European Monitoring Centre for Drugs and Drug Addiction

ADVANCED RELEASE

EMCDDA initial report on the new psychoactive substance 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC)

In accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended)

Note: In the interests of public health protection the EMCDDA is releasing this report before formal page layout in the EMCDDA house style. The final report will be available on the EMCDDA website in due course.

Tel. + 351 211210200

info@emcdda.europa.eu | www.emcdda.europa.eu twitter.com/emcdda | facebook.com/emcdda

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Contents

1. Introduction

2-(Methylamino)-1-(3-methylphenyl)propan-1-on (3-methylmethcathinone, 3-MMC) is a synthetic cathinone stimulant. It is a ring-substituted cathinone, which is structurally related to methcathinone ([1]) and 4-methylmethcathinone (mephedrone) ([2]).

In Europe, 3-MMC is monitored by the EMCDDA as a new psychoactive substance ([3]) through the European Union Early Warning System (EWS) in accordance with Article 5a of Regulation (EC) No 1920/2006 (as amended) ([4,5]).

3-MMC was formally notified as a new psychoactive substance ([6,7]) by the EMCDDA on behalf of Sweden on 5 September 2012. The notification was based on the identification of the substance in a customs seizure of 51.1 grams of powder made on 27 June 2012 in Gothenburg.

Since the formal notification, information on 3-MMC has been exchanged between the EMCDDA and the European Union EWS Network (EMCDDA, Europol, Reitox national focal points, and the Commission); the EMA have been kept duly informed.

Based on signals suggesting increased availability and harms related to 3-MMC in some parts of Europe, on 2 March 2021, the EMCDDA added 3-MMC to the list of new psychoactive substances under intensive monitoring ([8]) and requested that the Network expedite reporting of any event involving 3-MMC to the EMCDDA until further notice.

The EMCDDA is currently monitoring 161 synthetic cathinones through the European Union Early Warning System (EU EWS).

While the quantities of cathinone powders seized in Europe have been decreasing since they peaked in 2015 and 2016, at around 1 800 kg per year, and falling to 750 kg by 2019, during 2020 there was a significant increase, with approximately 3 300 kg of powders seized. It appears, that at least in part, this increase has been driven by 3-MMC which accounted for almost a quarter of the quantity of powders seized during 2020. In addition, 3-chloromethcathinone (3-CMC), which is also currently the subject of an initial report following its emergence in Europe, accounted for a similar quantity.

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[1] Listed in Schedule I of the 1971 United Nations Single Convention on Psychotropic Substances.
[2] Listed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.
[3] As defined in point 4 of Article 1 of Council Framework Decision 2004/757/JHA of 25 October 2004 laying down minimum provisions on the constituent elements of criminal acts and penalties in the field of illicit drug trafficking (OJ L 335, 11.11.2004, p. 8).
[4] Regulation (EC) No 1920/2006 of the European Parliament and of the Council of 12 December 2006 on the European Monitoring Centre for Drugs and Drug Addiction (recast) (O J L 376, 27.12.2006, p.1-13).
[5] Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances (O J L 305, 21.11.2017, p.1-7).
[6] EMCDDA. 2020. EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances. p. 15–6. http://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en
[7] EMCDDA. 2020. EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances. Guidance note 2. Formal notification of a new psychoactive substance. https://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%202-%20Formal%20notification%20of%20a%20new%20psychoactive%20substance.pdf
[8] EMCDDA. 2020. EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances. Guidance note 6. Intensive monitoring. http://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%206-%20Intensive%20monitoring.pdf

While information reported to the EMCDDA through the Early Warning System suggests that some synthetic cathinones seized in Europe have originated from China, recently, there have been an increasing number of reports of seizures that have originated from India, including those relating to seizures of 3-MMC and 3-CMC. In addition, there has also been a recent increase in the number of laboratories producing cathinones, including 3-MMC and 3-CMC, seized in Europe.

Article 5b of Regulation (EC) No 1920/2006 (as amended) requires that '*Where the Centre, the Commission or a majority of the Member States considers that information shared on a new psychoactive substance collected pursuant to Article 5a in one or more Member States gives rise to concerns that the new psychoactive substance may pose health or social risks at Union level, the Centre shall draw up an initial report on the new psychoactive substance'*.

The initial report is submitted to the Commission and the Member States. The purpose of the initial report is to provide scientific evidence to the Commission to allow it to make an informed decision regarding whether or not there is a need to request a risk assessment on a new psychoactive substance as set out in Article 5c of Regulation (EC) No 1920/2006 (as amended).

Based on the information reported by the Network, on 9 September 2021, the EMCDDA assessed the existing information ([9,10]) on 3-MMC, based on the following criteria:

- reports of health problems;
- reports of social problems;
- reports of seized material;
- pharmacological and toxicological properties and analogy with better-studied substances; and,
- potential for further spread.

The EMCDDA concluded that the assessment gave rise to concerns that 3-MMC may pose health or social risks at Union level, and, consequently, determined that an initial report should be produced.

2. Information collection process

In accordance with the requirements of Article 5b of the Regulation, on 13 September 2021, the EMCDDA launched a procedure for the collection of additional information on 3-MMC in order to support the production of the initial report.

The EMCDDA collected information through:

[9] European Monitoring Centre for Drugs and Drug Addiction (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Publications Office of the European Union, Luxembourg. http://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

[10] This included information reported to the EMCDDA through the Early Warning System, including case reports and aggregated datasets.

- a structured reporting form to the Reitox national focal points in the Member States, Turkey, and Norway (Article 5b(4));

- routine monitoring of open source information;

- a search of open source information conducted specifically for the production of the initial report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and online vendors.

In addition, the EMCDDA also submitted requests to:

- The World Health Organization (WHO) in order to determine if 3-MMC is under assessment or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances ('United Nations system').

- The European Medicines Agency (EMA) in order to determine if 3-MMC is used as an active substance in a medicinal product for human or veterinary use at Union or national level (Article 5b(5)). Specifically, the EMA was asked if 3-MMC is an active substance in:

    a. a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/EC of the European Parliament and of the Council ([11]), Directive 2001/82/EC of the European Parliament and of the Council ([12]) or Regulation (EC) No 726/2004 of the European Parliament and of the Council ([13]);

    b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;

    c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority;

    d. an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;

    e. an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council ([14]).

[11] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).
[12] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).
[13] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).
[14] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

- Europol in order to provide information on the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of 3-MMC, and in any use of 3-MMC (Article 5b(6)).

- The European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) in order to provide the information and data at their disposal on 3-MMC (Article 5b(7)).

The information collection process was concluded on 8 October 2021. The EMCDDA received responses from all 27 Member States, Turkey, and Norway. In addition, the EMCDDA received responses from WHO, EMA, Europol, ECHA, ECDC, and EFSA.

3. Methodological note

3-MMC has been available on the drug market since 2012. Although 3-MMC is screened for in many forensic and toxicology laboratories in Europe, it cannot be excluded that some cases of 3-MMC are undetected or unreported, in particular in serious adverse events.

3-MMC has two positional isomers, whose discrimination poses analytical challenges. Due to differences in reporting practices across Europe, the discrimination of 3-MMC from its positional isomers is done in many, but not all, forensic and toxicology laboratories. For the purposes of preparing this report, all detections where the positional isomer of 3-MMC has not been specified to the EMCDDA have been excluded from the data analysis of physical and biological samples. However, due to different reporting practices across Europe, it remains possible that some detections reported as 3-MMC but that are actually a different positional isomer, have been included.

For serious adverse events (SAEs), cases reported to the EMCDDA where the positional isomer has not been specifically denoted have been included in the data analysis. However, these cases are classified in the text as cases of ‘suspected exposure’ and not as analytically confirmed cases. Certainty of exposure according to the Drug Exposure Classification System (DECS) follows the same classification employed for SAEs.

Complementary data sources have been used in the preparation of the Initial Report:

- For the period comprised between 1 January 2014 and 31 December 2020, annual aggregated seizure data which is systematically reported to the EMCDDA has been used.

- For the period comprised between 1 January and 30 September 2021, event-based data reported spontaneously to the EMCDDA, as well as data reported through targeted requests for information (a structured reporting form sent to the Reitox national focal points and responses to ad hoc information requests) have been used. The bulk of this data, which is partial for the year 2021 and subject to change, has been collected in two weeks and is not comparable to aggregated seizure data.

- Open source information identified through routine monitoring has also been used throughout the report, when confirmed by Reitox national focal points.

Information on seizures reported by police and customs agencies is analysed separately. In some cases, the seizure was either reported by the laboratory that analysed the sample, without specifying whether the seizure was made by police or customs, the identity of the reporting authority was either not specified by the reporting country or not clear from the reports submitted to the EMCDDA. These cases are referred to as 'Other seizures'.

4. Information required by Article 5b(2) of the Regulation

The order and titles of subsections 4.1 to 4.9, below, are as they appear in Article 5b(2) of Regulation (EC) No 1920/2006 (as amended); sections 4.1 to 4.4 are cross-referenced with the headings of Article 5b(2a) to Article 5b(2d) of the Regulation.

4.1 Nature, number and scale of incidents showing health and social problems in which the new psychoactive substance may potentially be involved, and the patterns of use of the new psychoactive substance (Article 5b(2a))

4.1.1 Information from seizures, collected samples and biological samples

The available evidence suggests that 3-MMC has been present on the European drugs market since June 2012. As of 8 October 2020, the substance has been detected across a total of 23 Member States, Turkey and Norway. These detections relate to 9 038 seizures, 672 collected samples and 716 biological samples.

Most of the first identifications of 3-MMC in a reporting country occurred between 2012 and 2014 (n=17; 68%), around the date of its first identification in Europe.

Information from seizures

In total, 9 038 seizures, amounting to 2.8 tonnes of material (in all physical forms) were reported by 25 countries. Of these, 2.7 tonnes were reported in the period of 2012 to 2020. The remaining 138 kg were reported in 2021.

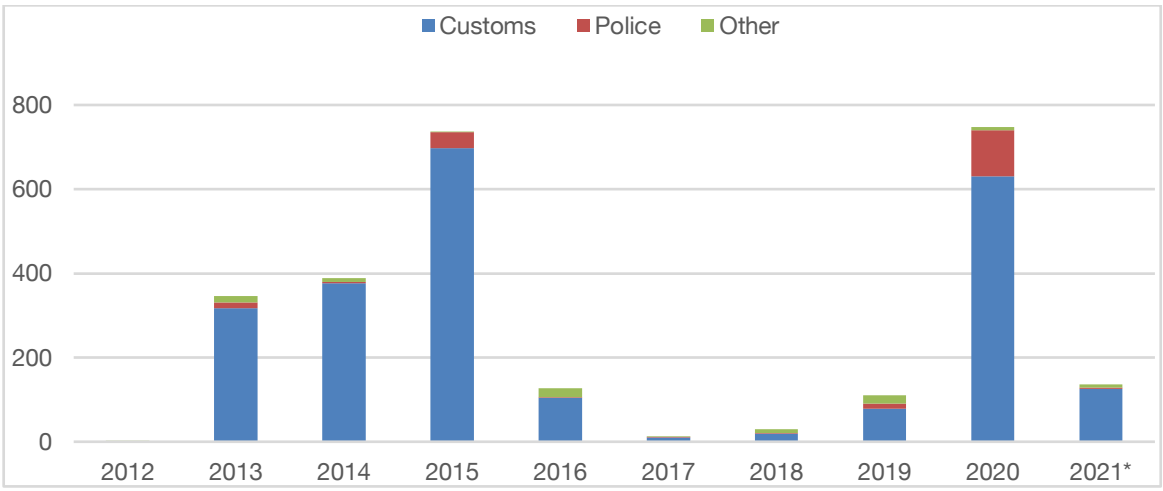
The majority of the cases reported (8 343; 92%) were seizures of powders, amounting to 2.63 tonnes (Figure 1). To a much lesser extent, seizures of tablets and capsules (560), other or unknown physical forms (79), liquids (33), herbal material (16), and blotters (7 cases), were also reported. For this reason, the following analysis is focused on seizures of powders.

A total of 8 343 seizures of powders were reported by police (3 365 cases; 40%), customs (3 058; 37%) and other authorities (1920; 23%).

Half of the cases were reported by Poland (4 454 cases; 53%) and amounted to over 78 kg. The country reporting the largest quantities of seized powders was the Netherlands (1.6 tonnes; 61%).

A summary of the information reported is provided below.

Figure 1. Quantity of 3-methylmethcathinone (3-MMC) powder seized in kg — Europe, 1 January 2012– 30 September 2021



Customs seizures

Since 2012, customs authorities have reported 3 058 seizures of 3-MMC amounting to 2.36 tonnes of powders. Of these, 1014 seizures (757 kg; 32% of all powders seized by Customs) occurred over the course of 2020 and 2021. While most seizures were reported by French Customs (2 119 cases; 69%), the largest quantities of powders were seized in the Netherlands (1.58 tonnes; 67% of customs seizures).

Customs seizures were typically larger in quantity than those reported by police and provide some evidence of attempts to import large amounts of pure 3-MMC powders to Europe.

For the majority of customs seizures, the origin of the consignment was not reported (3 018 cases; 1.1 tonnes). For the 40 cases where the origin of the consignment is known, the largest quantity of powders originated in China (5 seizures, 658 kg, all of which made by Spanish customs in 2015), India (6 seizures; 605 kg, all of which made by Dutch customs in 2020), the Netherlands (24 seizures; 18 kg), Poland (1 seizure; 5 kg), Spain (3 seizures; 0.8 kg) and Slovakia (1 seizure; less than 1 g).

The seizures originating in India were all reported by Dutch Customs in 2020 and consisted of 605 kg of pure 3-MMC powders. In 2021, Dutch Customs have reported a single seizure of 3-MMC powders weighing 122 kg. The country of origin of the latter consignments is unknown at present.

The largest single seizure was reported by Spanish customs and occurred in February 2015 at Barcelona Airport. The seizure consisted of 166 kg of white powder in 13 boxes, delivered from China. In March of that same year a truck was seized by customs authorities in Girona (bordering France) with 136.5 kg of 3-MMC, which were destined for Poland.

Whenever European countries were mentioned as the country of origin (n=29), The Netherlands was the most frequently mentioned country. At least 24 seizures totaling 18 kg of powders containing 3-MMC were shipped from the Netherlands to a number of European countries (Estonia, Finland France, Germany and Italy). Custom seizures originating in the Netherlands varied between 18 kg to 0.1 g. In one of these cases, reported by Finland, a

Customs inspection in 2020 found close to 18 kg of powders containing 3-MMC which had been shipped from the Netherlands, via Germany to Finland and destined for Russia.

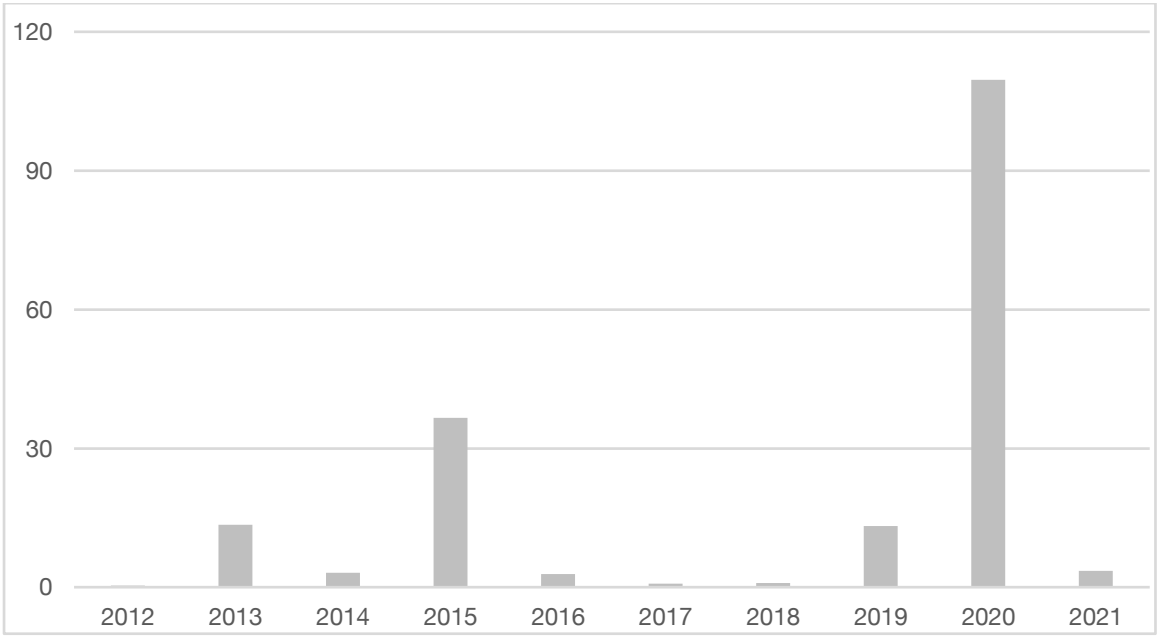
In some customs seizures, 3-MMC appeared as ‘crystals’ or ‘rocks’. Information on the purity of the powders was typically not provided. In some cases, the powders were described as ‘pure’. When quantitative information was available purity was reported between [83 – 89%].

For the cases were other substances were reported, the powders typically contained other stimulants such as other cathinones (including 3-CMC, alpha-PVP, ethylcathinone, eutylone, dibutylone, pentedrone and MDPBP) and, to a lesser extent, illicit substances such as ketamine. Adulterants and diluents reported included caffeine and benzocaine. In one case, 0.6 grams (total amount unknown) of a white powder seized in 2021 by French Customs in Postal freight was found to contain 3-MMC, MDMB-4en-PINACA, 5F-EDMB-PICA and benzocaine (in a mixture called ‘synthacaine lite’). The consignment originated in the Netherlands.

Police seizures

Since 2012, police authorities have reported 3 365 seizures of powders containing 3-MMC, amounting to 184 kg (Figure 2). Poland reported 93% of all Police seizures (3 116 cases) and just over a quarter of the quantity of powders seized by police (48 kg). German Police reported the majority of the quantity of 3-MMC powders seized (106 kg).

Figure 2. Quantity of 3-methylmethcathinone (3-MMC) powder seized by police in kg — Europe, 1 January 2012– 30 September 2021



The largest single seizure of 3-MMC by police occurred in 2020 in Germany, in Bavaria. The seizure consisted of 105 kg of powders contained in barrels labelled ‘3-MMC’. No other substances were detected.

Slovakian Police reported a seizure of approximately 5 kg of 3-MMC at a production site in in April 2013. In that same year, several police controls of cars resulted in 11 seizures of 3-MMC, totalling 8.4 kg.

In Spain, a large-scale police seizure occurred in 2019, where 8 kg of 3-MMC was found alongside powders containing other substances in different physical forms and packaging (total weight 24.4 kg). The other substances included other cathinones and synthetic cannabinoids.

Information on the purity of the powders was typically not provided. When quantitative information was available purity was reported between 45.7% and pure. Both '3-MMC base' and '3-MMC HCl' were reported, albeit in a small number of seizures.

In at least 31 kg of seized powders by police, 3-MMC was found mixed with other substances. These included other cathinones (including 3-CMC, 4-CMC, ethylcathinone, brephedrone, and 4-MMC) and to a lesser extent controlled substances (namely cocaine, metamphetamine, MDMA) as well as ketamine. Adulterants and diluents reported included caffeine, benzocaine and lidocaine.

From the reports of labels in seizures, 3-MMC may be sold under its own name, or as other new psychoactive substances (including '5CL-ADB-A', a synthetic cannabinoid; and mephedrone). In one case in 2020, 10 grams of powder seized by German Police were found to contain a mixture of 3-MMC, benzocaine and caffeine in a mixture called 'synthacaine'. Mixtures containing 3-MMC with a similar name have been reported by French Customs in 2021. In another case in 2021, 2 grams of 3-MMC powder mixed with methamphetamine were found in bags labelled 'THC' and branded 'Black Leaf'.

Descriptions of the material seized ranged from 'white rocks' to white/off-white powders, and in some cases yellow and orange.

Other seizures

In 1920 cases, the reporting authority was not reported or unknown. These cases amounted to 90 kg of powders.

Seizure of note

In one case reported by the Netherlands Forensic Institute in 2019, 154 kg of 3-MMC in physical form not specified were seized from a dealer/producer (CAM, 2021). The seizure of 3-MMC was distributed in a number of bags and barrels, ranging from 0.5 kg to 14 kg.

Related to the same seizure, approximately 350 kg of *N*-acetyl-3-MMC, an uncontrolled substance which can yield 3-MMC when hydrolysed with hydrochloric acid, were also found in jerrycans and barrels of 50 kg. The 3-MMC and the *N*-acetyl-3-MMC seized were imported from a chemical company in India, as well as other 'research chemicals' found in the location. There is limited information available what exactly happened within the laboratory location. Although there was laboratory glass wear, several pieces of laboratory equipment, a fume hood and some precursor chemicals seized that could be used for the production of known NPS at the site, there were no indications that other NPS were being synthesised at the time of the seizure of the lab. The location also was used as a packaging/distribution centre for NPS.

Information from collected samples

A total of 672 collected samples were reported to the EMCDDA, between 2012 and 2021, by 9 Member States: Austria (20), Belgium (3), Czechia (4), France (99), the Netherlands (443), Poland (40), Portugal (8), Slovenia (52), and Spain (3). Collected samples of 3-MMC were mostly in powder form (577), but tablets (36), capsules (28), and samples in liquid form (16) were also reported. Samples were mostly collected by drug-checking services (590 cases), but also by the Polish National Medicinal Institute (29) and by the Slovenian National Laboratory of Health, Environment and Food (23).

3-MMC was the only substance detected in 628 cases. In 35 cases it was detected in combination with other cathinones: methylethcathinone (13), 4-CMC (5), ethcathinone (3), MPHP (2), chloromethcathinone (2), alpha-PVP (2), alpha-PVP and N-ethylhexedrone (1), alpha-PVP and ethcathinone (1), 3-CMC (1), 3-MEC (1), 4-EMC (1), 4-methylbuphedrone (1), alpha-PHP (1), and 4-Cl-PVP (1). In 10 cases it was detected in combination with other recreational substances: 4-FMA, 5-APB and 5-MAPB (2), DOC (2), 2C-B and tramadol (1), methoxyphenidine (1), diphenidine (1), methoxetamine (1), 4,4'-DMAR (1) and methamphetamine (1). 3-MMC was detected in 8 cases in combination with diluents: caffeine (2), benzocaine (2), caffeine and lidocaine (2), caffeine and benzocaine (1), and lidocaine (1).

From the 102 samples that were quantitatively tested, purities ranged from 11% to 100%, with a mean of 76.3%. Adulterants and diluents were reported in 18 of these cases: methylethcathinone (13 cases, 85.4% average 3-MMC content), 3-CMC (1 case, 37.8% 3-CMC), alpha-PHP (1 case, 87,20% 3-MMC), caffeine (1 case, 82% 3-MMC), caffeine and benzocaine (1 case, 15% caffeine and 28% benzocaine), and benzocaine (1 case, 28% benzocaine). In these last two cases, the sample was sold as the branded product ‘Synthacaine’. Two other instances of branded products containing 3-MMC were reported: ‘Pink Panther’, containing 3-MMC, tramadol and 2-CB, and ‘Bloom’, with only 3-MMC.

3-MMC was sold as 3-MMC in 6 cases, and as other substances in 7 collected samples: as mephedrone (4 cases, one of them in combination with 3-MEC), as ecstasy (1), as methoxyphenidine (1) and as DOC (1).

When reported, prices ranged from 8€ to 37.5€ per gram (average 20€ from 9 collected samples). Price for tablets was reported in one case (5€ per tablet). Information on sources was only present in 16 samples, indicating that most samples were bought online (13 cases, two of them on the Darknet), though some were bought by a local dealer (3).

From all the samples submitted to the Dutch drug checking project DIMS ([15]) in 2020, which consisted of a total of 8078 samples, around half of them contained ecstasy, while 2% contained either 3- or 4-MMC (DIMS, 2021). This study reports that 49% of the samples sold in the Netherlands as ‘4-MMC’ contained 3-MMC. Samples sold as ‘3-MMC’ were reported to never contain 4-MMC (DIMS 2021, CAM 2021)

[15] Drugs Information and Monitoring System

Information from biological samples

A total of 716 detections where 3-MMC was analytically confirmed in biological samples were reported by 11 Member States: Belgium (15), Denmark (1), France (50), Germany (1), Hungary (214), Lithuania (1), Norway (16), Poland (37), Slovenia (12), Spain (4), and Sweden (365).

Serious adverse events with confirmed exposure to 3-MMC from biological samples — 8 acute poisonings reported by France (6), Germany (1), and Spain (1), and 19 deaths reported by Sweden (9), France (6), Spain (3), and Slovenia (1) — are discussed in Section 4.1.2.

In addition to these, 689 detections of 3-MMC in biological samples were reported by Sweden (356), Hungary (214), France (38), Poland (37), Norway (16), Belgium (15), Slovenia (11), Denmark (1), and Lithuania (1).

The biological samples were reported between 2012 and 2021 as follows: 2012 (28 samples), 2013 (314), 2014 (128), 2015 (87), 2016 (30), 2017 (6), 2018 (13), 2019 (19), 2020 (23), 2021 (41).

Detections included:

- 18 samples associated with deaths, reported by Hungary (5), France (4), Slovenia (4), Sweden (4), and Norway (1) ([16]);
- 18 samples associated with non-fatal poisonings, reported by France (7), Hungary (6), and Slovenia (5) ([17]);
- 170 samples associated with drug consumption, all reported by Hungary;
- 45 cases of persons suspected of driving under the influence of drugs (including 4 traffic accidents), reported by Hungary (20), France (15), Norway (5), Sweden (4), and Denmark (1);
- 24 samples analysed for other purposes, including drug treatment purposes, petty drug offense, emergency room visit, possession of drugs, car accident, working under influence of drugs, reported by Norway (9), Sweden (5), Belgium (3), France (3), Poland (2), Hungary (1), and Lithuania (1);
- 11 samples analysed for criminal justice purposes, reported by Hungary (8) and France (3);
- 7 samples associated with violence, sexual abuse, homicide, or criminal act, reported by France (5) and Slovenia (2);

[16] These samples were reported in aggregated datasets, and there is no correspondence between the number of samples and number of serious adverse events (SAEs), as more than one sample may have been taken from the same patient. SAEs reported in aggregated datasets may or may not overlap with event-based SAEs discussed in Section 4.1.2.
[17] These samples were reported in aggregated datasets, and there is no correspondence between the number of samples and number of serious adverse events (SAEs), as more than one sample may have been taken from the same patient. SAEs reported in aggregated datasets may or may not overlap with event-based SAEs discussed in Section 4.1.2.

- 396 samples reported as aggregated data associated with forensic case work (details not specified), reported by Sweden (343), Poland (35), Belgium (12), Hungary (4), France (1), and Norway (1).

4.1.2 Health problems

Acute poisonings

- *Confirmed exposure*

  A total of 8 acute non-fatal poisonings with confirmed exposure to 3-MMC were reported by France (6), Germany (1), and Spain (1). Where reported, the cases occurred between 2014 and 2021: 2014 (1 case), 2016(2), 2017 (2), 2021 (2). Where known, 6 of the individuals were male and 1 was female. The males were aged between 22 and 51 (mean 38; median 37).

  Based on the reported information, four of the cases could be classified as life-threatening (required admission to intensive care unit or involved life-threatening condition such as respiratory arrest or coma).

  In 6 cases other substances were identified, including central nervous system depressants (such as GHB/GBL, synthetic cannabinoids and benzodiazepines) and central nervous system stimulants (such as cocaine, amphetamine, methamphetamine, 3-CMC, 3-fluoroamphetamine, 3F-phenmetrazine, and N-ethylhexedrone).

  Of particular note is that one acute poisoning was reported as a case of sexual assault. Two other cases were reported as related to sexual practice (chemsex ([18]) or sadomasochism).

- *Suspected exposure*

  Four Member States reported 82 cases of acute poisoning with suspected exposure to 3-MMC: Sweden (71), Slovenia (6), France (3), and Italy (2). The cases occurred between 2012 and 2021: 2012 (3 cases), 2013 (54), 2014 (3), 2015 (5), 2016 (2), 2018 (2), 2019 (3), 2020 (4), and 2021 (6). These cases are not discussed further in this report.

- *Additional information*

  In addition, 6 acute non-fatal poisonings with confirmed exposure to 3-MMC and 110 cases of acute poisoning with suspected exposure to 3-MMC were reported by the Netherlands, after the data collection closed (CAM, 2021).

[18] Chemsex is a term used to describe intentional sex under the influence of psychoactive drugs, mostly among men who have sex with men.

Deaths

- *Confirmed exposure*

  A total of 19 deaths with confirmed exposure to 3-MMC were reported by Sweden (9), France (6), Spain (3), and Slovenia (1). Where known, the cases occurred between 2013 and 2021: 2013 (7 cases), 2016 (3), 2019 (4), 2020 (1), 2021 (1). Where reported, 12 were male and 1 was female. Age was reported for 7 of the males. The males were aged between 22 and 46 (mean: 29; median 27).

  In 7 of the cases, other substances were identified, including central nervous system depressants (such as alcohol, opioids, and benzodiazepines) and central nervous system stimulants (such as amphetamine, 4-fluoromethylphenidate and other synthetic cathinones).

  In 3 of the cases, the individuals were found dead. A cause of death was reported in 11 cases. In at least 3 cases, 3-MMC was the cause of death or contributed to the death.

  Three of the deaths were related to sexual practice (chemsex ([17])).

- *Suspected exposure*

  France reported two deaths with suspected exposure to 3-MMC. These cases are not discussed in this report.

- *Additional information*

  A total of 8 deaths with confirmed exposure to 3-MMC were reported by the Netherlands, after the data collection closed (CAM, 2021). Where known, 1 of the deaths occurred in 2019 and 4 in 2020. In 2 of the cases, no other substances were identified. In addition, 2 deaths with suspected exposure to 3-MMC were also reported by the Netherlands (CAM, 2021).

Substance dependence

Two cases of substance dependence with confirmed exposure to 3-MMC were reported by France. Both cases involved males aged 22 and 28. In one of the cases, the patient reported injecting 3-MMC (slamming) and was hospitalised for withdrawal from 3-MMC and 4-fluoromethylphenidate.

In addition, France reported three cases of substance dependence with suspected exposure to 3-MMC. These cases are not discussed in this report.

Other types of serious adverse evhents

France reported one case of sexual assault with confirmed exposure to 3-MMC. This case is not discussed in this report.

In addition, France reported one case of allergic reaction with suspected exposure to 3-MMC. This case is not discussed in this report.

ECDC reported that currently they do not have any information on 3-MMC.

4.1.3 Social problems

It is possible that the social risks related to the use of 3-MMC share some similarities with those associated with other synthetic cathinones, such as 4-MMC, as well as other stimulant drugs. Depending on the user group, these might include changes in the social and economic conditions of the individual, impact their family structure and employment or schooling performance, as well as confer increased vulnerability (Brookman et al. 2016, de Jonge et al. 2021, Nijkamp et al. 2021).

Based on the available information, it appears that 3-MMC is currently being used by some vulnerable groups including young people in the Netherlands and Slovenia (CAM 2021, de Jonge et al. 2021, Nijkamp et al. 2021). The use of 3-MMC among high-risk drug users has also been reported by France and Slovenia.

4.1.4 Patterns of use

The limited information reported to the EMCDDA and available in the literature suggests that 3-MMC is typically sold and sought after as a stimulant drug in its own right, but it may also be mis-sold as other drugs including 4-MMC. Similar to other cathinones, such as 4-MMC, 3-MMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It appears to be used by existing stimulant users, such as those who use cocaine, amphetamines, ecstasy, and other cathinones, who either add it to their existing repertoire or use it as a replacement substance. This includes recreational use, and, in some cases high risk use, such as injecting. In addition, in at least one country, it may also be used by vulnerable groups such as young people partly because it is easily available, not controlled, and has a relatively low cost. It appears that 3-MMC is used in private spaces (such as homes and domestic parties), as well as recreational settings (such as nightclubs, bars/pubs, music festivals), and as part of chemsex settings (CAM 2021; de Jonge et al. 2021; Drevin et al., 2021; Nijkamp et al. 2021).

4.2 Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction (Article 5b2(b))

4.2.1 Chemical description and names

3-MMC is a synthetic derivative of the naturally occurring substance cathinone which is internationally controlled ([19]), and one of the psychoactive principles in khat (*Catha edulis* Forsk). 3-MMC was described in the scientific literature in the months prior to its first detection on the drug market in Europe in June 2012 (Power et al., 2011).

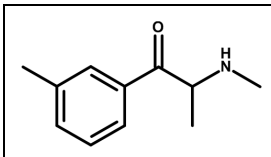
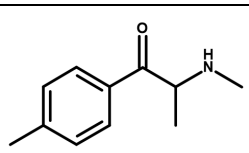
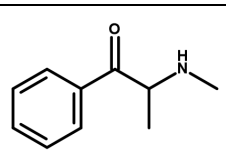
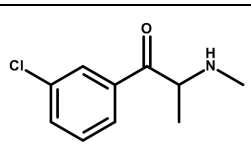
As with many other synthetic cathinone derivatives monitored by the EMCDDA through the EU Early Warning System, 3-MMC is an *N*-alkylated and ring-substituted cathinone.

[19] Listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances.

The common name 3-MMC is derived from 3-methylmethcathinone ([20]). 3-MMC is the 3-methyl derivative of methcathinone ([21]) and a positional isomer ([22]) of 4-MMC (4-methylmethcathinone, also known as mephedrone) ([23]), which are both internationally controlled. 3-MMC is structurally related to 3-CMC (3-chloromethcathinone) ([24]), differing on the substituent present at the 3-position of the phenyl ring. 3-MEC (3-methylethcathinone) ([25]) is a higher homologue of 3-MMC, monitored by the EMCDDA.

The molecular structure, molecular formula and molecular mass of 3-MMC are provided in Figure 3.

Figure 3. Molecular structure, molecular formula, and molecular mass of 3-MMC. Information on methcathinone, 4-MMC and 3-CMC is provided for comparison

				
	3-MMC (metaphedrone)	4-MMC (mephedrone)	Methcathinone	3-CMC (clophedrone)
Molecular formula	$C_{11}H_{15}NO$	$C_{11}H_{15}NO$	$C_{10}H_{13}NO$	$C_{10}H_{12}ClNO$
Molecular mass	177.24	177.24	163.22	197.66

Common name(s):

3-MMC

3-Methylmethcathinone

Systematic (IUPAC) name:

2-(Methylamino)-1-(3-methylphenyl)propan-1-one

[20] The origin for the abbreviated common name is indicated by underlining the relevant letters in the common name.

[21] 2-(Methylamino)-1-phenyl-propan-1-one; listed in Schedule I of the 1971 United Nations Single Convention on Psychotropic Substances.

[22] Positional isomers (also known as regioisomers) have the same molecular formula and molecular weight, differing only in the position of a functional group or substituent.

[23] 2-(Methylamino)-1-(4-methylphenyl)-1-propanone; formally notified by the EMCDDA in March 2008; listed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.

[24] 1-(3-Chlorophenyl)-2-(methylamino)propan-1-one; formally notified by the EMCDDA in October 2014.

[25] 2-(Ethylamino)-1-(3-methylphenyl)propan-1-one; formally notified by the EMCDDA in July 2014.

(*RS*)-2-(methylamino)-1-(3-methylphenyl)propan-1-one

Other chemical names:

1-(3-Methylphenyl)-2-(methylamino)propane-1-one

2-(Methylamino)-1-(3-methylphenyl)-1-propanone

2-(Methylamino)-1-(*m*-tolyl)propan-1-one

Other names:

3-Methyl-methcathinone

3-Me-methcathinone

3-Methyl-*N*-methylcathinone

3-Me-MCAT

3-Methyl MC

Metaphedrone

Mepedrone

3-Mephedrone

Chemical Abstracts Service (CAS) registry numbers:

1246911-86-3 (base)

1246816-62-5 (hydrochloride salt)

2291027-30-8 (*R*-isomer)

2107851-15-8 (*S*-isomer)

IUPAC International Chemical Identifier Key (InCHI Key):

QDNXSIYWHYGMCD-UHFFFAOYSA-N (base)

RPFQEIQTWQWCQH-UHFFFAOYSA-N (hydrochloride salt)

QDNXSIYWHYGMCD-SECBINFHSA-N (*R*-isomer)

QDNXSIYWHYGMCD-VIFPVBQESA-N (*S*-isomer)

IUPAC International Chemical Identifier String (InchI string):

InChI=1S/C11H15NO/c1-8-5-4-6-10(7-8)11(13)9(2)12-3/h4-7,9,12H,1-3H3 (base)

InChI=1S/C11H15NO.ClH/c1-8-5-4-6-10(7-8)11(13)9(2)12-3;/h4-7,9,12H,1-3H3;1H (hydrochloride salt)

InChI=1S/C11H15NO/c1-8-5-4-6-10(7-8)11(13)9(2)12-3/h4-7,9,12H,1-3H3/t9-/m1/s1 (*R*-isomer)

InChI=1S/C11H15NO/c1-8-5-4-6-10(7-8)11(13)9(2)12-3/h4-7,9,12H,1-3H3/t9-/m0/s1 (*S*-isomer)

Simplified Molecular-Input Line-Entry System (SMILES):

Cc1cccc(c1)C(=O)C(C)NC (base)

Cl.CNC(C)C(=O)c1cccc(C)c1 (hydrochloride salt)

CN[C@H](C)C(=O)c1cccc(C)c1 (*R*-isomer)

CN[C@@H](C)C(=O)c1cccc(C)c1 (*S*-isomer)

Finally, the following labelled products have been reported to contain 3-MMC:

'Synthacaïne'/'Synthacaine'

'Charly Sheen'

'Crystal'

4.2.2 Physical description

The hydrochloride salt of 3-MMC is a white crystalline powder, reported to be soluble in DMF (1 mg/ml); DMSO (2 mg/ml); ethanol (5 mg/ml); and PBS (pH 7.2; 10 mg/ml) (Cayman Chemical, 2012a). Solubility in water is reported as 2.0±0.1 mg/ml (Shimsoni et al., 2015). A λmax (ultraviolet wavelength of maximum absorbance) of 252, 292 nm (Cayman Chemical) and a UV-absorption max in water of 206.2 nm is reported (Shimsoni et al., 2015). PKa values of 7.84±0.1 (Shimsoni et al., 2015) and 8.68 by capillary electrophoresis are reported (Woźniakiewicz et al., 2018) have been reported. Melting point ranges of 188 – 190 °C (Power et al., 2011), 193.2± 0.2°C (WHO, 2016) and 193 – 195 °C (Walther et al., 2018) have been reported for the hydrochloride salt of 3-MMC. A boiling point of 280.5 ± 23.0°C at 760 mm Hg has also been reported for 3-MMC (WHO, 2016).

To date, seizures and collected samples containing 3-MMC reported to the EMCDDA have been mostly in powder form and to a lesser extent, in tablet, capsule and liquid form. 3-MMC has also been identified in herbal material and blotters.

3-MMC has been identified in combination with other cathinones, including but not limited to: 2-MMC ([26]), 4-MMC, 3-CMC, 4-CMC ([27]), 3-CEC ([28]), 4-CEC ([29]), 4-MEC ([30]), α-PVT ([31]),

[26] 2-(Methylamino)-1-(2-methylphenyl)propan-1-one
[27] 1-(4-Chlorophenyl)-2-(methylamino)propan-1-one
[28] 1-(3-Chlorophenyl)-2-(ethylamino)propan-1-one
[29] 1-(4-Chlorophenyl)-2-(ethylamino)propan-1-one
[30] 2-(Ethylamino)-1-(4-methylphenyl)propan-1-one
[31] 2-(Pyrrolidin-1-yl)-1-(thiophen-2-yl)pentan-1-one

ethylone ([32]), pentedrone ([33]) and *N*-ethylhexedrone ([34]). 3-MMC has also been identified in combination with a variety of other categories of substances including synthetic cannabinoids such as 4F-MDMB-BINACA (4F-MDMB-BUTINACA) ([35]) and internationally controlled substances such as cocaine and MDMA.

In at least some of the detections, the free base form and the hydrochloride salt form of 3-MMC was identified.

A more detailed description of seizures and collected samples can be found in section 4.1.1.

4.2.3 Methods and chemical precursors used for the manufacture or extraction

Limited information is available about the chemical precursors or manufacturing methods used to make the 3-MMC which has been identified within Europe. General methods for the synthesis of cathinones, including 3-MMC are described below.

General methods for the synthesis of cathinones, including 3-MMC

Cathinones may be prepared using several synthetic approaches. For ring-substituted cathinones, such as 3-MMC and 3-CMC, the simplest approach involves a 2-step bromination-amination procedure which is a relatively straightforward process, using equipment and knowledge similar to those required for the synthesis of other synthetic drugs such as MDMA and amphetamine (EMCDDA, 2011).

The first step of the process consists in the α-bromination of a suitable arylketone (commonly called a 'propiophenone'), to produce an α-bromoketone under acidic or basic conditions. The bromine for this step can be commercially obtained as a liquid or prepared from a bromide salt (e.g. KBr), an acid (e.g. H_2SO_4), and an oxidizer (e.g. H_2O_2). Importantly, bromine is toxic by inhalation, accelerates the burning of combustible material, is very corrosive to tissue and to metals and dangerous for the environment.

After the preparation of the α-bromoketone, the product is reacted with an amine (for ring substituted cathinones the amine is typically methylamine hydrochloride and triethylamine in an acidic scavenger). This step promotes the nucleophilic substitution of the bromine to obtain a free cathinone base (EMCDDA, 2011; Wrzesień, 2018). Due to the instability of the free base, the product is converted into suitable salts (hydrochlorides or hydrobromides) which are then recrystallised (EMCDDA, 2011; Wrzesień, 2018). Unless steps are taken to resolve the reaction products, the synthesis produces racemic mixtures. In case the starting arylketone precursor is unavailable or controlled, it can be easily prepared by a standard Friedler-Crafts reaction, mixing the appropriate aryl derivative (Step 0) with propionyl chloride in the presence of aluminium chloride (Wrzesień, 2018). A standard Grignard reaction with the corresponding ring-substituted benzene is also possible.

[32] 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)propan-1-one

[33] 2-(Methylamino)-1-phenylpentan-1-one

[34] 2-(Ethylamino)-1-phenylhexan-1-one

[35] Methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate

The preparation of cathinones using this method is an 'industrially efficient' process. Intermediate can be produced on a large scale, sub-divided into lots and each lot reacted with a different amine to produce a number of different cathinones (Collins, 2016).

Numerous alternative synthetic methods exist. One of the most relevant one is the so-called 'permanganate process', which involves the direct oxidation of a suitable ephedrine analogue with a strong oxidant (potassium permanganate (VII) or potassium dichromate in diluted sulfuric acid) to yield the desired cathinone. If is obtained in a specific enantiomeric form, the synthesis is stereoselective and the resulting cathinone will be enantiopure, which may be of interest if one of the forms is more active than the other. Although this method can yield stereoselective products, it presents important disadvantages in that manganese impurities can contaminate the end products, unless careful and thorough purification steps are taken. Cathinone products contaminated with manganese may cause serious poisoning in consumers (EMCDDA, 2011).

The synthesis of the hydrochloride salt of 3-MMC has been described in the literature (Power et al., 2011). 3-MMC (*compound 6b*) was synthesized through the reaction of 3-methylbenzaldehyde with ethyl magnesium bromide, followed by oxidation with pyridinium chlorochromate (PCC) on silica gel and bromination with hydrobromic acid/hydrogen peroxide, to obtain the bromo ketone. This was then reacted with ethanolic methylamine in acetonitrile and the product was purified by flash chromatography. The free base form of 3-MMC was converted to the hydrochloride salt of 3-MMC, using ethereal hydrogen chloride (Power et al., 2011). The synthesis of the hydrochloride salt of 3-MMC (*compound 3c*) has also been described by Walther et al. (Walther et al., 2018).

'Designer' Precursors

Other than standard organic synthesis methods using known precursors, cathinones can be prepared using so-called 'designer precursors'. These are 'purpose-made, close chemical relatives of controlled precursors and can easily be converted into a controlled precursor and usually have no legitimate use.' (CND, 2020). They can be, for example, stable chemical intermediates, masked derivatives of controlled precursors, or masked derivatives of controlled drugs. (CND, 2020). Amine compounds, including cathinones, are especially suited for the latter approach, in that 'masking' or 'protecting' groups (such as acetyl protecting groups, 'Boc' groups, CBZ groups and/or 'Tosyl' groups for example) can be easily introduced into the molecule (making it a different chemical entity) and then easily cleaved off, often in quantitative yields to produce the controlled amine of choice.

Illicit production of 3-MMC

Information on the synthetic pathways used to produce the 3-MMC seized in Europe can come from impurity profiling of seized/collected samples, from seizures of cathinone precursors and from law enforcement intelligence collected in seizures of illicit cathinone production sites.

No information exists on the synthetic impurities present in 3-MMC samples (synthetic impurity profiling).

Seizures of precursors reported to the European Commission do not contain information on specific chemicals needed for the synthesis of 3-MMC. Most of the reports consisted of

precursors for 4-MMC and 4-CMC, which can nonetheless be taken as indicative of the processes used for their positional isomers. The majority of cathinone precursors seized between 2015 and 2019 were chemicals needed for amination step in the bromination/amination. This suggests that cathinone labs in Europe may be using the pathway in question but and that they may be focused on the final stages of cathinones production ('finishing labs').

In one case, reported by The Netherlands in 2019, approximately 350 kg of *N*-acetyl-3-MMC imported from India was seized alongside 154 kg of 3-MMC at a 'dealer/producer' site (CAM 2021). *N*-acetyl-3-MMC is an uncontrolled chemical that can be converted into 3-MMC by acid or base hydrolysis. It can be considered a masked designer precursor as explained above.

Law enforcement information reported to the EMCDDA by law enforcement authorities indicates that at least 55 cathinone illicit laboratories have been dismantled in Europe since 2011. Close to 50% of the laboratories were seized between 2019 and 2021, suggesting that there has been an increase in the interest in producing cathinones in Europe.

Of the 55 laboratories seized, 3 sites were reported to be involved in the production of 3-MMC. The first one was seized in Slovakia in 2013; the other two were seized in the Netherlands in 2017 and 2020. Whereas the laboratory in Slovakia was considered an operational site, the two Dutch sites were considered storage and packaging plants.

Information provided by Europol to the EMCDDA indicates that a number of abandoned clandestine laboratories were seized in Slovakia in 2018, dedicated to the production of high volumes of 3-MMC, one of which exploded due to 'incompetent handling', resulting in 'environmental damage'.

4.2.4 Detection and analysis

Methods documented in the literature for the identification of 3-MMC in physical samples and biological samples are referenced in Table 1.

Table 1. Methods documented in the literature for the identification of 3-MMC in physical samples and biological samples.

Physical samples	
Method	**References**
Gas chromatography–mass spectrometry (GC-MS)	Armenta et al., 2015 Bertol et al., 2018 Carnes et al., 2017 Frison et al., 2020 Johnson et al., 2020 Levitas et al., 2018 Kranenburg et al., 2019 Kranenburg et al., 2020a Kranenburg et al., 2020b Power et al., 2011 RESPONSE, 2012 Rowe et al., 2017 Strano Rossi et al., 2014 SWGDRUG, 2013
Gas chromatography–infra red detection spectroscopy (GC–IRD)	Lee et al., 2019
Solid deposition-gas chromatography-Fourier transform infrared spectroscopy (sd-GC-FTIR)	Frison et al., 2020
Gas chromatography-flame ionization detector (GC-FID)	Bertol et al., 2018
Gas chromatography–vacuum ultraviolet spectroscopy (GC–VUV)	Kranenburg et al., 2019 Skultety et al., 2017
High-resolution mass spectrometry (HRMS)	Power et al., 2011 Strano Rossi et al., 2014
Liquid chromatography tandem mass spectrometry (LC-MS/MS)	Bäckberg et al., 2018 Bertol et al., 2018 Grumann and Auwärter, 2018 Shimsoni et al., 2015
Liquid chromatography-high resolution accurate mass-mass spectrometry (LC-HRAM-MS)	Frison et al., 2020
Liquid chromatography-diode array detection (LC-DAD)	Armenta et al., 2015

High-performance liquid chromatography-ultraviolet (HPLC-UV)	Hägele et al., 2020 Kadkhodaei et al., 2018 Kadkhodaei et al., 2020 May et al., 2020 Taschwer et al., 2014
Ultra-high performance liquid chromatography (UHPLC)	Carnes et al., 2017
Ultra-high performance supercritical fluid chromatography (UHPSFC)	Carnes et al., 2017 Pauk et al., 2015 Rowe et al., 2017
Fourier transform infrared spectroscopy (FTIR)	Armenta et al., 2015 Christie et al., 2013 Johnson et al., 2020 Kolodziejczyk et al., 2017 Piorunska-Sedlak and Stypulkowska, 2020 Power et al., 2011 RESPONSE, 2012 SWGRDUG, 2013
Infrared ion spectroscopy (IRIS)	Kranenburg et al., 2020c
Raman spectroscopy	Christie et al., 2013 Johnson et al., 2020 Kranenburg et al., 2021
^{1}H nuclear magnetic resonance spectroscopy (NMR)	Bäckberg et al., 2018 Power et al., 2011 Strano Rossi et al., 2014 Stolarska et al., 2020 SWGRDUG, 2013 Walther et al., 2018
^{13}C NMR	Bäckberg et al., 2018 Power et al., 2011 Stolarska et al., 2020
Ion mobility spectrometry (IMS)	Armenta et al., 2015
Capillary electrophoresis (CE)	Hägele et al., 2019 Nowak et al., 2018a Nowak et al., 2018b Woźniakiewicz et al., 2018
Biological samples	
Method	**References**

GC-MS	Alremeithi et al., 2016 Alremeithi et al., 2018 Institóris et al., 2015 Maas et al., 2015 Maas et al., 2017 Mercieca et al., 2018
GC-MS/MS	Woźniak et al., 2020
LC-MS	Labuz et al., 2019
LC-MS/MS	Adamowicz and Tokarczyk, 2016a Adamowicz et al. 2016b Bäckberg et al., 2018 Boumba et al., 2017 Grumann and Auwärter, 2018 Helander et al., 2020 Labuz et al., 2019 Maas et al., 2015 Maas et al., 2017 Vaiano et al., 2016
Liquid chromatography-high resolution mass spectrometry (LC–HRMS)	Bäckberg et al., 2018 Frison et al., 2016 Stephanson et al., 2017
Liquid chromatography-high resolution mass spectrometry tandem mass spectrometry (LC-HRMS/MS)	Bäckberg et al., 2018 Helander et al., 2020
Ultra-high performance liquid chromatography-mass spectrometry (UHPLC-MS)	Borovcová et al., 2018 Sorribes-Soriano et al., 2019
Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS)	Odoardi et al., 2015
Ultra-high performance supercritical fluid chromatography-mass spectrometry (UHPSFC-MS)	Borovcová et al., 2018
HPLC-DAD	Romanek et al., 2017
HPLC-MS/MS	Sánchez-González et al., 2019

Quantification of 3-MMC in products can be carried out according to the general procedure described by the UNODC (UNODC, 2020). Quantification of 3-MMC in biological samples can be carried out according to methods described by Adamowicz et al. (Adamowicz et al.

2016b) and others (Frison et al., 2016; Grumann and Auwärter, 2018; Mercieca et al., 2018; and Woźniak et al., 2020.

Methods documented in the literature for the detection of 3-MMC in wastewater include: LC-MS/MS (Bade et al., 2020; Bade et al., 2021); and LC-HRMS (Bade et al., 2021).

Discrimination of 3-MMC from its positional isomers

3-MMC has two positional isomers, 2-MMC ([36]) and 4-MMC, differing only in the position of the methyl group on the phenyl ring. Reference standards of the hydrochloride salt of 3-MMC (Cayman Chemical, 2012a), 2-MMC (Cayman Chemical, 2012b), and 4-MMC (Cayman Chemical, 2018) are commercially available. Reference standards are also commercially available for the base form and the *S*-isomer of 3-MMC (Aurora Fine Chemicals, 2021a; Aurora Fine Chemicals, 2021b).

Positional and structural isomers have the same molecular formula and molecular mass, therefore the discrimination of these isomers of 3-MMC poses analytical challenges, as techniques solely relying on mass will not allow an unequivocal identification. The positional isomers of 3-MMC, 2-MMC and 4-MMC, can be discriminated for in many, but not all, forensic and toxicology laboratories in Europe. The discrimination of positional isomers can be achieved through the use of analytical reference standards, access to reference spectra for the positional isomers and/or analytical methods in addition to GC-MS, such as FTIR or NMR. The discrimination of these isomers is described in further detail below.

Analysis of 2-, 3-, and 4-MMC by GC-MS will result in very similar mass spectrometry fragmentation patterns (Power et al., 2011; Lee et al., 2019). The ability to distinguish between these isomers requires the use of analytical reference standards, access to reference spectra for the isomers, and/or additional analytical methods, such as FTIR (Lee et al., 2019; Piorunska-Sedlak and Stypulkowska, 2020) or NMR (Power et al., 2011). Christie et al., demonstrated the discrimination of the positional isomers of 3-MMC using Raman spectroscopy and FTIR (Christie et al., 2014). Lee et al. and Frison et al. achieved the unambiguous identification of the positional isomers of 3-MMC using GC-IRD (Lee et al., 2019), LCHRAM-Orbitrap-MS and sd-GC-FTIR (Frison et al., 2020). Grumann and Auwärter highlighted that the unambiguous identification of positional isomers using LC–MS/MS can be challenging, however they successfully developed a liquid chromatography–electrospray ionization–tandem mass spectrometry (LC–ESI–MS/MS) method, with carefully optimized chromatographic conditions, which allowed for the separation of positional isomers, including those of 3-MMC, in different matrices such as seized materials, hair, serum, and urine specimens (Grumann and Auwärter, 2018). Maas et al. reported the application of an LC-ESI-MS/MS method capable of discriminating between the positional isomers of 3-MMC in real serum samples collected between June 2014 and August 2016 (Maas et al., 2017).

Carnes et al., highlighted that chromatographic analysis of cathinones can be problematic using gas chromatography due to the potential for sample decomposition in the hot injector port, with high injector temperatures potentially resulting in the production of enamine or imine cathinone artifacts, affecting peak shape and quantification (Carnes et al., 2017). The authors noted however that split mode injection and a relatively low injection port temperature can significantly reduce this issue (Carnes et al., 2017). Carnes et al.,

[36] 2-(Methylamino)-1-(2-methylphenyl)propan-1-one; formally notified by the EMCDDA in May 2014.

suggested the use of a combination of UHPSFC and GC for cathinone analysis and for the discrimination of positional isomers, such as 2-, 3- and 4-MMC (Carnes et al., 2017).

Hägele et al. demonstrated that positional isomers can be discriminated by use of CE, providing the example of the discrimination of three different fluorinated methcathinone derivatives, 2-FMC ([37]), 3-FMC ([38]) and 4-FMC ([39]), with carboxymethyl-β-CD as the chiral selector (Hägele et al., 2019). Kadkhodaei et al., also demonstrated that using an isocratic HPLC method with a specific chiral stationary phase (CSP) could discriminate between the positional isomers of 3-MMC (Kadkhodaei et al., 2020). Kranenburg et al. and Skultety et al. described the discriminating potential of GC-VUV (Kranenburg et al., 2019; Skultety et al., 2017). Kranenburg et al. also reported on the application of a derivatisation step for GC–MS-based NPS identification (Kranenburg et al., 2020a), and use of IRIS (Kranenburg et al, 2020c), for the discrimination of the positional isomers of 3-MMC.

Differentiation of enantiomers

Cathinones, such as 3-MMC, contain a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*R*)- and (*S*)-3-MMC. There is no information on the enantiomeric composition of the samples of 3-MMC detected within the European Union, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories.

Differentiation of enantiomers is possible using the following techniques: chiral chromatography, vibrational circular dichroism (VCD) spectroscopy and/or electronic circular dichroism (ECD) spectroscopy.

The separation of 3-MMC enantiomers by capillary electrophoresis has been described (Nowak et al., 2018a). Methodologies for enantiomeric discrimination by NMR (Stolarska et al., 2020) and HPLC using three types of CSPs (Wolrab et al., 2016) have been described. Alremeithi et al. demonstrated the determination of synthetic cathinone enantiomers in urine and plasma using GC-MS (Alremeithi et al., 2016; Alremeithi et al., 2018). Hägele et al., reported the use of a chiral capillary zone electrophoresis method (Hägele et al., 2019) and the use of an isocratic HPLC method with a specific chiral stationary phase (CSP) to successfully separate enantiomers of a range of synthetic cathinones, including 3-MMC (Hägele et al., 2020).

4.3 Pharmacological and toxicological description of the new psychoactive substance (Article 5b2(c))

3-MMC is a ring-substituted synthetic cathinone. Similar to closely related cathinones such as 4-methylmethcathinone (mephedrone, 4-MMC), 3-MMC has been shown to interact with the monoamine transporter system in a number of in vitro studies, which suggest that 3-methylmethcathinone acts as a psychostimulant. For example, 3-MMC was reported to inhibit the reuptake of dopamine (DA), noradrenaline (NA), and serotonin (5-HT) at their respective transporters DAT, NAT and SERT in human transporter stably transfected in

[37] 1-(2-Fluorophenyl)-2-(methylamino)propan-1-one
[38] 1-(3-Fluorophenyl)-2-(methylamino)propan-1-one
[39] 1-(4-Fluorophenyl)-2-(methylamino)propan-1-one

human embryonic kidney (HEK) 293 cells (Luethi et al. 2018, Eshleman et al. 2019). Furthermore, it was also shown that 3-MMC was able to act as a substrate-type releaser (Luethi et al. 2018, Blough et al. 2019, Walther et al. 2019), a feature also found in synthetic cathinones such as 4-MMC and methcathinone (Walther et al. 2019). Taken together, these results suggest that 3-MMC is likely to act as a stimulant in humans and might also show abuse liability. Acute effects of synthetic cathinones include stimulant effects such elevated mood, euphoria, and increased energy but undesired effects reflecting a sympathomimetic toxidrome are known to include hyperthermia, tachycardia, hypertension, and psychosis (Baumann et al. 2018).

The acute effects of 3-MMC share some similarities with other substituted cathinones such as mephedrone. These might include general stimulation, euphoria, sociability, increased heart rate and elevated blood pressure (Abdulrahim and Bowden-Jones, 2015; Ferreira et al., 2019; Soares et al., 2021). Synthetic cathinones also have an abuse liability and dependence potential (Bajaj et al., 2010; Batisse, et al., 2014; Dolengevich-Segal et al., 2016).

Based on the available information, the clinical features of poisoning with 3-MMC are similar to those observed with other synthetic cathinones. Adverse effects from overdosing 3-MMC might include neurological (e.g. hallucination, seizures, agitation, anxiety, psychosis, reduced consciousness), cardiovascular (e.g. tachycardia, hypertension, chest pain, cardiac arrest) and respiratory clinical features (Abdulrahim and Bowden-Jones, 2015; Bäckberg et al., 2015; Ferreira et al., 2019; Soares et al., 2021).

Similar to other stimulant cathinones, the use of 3-MMC with other central nervous system stimulants, including cocaine, amphetamine, methamphetamine or MDMA, is likely to produce synergistic effects which can increase the risk of an acute intoxication.

While there is limited information for 3-MMC, the chronic health risks might share some similarities to those seen with other synthetic cathinones such as mephedrone. This may include dependence.

ECHA reported to the EMCDDA that according to the Classification and Labelling (C&L) Inventory, 3-MMC hydrochloride salt has been labelled with the hazard statements ‘H335 may cause respiratory irritation’ and ‘H336 may cause drowsiness or dizziness’ (Section 4.6).

EFSA reported to the EMCDDA that while they do not currently have any information on 3-MMC, the available data suggest that 3-MMC is metabolised by a highly polymorphic cytochrome CYP2D6. As a result, pharmacokinetic and pharmacodynamic properties might vary between different individuals and extensive metabolisers might be at higher risk than poor metabolisers.

4.4 Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance (Article 5b2(d))

Europol received replies from 14 Member States: Austria, Bulgaria, Croatia, Cyprus Denmark, Finland, France, Germany, Greece, Latvia, Luxembourg, Poland, Portugal and Slovakia.

Replies were also received from Iceland ([40]), the United Kingdom (UK) ([41]) and the United States Drug Enforcement Administration (DEA) ([42]).

Involvement of criminal groups in the manufacture or distribution of 3-MMC

Slovakia reported the discovery of several abandoned clandestine laboratories in 2018, where 3-MMC was known to have been produced in high volumes. An explosion occurred at one laboratory in June 2018, reported to be due to incompetent handling, which resulted in environmental damage. Slovakia also reported a significant decrease in the activities of foreign criminal groups, dealing with the production of 3-MMC and 3-CMC, according to information from the police. This decrease is considered to be as a result of Covid-19 restrictions.

Poland reported that, while there was no information on clandestine laboratories producing 3-MMC, three clandestine laboratories were seized producing 4-MMC (mephedrone). No further information is currently available on these laboratories and the dates of the seizures were not specified.

No other information was received on the involvement of criminal groups in the manufacture or distribution of 3-MMC.

Information on seizures of 3-MMC

Generally, seizures of 3-MMC reported to Europol occurred between 2013 and 2021.

- Austria reported that a slight increase in cases involving 3-MMC in recent years. The largest seizure of 3-MMC reported during 2021 was approximately of 66 grams. 3-MMC has been seized as a white powder, a yellow powder (referred to as 'Synthacaine'), in crystalline form (referred to as 'Charly Sheen'), in pills or tablets (including ecstasy-type tablets such as pink 'Bitcoin'), and also mixed with cocaine.

- Bulgaria reported four seizures of 3-MMC in the mail, en-route from the Netherlands, by the National Customs Agency between 2019 and 2021. On 28 June 2019, 3 transparent bags containing one gram of 3-MMC, as a light beige powder, were seized. In 2021, 120 grams of 3-MMC were seized as a yellow powder at Sofia Airport on 20 April; on 6 July, 120 grams and an additional one gram, in crystalline form, was seized in two separate bags, also at Sofia Airport; and lastly, on 9 July, five grams of 3-MMC were seized, in white crystalline form, in five separate bags.

[40] Iceland reported that they had no information on 3-MMC.
[41] The UK reported that according to records from the Border Force on the INCB IONICS system, there have been 76 seizures of 3-MMC in the UK in 2021. Of these, the Netherlands was the origin country for 74 of the shipments, while France (1) and Spain (1) were the other origin countries reported. In total, they reported that there have been 414 incidents worldwide, associated with 3-MMC, which have been recorded in the system since March 2015.
[42] The DEA reported that information on seizures of 3-MMC have been provided by the DEA laboratory information management system (LIMS) since it became the official record in October 2014. Information on other detections from forensic laboratories other than the DEA system has also been provided by the Diversion Control Division's NFLIS database. The DEA reported that it is not aware of any domestic synthesis of 3-MMC and the substance is often purchased via the surface or dark web and then shipped to the US. They noted that some of the seizures appeared to be labelled as research chemicals, they believe could have been purchased from chemical supply companies. A total of four detections of 3-MMC were identified in the DEA LIMS in 2020, in powder form, ranging in quantity from 3.03 to 49.5 grams. In three of the cases the hydrochloride salt form of 3-MMC was identified and in the other case 3-MMC was identified with *N*-ethylhexedrone. A total of 52 detections of 3-MMC were registered in the Diversion Control Division's NFLIS database, recorded between 2012 and 2021.

- Denmark reported that most seizures of 3-MMC, approximately 100, were of small quantities associated with personal consumption, seized in postal packages originating from countries within the EU.

- Finland reported minor and infrequent seizures of 3-MMC, by police and customs, also reported to the EMCDDA.

- France reported that 3-MMC has been identified in detections since 2014 and is known to be consumed in party settings, particularly in the context of chemsex. Users of 3-MMC reportedly compare it with MDMA, cocaine or speed, and has been marketed as a substitute for 4-MMC following its control nationally in 2010.

  According to information available to French police and OFDT (43), 3-MMC is mainly purchased online from the surface web, through websites selling 'research chemicals' mostly based in the Netherlands, and from the dark web, for a reported price of ten euro per gram. The online purchase of 3-MMC is considered cheaper than through a dealer. It was stated that while some users buy 3-MMC for individual consumption, group orders of 25 to 50 grams, and up to 500 grams, are known. Products sold online as 3-MMC have been found to contain 3-CMC. 3-MMC is sold in powder and solid (known as 'crystal') form and the price can vary from 40 to 1500 euro for between 2.5 and 200 grams. In the case of injection of 3-MMC, France reported that the average dose is between 0.1 and 0.3 grams, while problematic drug users can use up to 7 grams in a 24-hour period.

  France reported that seizures of 3-MMC remain low, with 12 seizures of 3-MMC reported in 2020. 3-MMC was often identified in combination with other substances, such as other synthetic drugs or cocaine, and in quantities varying from one gram to one kilogram. In October and December of 2020, 982 and 1587 grams of 3-MMC was seized in Paris, respectively.

  France reported one suspected death associated with 3-MMC in 2020 and two death cases associated with the consumption of 3-MMC and cocaine in one case, and 3-MMC and GHB in the other case, in 2021.

- Germany reported that all information has been sent to the EMCDDA by the DBDD (44).

- Greece reported seizures of 3-MMC by Hellenic police in 2013 and 2019. While they report no street or trade name of 3-MMC, it is commonly referred to as 'crystal' but they caution that this term may also refer to various substances in crystalline form. 3-MMC was identified in 1.2 and 13.8 grams of white powder, seized in two separate seizures by police in Rhodes, following police checks in June 2013. Both seizures were reported as cases of personal possession, with the smaller quantity reportedly purchased from an unknown individual for 70 euro, whereas the larger quantity was reportedly purchased online as 'HERBAL HIGH' for four euro. A total of 2007 grams of 3-MMC, as off-white crystals, was seized by the Security Department of Thiva, in Thive in January 2019. No further information is available on this seizure.

43 The French Observatory for Drugs and Drug Addiction (OFDT)
44 The German Monitoring Centre for Drugs and Drug Addiction (DBDD)

- Latvia reported six seizures of 3-MMC, amounting to a total of 13.4889 grams, in postal packages originating from outside of Latvia, in 2019. No seizures of 3-MMC were reported in 2020 and 2021.
- Portugal reported that there have been no seizures of 3-MMC, also known as 'mepedrona'.
- Slovakia reported seizures by police of 3.31 grams of 3-MMC and 148.2 grams of 3-CMC in 2019. A total of 3.54 grams of 3-MMC was seized by police in 2020.

Austria, Bulgaria, Denmark, France, Greece, and Portugal reported information on the national control measures applied to 3-MMC and/or 4-MMC. Croatia, Cyprus and Luxembourg reported that no information was available.

4.5 Information on the human and veterinary medical use of the new psychoactive substance, including as an active substance in a medicinal product for human use or in a veterinary medicinal product

Based on the reported information from the EMA ([45]), it appears that 3-MMC is not an active substance in:

a. a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/ EC of the European Parliament and of the Council, Directive 2001/82/EC of the European Parliament and of the Council or Regulation (EC) No 726/2004 of the European Parliament and of the Council;

b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;

c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority.

In addition, it appears that 3-MMC is not an active substance in the following, although the information, especially in relation to use in extemporaneously prepared products, is unknown in some cases:

d. an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/ EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;

e. an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council.

[45] 26 Member States, as well as Norway and Iceland provided a response to the EMA's request regarding human and/or veterinary medicinal products.

4.6 Information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes

3-MMC is available as an analytical reference material in clinical and forensic case work and is used scientific research. There is currently no information that suggests 3-MMC is used for other legitimate purposes.

ECHA reported that there are no registrations or classification and labelling (C&L) notifications for 3-MMC in the C&L Inventory database ([46]).

ECHA reported a C&L notification for the hydrochloride salt of 3-MMC that has been labelled with the hazard statements H335 ('may cause respiratory irritation') and H336 ('may cause drowsiness or dizziness') (ECHA). The identity of C&L notifiers is not published on the ECHA dissemination website, due to the sensitivity of this information.

EFSA holds no information on 3-MMC and has not assessed this substance in any context.

4.7 Information on whether the new psychoactive substance is subject to any restrictive measures in the Member States

Six Member States (Bulgaria, Greece, Luxembourg, the Netherlands, Romania, and Spain) reported that 3-MMC is not subject to restrictive measures at national level. The Netherlands reported that 3-MMC has been subjected to a national risk assessment and will be scheduled as a list II substance under the Opium Act, as of 1 November 2021.

When reporting whether 3-MMC is subjected to restrictive measures, 9 Member States (Austria, Belgium, Croatia, Denmark, Hungary, Ireland, Latvia, Lithuania, and Malta) mentioned that this substance is covered by the generic definition of cathinones.

Drug control legislation

Thirteen Member States (Croatia, Czechia, Denmark, Estonia, France, Germany, Italy, Latvia, Poland, Portugal, Slovenia, Slovakia, and Sweden), Turkey and Norway reported that 3-MMC is controlled under drug control legislation.

- Croatia reported that 3-MMC is controlled by generic definition since 2014;
- Czechia reported that 3-MMC is controlled since 2015;
- Denmark reported that 3-MMC is covered by generic cathinone classification since 2012;
- Estonia reported that 3-MMC is controlled under the Act on Narcotic Drugs and Psychotropic Substances and Precursors thereof, List I, since 2015;

[46] ECHA's C&L Inventory database contains classification and labelling information on notified and registered substances received from manufacturers and importers. It also includes the list of harmonised classifications. The information included in the preparation of this report is public

- France reported that 3-MMC is controlled since 2012;
- Germany reported that 3-MMC is controlled as a non-marketable narcotic drug (Annex I) of the German Narcotic Drugs Act, since 2014;
- Italy reported that 3-MMC was included in the list of new psychoactive substances in the update of 29 December 2020 of the decree of the President of the Republic n. 309;
- Ireland reported that 3-MMC is covered by the generic cathinone definition under Statutory Instrument 551/2011, in force since November 2011;
- Latvia reported that 3-MMC is covered by generic definition in the law On the Procedures for the Coming into Force and Application of the Criminal Law;
- Poland reported that 3-MMC is controlled by a regulation of the Minister of Health since 2015;
- Portugal reported that 3-MMC is included in Law No. 13/2012 of 26 March which amends for the nineteenth time the Decree-Law No. 15/93 of 22th January, as of 2012.
- Slovenia reported that 3-MMC is controlled by the Regulation on the Classification of Illicit Drugs since 2011;
- Slovakia reported that 3-MMC is controlled by Act No. 139/1998 Coll. on Narcotics and Psychotropic Substances and Preparations since 2014;
- Sweden reported that 3-MMC is controlled as a narcotic drug since 2013;
- Turkey reported that 3-MMC is controlled by Law on Control of Drugs numbered 2313, since 2014;
- Norway reported that 3-MMC is classified as a narcotic in Norway and is listed in Narcotics legislation. Private import by mail is not permitted and companies need licenses to import, export, or manufacture 3-MMC. 3-MMC is also classified as a ‘forbidden’ narcotic, meaning even stricter regulations regarding licenses for import/export/manufacture.

New psychoactive substance legislation

Six Member States (Austria, Belgium, Cyprus, Finland, Hungary, Malta) reported that 3-MMC is controlled under new psychoactive substance legislation.

- Austria reported that 3-MMC is covered by generic definition by the Austrian Act on New Psychoactive Substances of 2012;
- Belgium reported that 3-MMC is covered by generic definition;
- Cyprus reported that 3-MMC is controlled since 2011;

- Finland reported that 3-MMC is banned by a government decree on psychoactive substances since 2014;
- Hungary reported that 3-MMC is covered by the definition of cathinones in Annex I of Decree no. 55/2014 of the Ministry of Human Capacities, Substances since 2012.
- Malta reported that 3-MMC is not explicitly mentioned in their laws. Police prosecutes the substance, as it is considered a derivative of cathinone and a new psychoactive substance.

Medicines legislation

Lithuania reported that 3-MMC is controlled under medicines legislation (included in the group of cathinone derivatives) since 2015.

Other countries

3-MMC is controlled in China since October 2015.

4.8 Information on whether the new psychoactive substance is currently or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific, and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971.

On 29 September 2021, the World Health Organization informed the EMCDDA that 3-MMC has been under assessment. Specifically, 3-MMC has been subject to critical review by the WHO Expert Committee on Drug Dependence (ECDD) at the Thirty-Eight ECDD meeting that was held 14–18 November 2016 (WHO, 2016). The Committee did not make recommendations for scheduling to CND or recommended 3-MMC for surveillance. The Committee was unable to reach consensus, and instead it deferred an opinion, and requested the Secretariat to arrange another critical review of 3-MMC at a subsequent meeting of the Expert Committee. A further ECDD review of 3-MMC has not taken place yet.

4.9 Other relevant information

Cases of acute poisonings, death investigations and suspected cases of driving under the influence with confirmed exposure to 3-MMC have been published in the scientific and medical literature. Some of the reported cases occurred in Europe: France, Norway, Poland, Sweden, and the United Kingdom (Bäckberg et al., 2015; Drevin et al., 2021; Ferreira et al., 2019; Margasińska-Olejak et al., 2019; Pieprzyca et al., 2021). The clinical features of poisoning were similar to those reported for other synthetic cathinones.

Austria

In Austria, the drug checking service CheckIt reported seven samples containing 3-MMC between February 2017 and September 2021. In five cases 3-MMC was sold as other substance: mephedrone (in 4 cases) and ketamine (1). Six samples contained other substances such as 4-CMC, 4-CEC, 4-CMC, lidocaine, methoxphenidine, or other unspecified compounds (CheckIt, 2021).

Netherlands

Based on signals suggesting increased availability and harms related to 3-MMC in the Netherlands, 3-MMC was subject to a national risk assessment procedure in 2021.

A total of eight deaths and six acute non-fatal poisonings with confirmed exposure to 3-MMC that occurred in the Netherlands have been reported in the Dutch risk assessment report (CAM, 2021) ([47]). Where known, four of the deaths occurred in 2020 and one in 2019. Two of the deaths were monointoxications with 3-MMC and one death was a mixed intoxication in which 3-MMC contributed to the death. The reported clinical features of poisoning were similar to those reported for other synthetic cathinones.

In addition, two deaths and 110 cases of acute poisoning with suspected exposure to 3-MMC have also been reported (CAM, 2021).

According to the Annual Report from the Drugs Information and Monitoring System (DIMS, 2021), in 2020 almost half of the samples submitted as mephedrone (4-MMC) contained 3-MMC instead of mephedrone.

Information from other countries

Switzerland

In Switzerland, the drug checking service SaferParty reported ten samples containing 3-MMC between November 2019 and September 2021. In all but two of the cases ([48]), 3-MMC was sold as other substance: mephedrone (in 4 cases), methylone (2), 3-MDMC (1), and 4-MDMC (1). Two samples contained other substances such as MDMA, 3-CMC, 4-MEC, N-ethylhexedrone, 4-MMC, ketamine, and caffeine (SaferParty, 2021).

United Kingdom

In the United Kingdom, 29 samples containing 3-MMC were submitted to WEDINOS ([49]) between December 2014 and September 2021. In the majority of cases, 3-MMC was sold as other substance: mephedrone (in 9 cases), ecstasy/MDMA (6), 2C-B (2), cocaine (2), ketamine (1), 3-FPM (1), and 4-FA (1). The self-reported effects from users were consistent with synthetic cathinones, and included euphoria, increased energy, agitation, irregular heartbeat, visual hallucinations, chest pains, confusion, and paranoia (WEDINOS, 2020).

[47] These cases (section 4.1.2) were reported after the data collection was closed and have not been included in the total counts.
[48] In one of these cases, the sample was sold as '5-MMC', which would be equivalent to 3-MMC.
[49] WEDINOS is a drug testing service in the United Kingdom operated by Public Health Wales. http://www.wedinos.org/about_us.html

Of particular note is a recent increase in ecstasy tablets containing 3-MMC in the United Kingdom. All six samples submitted to WEDINOS as MDMA/ecstasy tablets were received between August and September 2021. Similar cases of ecstasy tablets containing 3-MMC have been also recently reported by other drug checking services in the United Kingdom, such as the Loop (The Loop, 2021).

5. Analysis and assessment

2-(Methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) is a synthetic cathinone with stimulant effects that is monitored as a new psychoactive substance by the EMCDDA in accordance with Regulation (EC) No 1920/2006. The substance is an *N*-alkylated and ring-substituted cathinone and contains a chiral centre so two enantiomers may exist: (*R*)-3-MMC and (*S*)-3-MMC. It is a derivative of cathinone, the naturally occurring stimulant and main psychoactive substance in the khat plant *Catha edulis*. 3-MMC is also closely related to and shares similar stimulant effects with methcathinone (ephedrone) and 4-methylmethcathinone (4-MMC; mephedrone). Cathinone, methcathinone, and 4-MMC are controlled under the 1971 United Nations Convention on Psychotropic Substances because of the public health and social risks that they pose.

3-MMC was first identified in Europe in June 2012 based on a customs seizure made in Sweden. The appearance of 3-MMC on the drug market coincided with the control of 4-MMC in Europe, after the latter spread rapidly between 2009 and 2010 when it was produced, distributed, and sold openly as a 'legal' stimulant. At least in part, it appears that 3-MMC is being used as a 'legal' replacement to 4-MMC.

The limited information suggests that 3-MMC is typically sold and sought after as a stimulant drug in its own right, but it may also be mis-sold as other drugs. Similar to other cathinones, such as 4-MMC, 3-MMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It appears to be used by existing stimulant users, such as those who use cocaine, amphetamines, ecstasy, and other cathinones, who either add it to their existing repertoire or use it as a replacement substance. This includes recreational use, and, in some cases high risk use, such as injecting. In addition, in at least one country, it may also be used by vulnerable groups such as young people partly because it is easily available, not controlled, and has a relatively low cost. It appears that 3-MMC is used in private spaces (such as homes and domestic parties), as well as recreational settings (such as nightclubs, bars/pubs, music festivals), and as part of chemsex settings.

Since 2012, 3-MMC has been identified in 23 Member States, as well as Turkey and Norway. In total, approximately 2 630 kg of 3-MMC powder has been seized, including at least 2 360 kg by customs and 184 kg by police. Following a decline in seizures in Europe between 2016 and 2019, which coincides with the control of 3-MMC in China in October 2015, the substance appears to have re-emerged during 2020. During that year, approximately 740 kg of powder was seized, including 630 kg by customs (of which approximately 600 kg (95%) originated from India) and 110 kg by police. This represents just over a quarter of the total quantity of 3-MMC powders seized since monitoring of the substance began in Europe in 2012. During 2021, 3-MMC continues to be imported, distributed, and used in parts of Europe; this includes a single large-scale seizure of 122 kg of powder at the external EU border.

The available information suggests that 3-MMC is currently imported into Europe in bulk quantities mainly from India, with approximately 600 kg of pure powders that originated from the country seized in 2020. It is then processed, packaged, and then distributed in wholesale and retail amounts in Europe either online or by street dealers. The substance may also be imported as a masked drug (where non-controlled chemicals are used) and then presumably

converted into 3-MMC in Europe. In addition, at least three illicit laboratories producing 3-MMC have been seized in Europe, with the most recent laboratory seized in 2020.

Of particular note, is that while the quantities of cathinone powders seized in Europe have been decreasing since they peaked in 2015 and 2016, at around 1 800 kg per year, and falling to 750 kg by 2019, during 2020 there was a significant increase, with approximately 3 300 kg of powders seized. It appears, that at least in part, this increase has been driven by 3-MMC which accounted for almost a quarter of the quantity of powders seized during 2020. In addition, 3-chloromethcathinone (3-CMC), which is also currently the subject of an initial report following its emergence in Europe, accounted for a similar quantity.

A total of 8 acute non-fatal poisonings with confirmed exposure to 3-MMC have been reported by three Member States: France, Germany, and Spain. In six cases other substances were identified. Where reported, the cases occurred between 2014 and 2021. Four of the cases could be classified as life-threatening.

A total of 19 deaths with confirmed exposure to 3-MMC have been reported by four Member States: Sweden, France, Spain, and Slovenia. In seven of the cases, other substances were identified. Where reported, the cases occurred between 2013 and 2021. In at least three cases, 3-MMC was the cause of death or contributed to the death.

In addition, 6 acute non-fatal poisonings and 8 deaths with confirmed exposure to 3-MMC have been reported by the Netherlands, after the data collection period for the initial report had closed. In two of the deaths, no other substances were identified. Where reported, one of the deaths occurred in 2019 and four in 2020.

Two cases of substance dependence have been reported by one Member State: France.

Currently, there is limited information on the involvement of criminal groups in the manufacture, trafficking, and distribution of 3-MMC within Europe. However, based on information reported to the EMCDDA, there is evidence of criminal acts, such as trafficking, illicit production, and supply offences, involving 3-MMC.

The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution and use of 3-MMC is currently unknown. However, seizures of more than of 720 kg of bulk powders by customs agencies during the pandemic suggest that 3-MMC continues to be imported and distributed in Europe. It is possible that, in case of a reduced availability of controlled stimulants (such as 4-MMC and MDMA) in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including 3-MMC.

Based on the available information, it appears that 3-MMC is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe. However, the use of 3-MMC as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States due to a lack of information. Aside from limited use as an analytical reference standard and in scientific research, there is currently no information that suggests that 3-MMC is used for other legitimate purposes.

3-MMC is subject to restrictive measures in 21 Member States, Turkey, and Norway – in some cases, being covered by a generic definition of cathinones. 3-MMC has been

controlled in China since October 2015. It is unknown if 3-MMC is controlled in India, from where bulk quantities of pure powder have originated and recently been seized by customs agencies in Europe.

3-MMC has been subject to critical review by the WHO Expert Committee on Drug Dependence in November 2016. The Committee did not make recommendations for scheduling to CND or recommended 3-MMC for surveillance. The Committee was unable to reach consensus, and instead it deferred an opinion, and requested the Secretariat to arrange another critical review of 3-MMC at a subsequent meeting of the Expert Committee. A further ECDD review of 3-MMC has not taken place yet.

Since the critical review in 2016, significant new information has been reported by the Member States to the EMCDDA that provides evidence that 3-MMC might pose health and social threats at Union level. This includes information on seizures of large quantities of bulk powders of pure 3-MMC during 2020 and 2021, illicit production of the substance in Europe, as well as recent reports of acute poisonings and deaths involving the substance. Taken together, this suggests that 3-MMC may be re-emerging in Europe.

The EMCDDA will continue to intensively monitor 3-MMC to ensure that new information is provided to the Member States, Europol, the Commission and the EMA through the European Union Early Warning System in a timely manner, to strengthen situational awareness as well as to continue to inform preparedness and response measures at both national and EU levels to protect public health.

Based on the analysis of the available information, especially the signals suggesting a recent re-emergence of 3-MMC, the EMCDDA considers that there are indications that 3-MMC may pose health or social risks at Union level. We conclude that the potential health and social risks posed by the use, manufacture, distribution and involvement of criminal groups could be thoroughly assessed through a risk assessment procedure in accordance with Article 5c of Regulation (EC) No 1920/2006.

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