MMC.pdf, accessed 23 July 2022).
4. Power JD, McGlynn P, Clarke K, McDermott SD, Kavanagh P, O’Brien J. The analysis of substituted cathinones. Part 1: Chemical analysis of 2-, 3- and 4-methylmethcathinone. Forens Sci Int. 2011;212(1–3):6–12 (doi: 10.1016/j.forsciint.2011.04.020).

5. Blough BE, Decker AM, Landavazo A, Namjoshi OA, Partilla JS, Baumann MH et al. The dopamine, serotonin and norepinephrine releasing activities of a series of methcathinone analogs in male rat brain synaptosomes. Psychopharmacology. 2019;236(3):915–24 (doi: 10.1007/s00213-018-5063-9).
6. Walther D, Shalabi AR, Baumann MH, Glennon RA. Systematic structure–activity studies on selected 2-, 3-, and 4-monosubstituted synthetic methcathinone analogs as monoamine transporter releasing agents. ACS Chem Neurosci. 2019;10(1):740–5 (doi: 10.1021/acschemneuro.8b00524).
7. 3-Methylmethcathinone. Springfield (VA): Drug Enforcement Administration's Special Testing and Research Laboratory; 2013 (https://www.swgdrug.org/Monographs/3-MMC.pdf, accessed 25 July 2022).
8. 3-Methylmethcathinone (hydrochloride. Product Information. Item No. 11224. Ann Arbor (MI): Cayman Chemical Co.; 2022 (https://cdn.caymanchem.com/cdn/insert/11224.pdf, accessed 25 July 2022).
9. 3-Methylmethcathinone (3-MMC). Critical review report. Expert Committee on Drug Dependence, thirty-eighth Meeting. Geneva: World Health Organization; 2016
10. WHO Expert Committee on Drug Dependence. Thirty-eighth report. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/255046/9789241210140-eng.pdf?sequence=1&isAllowed=y, accessed 23 July 2022).
11. Bak A, Kozik V, Kozakiewicz D, Gajcy K, Strub DJ, Swietlicka A et al. Novel benzene-based carbamates for AChE/BChE inhibition: Synthesis and ligand/structure-oriented SAR study. Int J Mol Sci. 2019;20:1524 (doi: 10.3390/ijms20071524).
12. Sreenivas P, Srinivas K, Reddy GM, Gopikrishna G, Ravi L, Kumar VR et al. Improved processes for the preparation of cathinone derivatives. IN 202041032606A. Telangana: Keminntek Laboratories; 2022.
13. Risk assessment report on the new psychoactive substance 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) in accordance with Article 5c of Regulation (EC) No. 1920/2006 (as amended). Risk assessments. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2022 (https://www.emcdda.europa.eu/system/files/publications/14509/Report on the risk assessment of 3-CMC.pdf, accessed 26 July 2022).
14. Shimshoni JA, Britzi M, Sobol E, Willenz U, Nutt D, Edery N. 3-Methyl-methcathinone: Pharmacokinetic profile evaluation in pigs in relation to pharmacodynamics. J Psychopharmacol. 2015;29(6)734–3 (doi: 10.1177/0269881115576687).
15. 3-Methylmethcathinone (hydrochloride). Safety data sheet. Revision: 4 October 2018. Ann Arbor (MI): Cayman Chemical Co.; 2018 (https://cdn.caymanchem.com/cdn/msds/11224m.pdf, accessed 25 July 2022).
16. Green list. 32nd edition, 2021. List of psychotropic substances under international control. In accordance with the Convention on Psychotropic Substances of 1971. Vienna: International Narcotics Control Board; 2021 (https://www.incb.org/documents/Psychotropics/forms/greenlist/2021/Green_list_ENG_V21.pdf).
17. 3-Methylmethcathinone (hydrochloride). GC–MS data sheet. Ann Arbor (MI): Cayman Chemical Co.; 2012 (https://cdn.caymanchem.com/cdn/gcms/11224-0435099-GCMS.pdf, accessed 25 July 2022).
18. Chapman SJ (2018) Novel psychoactive spectra: NMR of (mostly) novel psychoactive substances. Isomer Design. 6 (https://doi.org/10.16889/isomerdesign-6, accessed 25 July 2022).
19. Bäckberg M, Lindeman E, Beck O, Helander A. Characteristics of analytically confirmed 3-MMC-related intoxications from the Swedish STRIDA project. Clin Toxicol. 2015;53(1):46–53 (doi: 10.3109/15563650.2014.981823).
20. Aknouche F, Ameline A, Gheddar L, Maruejouls C, Kintz P. Fatal rectal injection of 3-MMC in a sexual context. Toxicological investigations including metabolites identification using LC-HRMS. J Anal Toxicol. 2022 (doi: 10.1093/jat/bkac048).

21. Nugteren-van Lonkhuyzen JJ, Essink S, Rietjens SJ, Ohana D, de Lange DW, van Riel A et al. 3-Methylmethcathinone (3-MMC) poisonings: Acute clinical toxicity and time trend between 2013 and 2021 in the Netherlands. Ann Emergency Med. 2022;80(3):P203–12 (doi: 10.1016/j.annemergmed.2022.04.022).
22. 3-MMC. Basic information. Springfield (PA): TripSit; 2022 (https://drugs.tripsit.me/3-MMC, accessed 1 August 2022).
23. Erowid experience vaults. Any reports with 3-methylmethcathinone. Grass Valley (CA): Erowid Center; 2022 (https://www.erowid.org/experiences/exp.cgi?S1=592&Cellar=1&OldSort=RA_PDD&NewSort=PDD&Start=0&ShowViews=0&Cellar=1, accessed 23 July 2022).
24. Sande M, Paš M, Nahtigal K, Šabić S. Patterns of NPS use and risk reduction in Slovenia. Substance Use Misuse. 2018;53(9):1424–32 (doi: 10.1080/10826084.2017.1411366).
25. Golan E, Haden M, Van Wettum R. Drug-assisted psychotherapy with 3-methylmethcathinone. WO2019026019A1. Therapeutic Adjuncts Inc., Canada; Recraceutical Corp. B.V. The Netherands; 2019.
26. Janssen M, Janssen J, Golan E. 3-Methylmethcathinone for the treatment of menstrual cycle-induced disorders and symptoms. WO2021038460A1. Period Pill B.V., The Netherlands; 2021.
27. 3-MMC/summary. PsychonautWiki; 2022 (https://psychonautwiki.org/wiki/3-MMC/Summary, accessed 2 August 2022).
28. Leban V, Grenc D, Brvar M. 3-MMC related intoxications. In: Vajd R, Griçar M, editors. Emergency medicine, selected topics. 22nd International Symposium on Emergency Medicine, 18–20 June 2015, Portorož, Slovenia. Ljubljana: Slovenian Society for Emergency Medicine; 2015 (https://www.szum.si/media/uploads/files/Urgentna medicina 2015_urgentna medicina.pdf - page=145, accessed 31 July 2022).
29. Adamowicz P, Gieron J, Gil D, Lechowicz W, Skulska A, Tokarczyk B. 3-Methylmethcathinone – interpretation of blood concentrations based on analysis of 95 cases. J Analy Toxicol. 2016;40(4):272–6 (doi:10.1093/jat/bkw018).
30. Ameline A, Dumestre-Toulet V, Raul JS, Kintz P (2019b) Determination of a threshold fatal 3-MMC concentration in human: mission impossible. Psychopharmacology. 2019;236(3):865–7 (doi: 10.1007/s00213-018-4941-5).
31. Jamey C, Kintz P, Raul J-S, Martrille L. Fatal combination with 3-methylmethcathinone (3-MMC) and gamma-hydroxybutyric acid (GHB). J Anal Toxicol. 2016;40(7):546–52 (doi: 10.1093/jat/bkw058).
32. Frison G, Frasson S, Zancanaro F, Tedeschi G, Zamengo L. Detection of 3-methylmethcathinone and its metabolites 3-methylephedrine and 3-methylnorephedrine in pubic hair samples by liquid chromatography–high resolution/high accuracy Orbitrap mass spectrometry. Forensic Sci Int. 2016;265:131–7 (doi: 10.1016/j.forsciint.2016.01.039).
33. Olesti E, Farré M, Papaseit E, Krotonoulas A, Pujadas M, de la Torre R et al. Pharmacokinetics of mephedrone and its metabolites in human by LC-MS/MS. AAPS J. 2017;19(6):176–78 (doi: 10.1208/s12248-017-0132-2).
34. Férec S, Abbara C, Le Roux G, Bretaudeau-Deguigne M, Deslandes G, Monteil-Ganière C et al. 3-MMC et α-PVP, 2 cathinones encore peu rencontrées : description clinico-analytique de 5 cas d'exposition [3-MMC and α-PVP, 2 cathinones that are still rare: clinico-analytical description of 5 cases of exposure. Toxicol Anal Clin. 2016;28 (2 Suppl):S40 (doi: 10.1016/j.toxac.2016.03.068).
35. Baumann MH, Walters HM, Niello M, Sitte HH. Neuropharmacology of synthetic cathinones. Handb Exp Pharmacol. 2018;252:113–42 (doi: 10.1007/164_2018_178).
36. Simmler LD, Buchy D, Chaboz S, Hoener MC, Liechti ME. In vitro characterization of psychoactive substances at rat, mouse, and human trace amine-associated receptor 1. J Pharmacol Exp Therapeut. 2016;357(1):134 (doi: 10.1124/jpet.115.229765).

37. Luethi D, Kolaczynska KE, Docci L, Krahenbuhl S, Hoener MC, Liechti ME. Pharmacological profile of mephedrone analogs and related new psychoactive substances. Neuropharmacology. 2018;134(Part A):4–12 (doi: 10.1016/j.neuropharm.2017.07.026).
38. Eshleman AJ, Nagarajan S, Wolfrum KM, Reed JF, Swanson TL, Nilsen A et al. Structure–activity relationships of bath salt components:Substituted cathinones and benzofurans at biogenic amine transporters. Psychopharmacology. 2019;236(3):939–52 (doi: 10.1007/s00213-018-5059-5).
39. Zwartsen A, Olijhoek ME, Westerink RHS, Hondebrink L. Hazard characterization of synthetic cathinones using viability, monoamine reuptake, and neuronal activity assays. Front Neurosci. 2020;14:9 (doi: 10.3389/fnins.2020.00009).
40. Zwartsen A, Hondebrink L, de Lange DW, Westerink RHS. Hyperthermia exacerbates the acute effects of psychoactive substances on neuronal activity measured using microelectrode arrays (MEAs) in rat primary cortical cultures in vitro. Toxicol Appl Pharmacol. 2020;397:115015 (doi: 10.1016/j.taap.2020.115015).
41. Chen Y, Zhang L, Ding Z, Wu X, Wang G, Shi J. Effects of 3-methylmethcathinone on conditioned place preference and anxiety-like behavior: Comparison with methamphetamine. Front Mol Neurosci. 2022;15 (doi: 10.3389/fnmol.2022.975820).
42. Al-Serori H, Ferk F, Angerer V, Mišík M, Nersesyan A, Setayesh T et al. nvestigations of the genotoxic properties of two synthetic cathinones (3-MMC, 4-methylethcathinone) which are used as psychoactive drugs. Toxicol Res. 2016;5(5):1410–20 (doi: 10.1039/C6TX00087H).
43. Dias da Silva D, Ferreira B, Roque Bravo R, Rebelo R, Duarte de Almeida T, Valente MJ et al. The new psychoactive substance 3-methylmethcathinone (3-MMC or metaphedrone) induces oxidative stress, apoptosis, and autophagy in primary rat hepatocytes at human-relevant concentrations. Arch Toxicol. 2019;93(9):2617–34 (doi.: 10.1007/s00204-019-02539-x).
44. Zhou X, Luethi D, Sanvee GM, Bouitbir J, Liechti ME, Krähenbühl S. Molecular toxicological mechanisms of synthetic cathinones on C2C12 myoblasts. Int J Mol Sci. 2019;20(7):1561 (doi: 10.3390/ijms20071561).
45. UNODC Early Warning Advisory Tox-Portal. Vienna: United Nations Office on Drugs and Crime; 2022 (https://www.unodc.org/tox/, accessed 28 July 2022).
46. Maas A, Sydow K, Madea B, Hess C. Separation of *ortho*, *meta* and *para* isomers of methylmethcathinone (MMC) and methylethcathinone (MEC) using LC-ESI-MS/MS: Application to forensic serum samples. J Chromatogr B. 2017;1051:118–25 (doi: 10.1016/j.jchromb.2017.01.046).
47. Maas A, Wippich C, Madea B, Hess C. Driving under the influence of synthetic phenethylamines: A case series. Int J Legal Med. 2015;129(5):997–1003 (doi: 10.1007/s00414-015-1150-1).
48. Adamowicz P, Gieroń J, Gil D, Lechowicz W, Skulska A, Tokarczyk B. The prevalence of new psychoactive substances in biological material – A three-year review of casework in Poland. Drug Testing Anal. 2016;8(1):63–70 (doi: 10.1002/dta.1924).
49. Turcant A, Deguigne M, Ferec S, Bruneau C, Leborgne I, Lelievre B et al. A 6-year review of new psychoactive substances at the Centre Antipoison Grand-Ouest d'Angers: Clinical and biological data. Toxicol Anal Clin. 2017;29(1):18–33 (doi: 10.1016/j.toxac.2016.12.001).
50. Romanek K, Stenzel J, Schmoll S, Schrettl V, Geith S, Eyer F et al. Synthetic cathinones in southern Germany – Characteristics of users, substance-patterns, co-ingestions, and complications. Clin Toxicol. 2017;55(6):573–8 (doi: 10.1080/15563650.2017.1301463).
51. Tomczak E, Wozniak MK, Kata M, Wiergowski M, Szpiech B, Biziuk M. Blood concentrations of a new psychoactive substance 4-chloromethcathinone (4-CMC) determined in 15 forensic cases. Forensic Toxicol. 2018;36(2):476–85 (doi: 10.1007/s11419-018-0427-8).
52. Ameline A, Dumestre-Toulet V, Raul J-S, Kintz P. Abuse of 3-MMC and forensic aspects: About 4 cases and review of the literature. Toxicol Anal Clin. 2019;31(4):251–7 (doi:10.1016/j.toxac.2018.11.001).

53. Wolfe CE, Wood DM, Dines A, Whatley BP, Yates C, Heyerdahl F et al. Seizures as a complication of recreational drug use: Analysis of the Euro-DEN Plus data-set. NeuroToxicology. 2019;3:183–7 (doi: 10.1016/j.neuro.2019.04.003).
54. Drevin G, Rossi LH, Férec S, Briet M, Abbara C Chemsex/slamsex-related intoxications: A case report involving gamma-hydroxybutyrate (GHB) and 3-methylmethcathinone (3-MMC) and a review of the literature. Forensic Sci Int. 2021;321:110743 (doi: 10.1016/j.forsciint.2021.110743).
55. Duguès P, Alvarez JC. Intoxication à l'acide gamma-hydroxybutyrique (GHB) : à propos d'un cas chez un slameur [Poisoning with gamma-hydroxybutyrate (GHB): a case in a slammer]. Toxicol Anal Clin 2020;32(4):247–8 (doi: 10.1016/j.toxac.2020.10.006).
56. Perier D, Eiden C, Mathieu O, Sebbane M, Peyriere H. Consommation de 3-méthylméthcathinone : mise en garde sur le risque de modifications électrocardiographiques ! À propos d'un cas [Consumption of 3-methylmethcathinone: warning about the risk of electrocardiographic changes! A case]. Toxicol Anal Clin. 2020;32(4,Suppl):S46 (doi: 10.1016/j.toxac.2020.09.014).
57. Batisse A, Peyrière H, Cazanave C, Donnadieu-Rigole H. « ChemSex », consommation en contexte sexuel : quelles substances ? Quelle prévention ? Données du réseau français d'addictovigilance. ["ChemSex", consumption and sexual context: which substances? What prevention? Data from the French addictovigilance network. Therapies. 2018;73(6):559 (doi : 10.1016/j.therap.2018.09.068).
58. Schreck B, Guerlais M, Laforgue E, Bichon C, Grall-Bronnec M, Victorri-Vigneau C. Cathinone use disorder in the context of slam practice: New pharmacological and clinical challenges. Front Psychiatry. 2020;11:article 705 (doi: 10.3389/fpsyt.2020.00705).
59. Wacrenier S, Coindre JP, Blanchi S, Piccoli GB. Cat on a hot tin roof (a nephrology zebra). J Nephrol. 2021;34(6):2105–7 (doi: 10.1007/s40620-021-01052-8).
60. van Dongen RM, Alderliefste GJ, Onderwater GLJ, Ferrari MD, Terwindt GM. Migraine prevalence in visual snow with prior illicit drug use (hallucinogen persisting perception disorder) versus without. Eur J Neurol. 2021;28(8):2631–8 (doi: 10.1111/ene.14914).
61. Adamowicz P, Zuba D, Byrska B. Fatal intoxication with 3-methyl-*N*-methylcathinone (3-MMC) and 5-(2-aminopropyl)benzofuran (5-APB). Forensic Sci Int 2014;245:126–32 (doi: 10.1016/j.forsciint.2014.10.016).
62. Report on the risk assessment of 3,4-dichloro-N-{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921) in the framework of the Council Decision on new psychoactive substances. Risk Assessments. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2014 (https://www.emcdda.europa.eu/system/files/publications/774/TDAK14002ENN_480892.pdf, accessed 31 July 2022).
63. Karinen R, Tuv SS, Rogde S, Peres MD, Johansen U, Frost J et al. Lethal poisonings with AH-7921 in combination with other substances. Forensic Sci Int. 2014;244:e21–4 (doi: 10.1016/j.forsciint.2014.08.013).
64. Kronstrand R, Thelander G, Lindstedt D, Roman M, Kugelberg FC. Fatal intoxications associated with the designer opioid AH-7921. J Anal Toxicol. 2014;38(8):599–604 (doi: 10.1093/jat/bku057).
65. Bottinelli C, Gaillard Y, Fanton L, Bévalot F À propos de deux décès par intoxication impliquant la 3-MMC [Two deaths by poisoning involving3-MMC.]. Toxicol Anal Clin. 2016;28(2 Suppl):S25 (doi: 10.1016/j.toxac.2016.03.040).
66. Bottinelli C, Cartiser N, Gaillard Y, Boyer B, Bévalot F. A fatal case of 3-methylmethcathinone (3-MMC) poisoning. Toxicol Anal Clin. 2017;29(1):123–9 (doi: 10.1016/j.toxac.2016.12.010).
67. Margasińska-Olejak J, Celiński R, Fischer A, Stojko J, A fatal case of poisoning of a 19-year-old after taking 3-MMC. Forensic Sci Int. 2019;300 e34–7 (doi: 10.1016/j.forsciint.2019.02.040).
68. Aknouche F, Maruejouls C, Kernalleguen A, Teston K, Mazoyer C, Gasnot W et al. Descente fatale après consommation de 3-méthylmethcathinone (3-MMC) : à propos d'un cas [Fatal outcome after consumption of 3-méthylmethcathinone (3-MMC): a case]. Toxicol Anal Clin. 2020;32(3):205–9 (doi: 10.1016/j.toxac.2020.01.001).

69. Gomez V, Batisse A, Gaulier JM. Place des analyses toxicologiques dans l'identification et la prise en charge des abus et risques en lien avec l'usage de dérivés synthétiques de la cathinone [Role of toxicological analyses in identification and management of abuse and riaks linked to use of synthetic derivatives of cathinone]. Rev Fr Lab. 2021;2021(535):20–30 (doi: 10.1016/S1773-035X(21)00249-5).
70. Batisse A, Eiden C, Deheul S, Monzon E, Djezzar S, Peyrière H. Chemsex practice in France: An update in addictovigilance data. Fundam Clin Pharmacol. 2022;36(2):397–404 (doi: 10.1111/fcp.12725).
71. Goncalves R, Castaing N, Titier K, Dumestre-Toulet V. Hair analysis of methoxphenidine in a forensic chemsex case. J Anal Toxicol. 2022;46(3):328–36 (doi: 10.1093/jat/bkab016).
72. Liechti ME. Treatment with an empathogen/entactogen such as MDMA-like compounds to enhance acute emotional effects profile of psychedelics such as LSD or psilocybin. Patent WO2021225796A1. Basel: Universitaetsspital Basel; 2021 (https://patents.google.com/patent/WO2021257169A1/en).
73. Institóris L, Árok Z, Seprenyi K, Varga T, Sára-Klausz G, Keller É et al. Frequency and structure of stimulant designer drug consumption among suspected drug users in Budapest and south-east Hungary in 2012–2013. Forensic Sci Int. 2015;248:181–6 (doi: 10.1016/j.forsciint.2015.01.002).
74. Schmoll S, Romanek K, Stich R, Bekka E, Stenzel J, Geith S et al. An internet-based survey of 96 German-speaking users of "bath salts": Frequent complications, risky sexual behavior, violence, and delinquency. Clin Toxicol. 2018;56(3):219–22 (doi: 10.1080/15563650.2017.1353094).
75. Johnson CS, Stansfield CR, Hassan VR. Festival testing: A survey of suspected drugs seized from New Zealand music festivals, December 2018 to March 2019. Forensic Sci Int. 2020;313:110367 (doi: 10.1016/j.forsciint.2020.110367).
76. Pascoe MJ, Radley S, Simmons HTD, Measham F. The cathinone hydra: Increased cathinone and caffeine adulteration in the English MDMA market after Brexit and COVID-19 lockdowns. Drug Sci Policy Law. 2022;8;20503245221099209 (doi: 10.1177/20503245221099209).
77. Hondebrink L, Nugteren-van Lonkhuyzen JJ, Hunault CC, van den Berg J, van der Gouwe D, van Riel AJHP. New psychoactive substances (NPS) in the Netherlands: Occurrence in forensic drug samples, consumer drug samples and poisons center exposures between 2013 and 2017. Addiction. 2020;115(4):716–25 (doi: 10.1111/add.14868).
78. Sample results search for 3-MMC. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances, Public Health Wales; 2022 (https://www.wedinos.org/sample-results, accessed 1 August 2022).
79. Erowid's anonymous drug analysis program, formerly called EcstasyData. Search results for 3-MMC. Grass Valley (CA): Erowid Center, DrugsData.org; 2022 (https://drugsdata.org/results.php?search_field=all&s=3-MMC, accessed 1 August 2022).
80. Bade R, White JM, Nguyen L, Tscharke BJ, Mueller JF, O'Brien JW et al. Determining changes in new psychoactive substance use in Australia by wastewater analysis. Sci Total Environ. 2020;731:139209 (doi: 10.1016/j.scitotenv.2020.139209).
81. Bade R, White JM, Chen J, Baz-Lomba JA, Been F, Bijlsma L et al. International snapshot of new psychoactive substance use: Case study of eight countries over the 2019/2020 New Year period. Water Res. 2021;193:116891 (doi: 10.1016/j.watres.2021.116891).
82. Bade R, White JM, Ghetia M, Adiraju S, Adhikari S, Bijlsma L et al. A taste for new psychoactive substances: Wastewater analysis study of 10 countries. Environ Sci Technol Lett. 2022;9(1):57–63 (doi: 10.1021/acs.estlett.1c00807).
83. Gerace E, Caneparo D, Borio F, Salomone A, Vincenti M. Determination of several synthetic cathinones and an amphetamine-like compound in urine by gas chromatography with mass spectrometry. Method validation and application to real cases. J Separation Sci. 2019;42(8):1577–84 (doi: 10.1002/jssc.201801249).
84. Richeval C, Gish A, Hakim F, Nachon-Phanithavong M, Wiart JF, Humbert L et al. Prevalence of new psychoactive substances in oral fluid samples from French drivers: A longitudinal survey (2016–2020). J Anal Toxicol. 2021;45(6):e20–1 (doi: 10.1093/jat/bkab045).

85. Malandain L, Blanc JV, Ferreri F, Giorgiadis T, Mosser S, Mouchabac S et al. First case report of tDCS efficacy in severe chemsex addiction. Dialogues Clin Neurosci. 2020;22(3):295–7 (doi: 10.31887/DCNS.2020.22.3/lmalandain).
86. Mariellier M, Batisse A, Richeval C, Labrouve V, Martinez M, Allorge D et al. Chemsex, NPS & risk reduction management: Preliminary results of a pilot study. Toxicol Anal Clin. 2017;29(1):47–56 (doi: 10.1016/j.toxac.2016.12.003).
87. Vincenti F, Gregori A, Flammini M, Di Rosa F, Salomone A. Seizures of new psychoactive substances on the Italian territory during the COVID-19 pandemic. Forensic Sci Int. 2021;326:110904 (doi: 10.1016/j.forsciint.2021.110904).
88. Bertol E, Bigagli L, D'Errico S, Mari F, Palumbo D, Pascali JP et al. Analysis of illicit drugs seized in the Province of Florence from 2006 to 2016. Forensic Sci Int. 2018;284:194–203 (doi: 10.1016/j.forsciint.2018.01.010).
89. UNODC Early Warning Advisory on new psychoactive substances (NPS) database. Vienna: United Nations Office on Drugs and Crime; 2022 (https://www.unodc.org/LSS/NpsFinding/List?pageNumber=0, accessed 1 August 2022).
90. Drug Enforcement Administration. 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. Fed Reg. 2022;87(148):47428–31 (https://www.federalregister.gov/documents/2022/08/03/2022-16572/international-drug-scheduling-convention-on-psychotropic-substances-single-convention-on-narcotic).