European Monitoring Centre for Drugs and Drug Addiction

ADVANCED RELEASE

EMCDDA initial report on the new psychoactive substance 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC)

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.

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for Drugs and Drug Addiction

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Contents

1. Introduction

1-(3-Chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) is a synthetic cathinone stimulant. It is a ring-substituted cathinone, which is structurally related to methcathinone ([1]) and 4-chloromethcathinone (4-CMC) ([2]).

In Europe, 3-CMC 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-CMC was formally notified as a new psychoactive substance ([6,7]) by the EMCDDA on behalf of Sweden on 14 October 2014. The notification was based on the identification of the substance in a police seizure of 0.72 grams of powder made on 22 September 2014 in Norrköping.

Since the formal notification, information on 3-CMC 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.

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-CMC which accounted for almost a quarter of the quantity of powders seized during 2020. In addition, 3-methylmethcathinone (3-MMC), which is also currently the subject of an initial report following its emergence in Europe, accounted for a similar quantity.

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-CMC and 3-MMC. In addition, there has also been a recent increase in the number of laboratories producing cathinones, including 3-CMC and 3-MMC, seized in Europe.

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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

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 ([8,9]) on 3-CMC, 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-CMC 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-CMC in order to support the production of the initial report.

The EMCDDA collected information through:

- 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

[8] 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

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

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-CMC 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-CMC 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-CMC 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 ([10]), Directive 2001/82/EC of the European Parliament and of the Council ([11]) or Regulation (EC) No 726/2004 of the European Parliament and of the Council ([12]);

    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 ([13]).

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

[10] 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).
[11] 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).
[12] 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).
[13] 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).

- 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-CMC (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-CMC has been available on the drug market since 2014. Although 3-CMC is screened for in many forensic and toxicology laboratories in Europe, it cannot be excluded that some cases of 3-CMC are undetected or unreported, in particular in serious adverse events.

3-CMC has two positional isomers, whose discrimination poses analytical challenges. Due to differences in reporting practices across Europe, the discrimination of 3-CMC 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-CMC 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-CMC 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-CMC has been present on the European drugs market since at least September 2014. The substance has been detected across a total of 23 Member States, and Norway. These detections relate to 9 607 seizures, 67 collected samples and 213 biological samples.

Most reports related to the first identification of 3-CMC in a country occurred between 2014 and 2016 (n=16; 67%), around the first identification in Europe.

Information from seizures

In total, 9 607 seizures, amounting to 2.7 tonnes of material (in all physical forms) were reported by 23 countries. Of these, 1.1 tonnes were reported in the period of 2014 to 2020. The remaining 1.6 tonnes were reported in 2021.

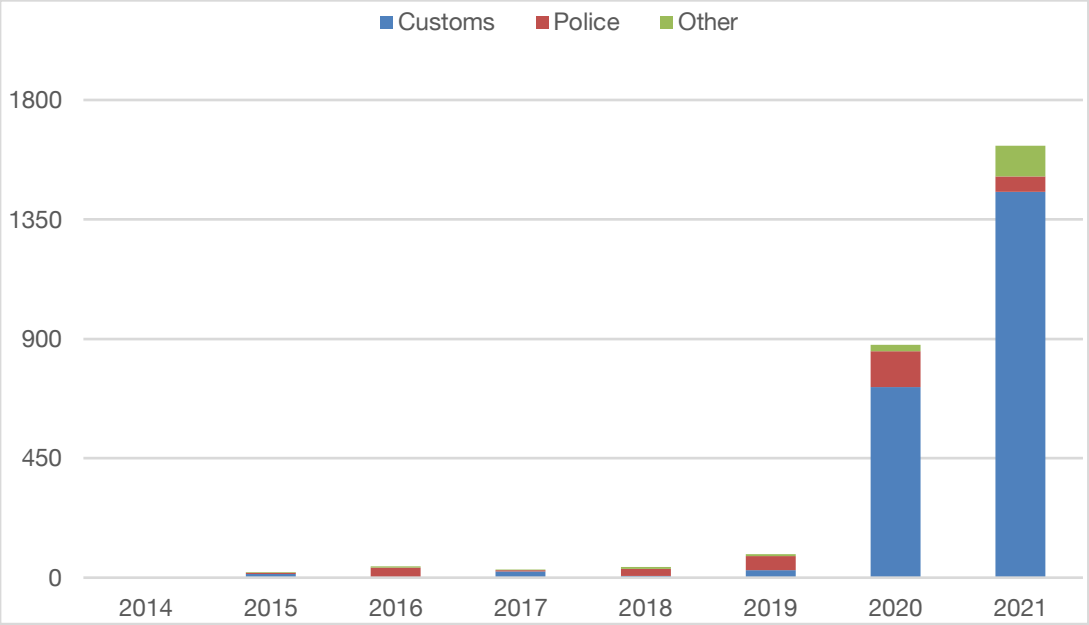
The large majority of the cases reported (9 375; 98%) were seizures of powders, amounting to 2.7 tonnes (Figure 1). To a much lesser extent, seizures of tablets and capsules (196 cases), other or unknown physical forms (21), herbal material (7), liquids (7), blotters (1), were also reported. For this reason, the following analysis is focused on seizures of powders.

A total of 9 375 seizures of powders were reported. The majority of cases comprise police seizures (6 702 cases; 71%). There were 533 cases reported by customs (6%) and 2 140 other seizures (23%) for which the seizing authority is either not reported or not known.

The majority of cases were reported by Poland (7 663 cases; 82%). The country reporting the largest quantities of seized powders was the Netherlands (2.1 tonnes; 78%). Of these, 697 kg were seized in 2020, and 1.4 tonnes in 2021, by Dutch customs.

A summary of the information reported is provided below.

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



Customs seizures

Since 2014, customs authorities have reported 533 seizures of 3-CMC amounting to 2.2 tonnes of powders. Of these, 165 seizures (1.4 tonnes; 65%) occurred in 2021. While most seizures were reported by Sweden (199 cases; 37%), the largest quantities of powders were seized in the Netherlands (2.1 tonnes; 94% 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 3-CMC powders to Europe.

The largest single seizure was also reported by Dutch customs and occurred in 2021. The seizure comprised of 400 kg of 3-CMC powders, also containing iso-3-CMC, which may have been leftover impurity of synthesis. An additional 4 seizures, weighing a total of 1 tonne of 3-CMC powders were also reported by Dutch customs in 2021.

For the majority of customs seizures, the origin of the consignment was not reported (520 cases; 1.5 tonnes). For the 13 cases where the origin of the consignment is known, the largest quantity of powders originated in India (6 seizures pure powder amounting to 695 kg, seized in the Netherlands, in 2020). In addition, 2 seizures were reported in 2015 which originated in China and amounted to 5.9 kg. Whenever European countries were mentioned as the country of origin (n=5), the consignments were typically small (less than 5 grams). Belgium and the Netherlands were the only countries of origin mentioned in those cases.

The purity of 3-CMC detected was rarely reported. In the seizures that originated in India, 3-CMC consisted of pure white powders. Sometimes, they were reported as ‘crystals’ or ‘rocks’. When reported, labels referred to “‘3-CMC’” or “‘Clophedrone’”.

For the very few cases were other substances were reported, the powders typically contained other stimulants such as other cathinones (including 3-MMC) and, amphetamine (in 8 cases). One noteworthy exception was the seizure mentioned above where iso-3-CMC

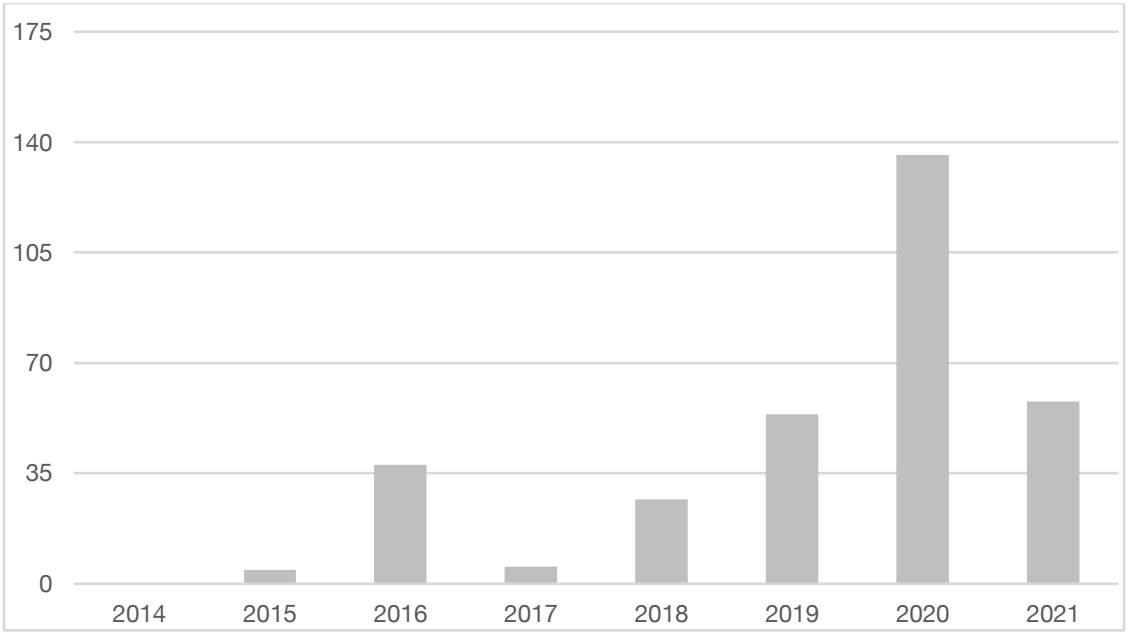
was detected in 3-CMC powders. Adulterants and diluents reported included caffeine, benzocaine, menthol and mannitol.

Police seizures

Since 2014, police authorities have reported 6 702 seizures of powders containing 3-CMC, amounting to 322 kg (Figure 2).

Poland, Germany and Sweden reported 99% of the powders seized (6624 seizures amounting to 318 kg). Poland reported 94% of all Police seizures (6329 cases) and half of the quantity of powders seized by police (160 kg); German Police reported 28 seizures (102 kg); and Swedish police reported 267 seizures (57 kg powders) all of which occurred in 2021. The remaining countries reported considerably smaller amounts.

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



The largest single seizure of 3-CMC by police occurred in 2020 in Germany, in Bavaria. The seizure consisted of 80 kg of powders contained in barrels labelled ‘‘‘Clophedron’’’. No other substances were detected.

In reports of police seizures, quantification of the purity of the powders is typically not provided. In the 12 cases where quantitative information on purity was provided (reported by Germany) powders ranged from 79.5% to 98.1% purity. The purest powders were reported as the hydrochloride salt of 3-CMC and the less pure were reported as the base form.

Other substances detected in police seizures (not quantified) included other cathinones (including 4-CMC, 191 cases) and to a lesser extent illicit substances (such as amphetamine, MDMA, and cocaine) as well as ketamine. Adulterants and diluents reported included caffeine, benzocaine, lidocaine, paracetamol, caffeine, alanine and citric acid.

Powders were often described from as crystals, ranging from 'colourless crystals' to white, or 'light-yellow' crystalline material.

Other seizures

In 2 140 cases, the reporting authority was not reported or unknown. These cases amounted to 157 kg of powders. Of these, 116 kg (74%) were seized in 2021 by Poland, in 624 cases. In these cases, other cathinones (including 3-MMC and 4-CMC), and illicit drugs (MDMA and amphetamine) were also detected.

Information from collected samples

A total of 67 collected samples were reported to the EMCDDA, between 2015 and 2021, by 7 Member States: Austria (6), Czechia (1), France (2), Poland (55), Portugal (1), Slovenia (1), and Spain (1). Of these, 66 samples were in powder form.

Samples were collected by drug-checking services (10 cases) or in the context of pilot drug checking projects (4). A total of 48 collected samples were also reported by the Polish Central Customs and Tax Laboratory in 2019.

3-CMC was the only substance detected in 50 cases. In 17 cases, it was detected in combination with other cathinones: 4-CMC (6 cases); 4-CMC and 4-CEC (4); 4-CMC, 4-FPD and 4-CEC (2), 4-CEC (1), methcathinone (1), *N*-methyl-*N,N*-dimethylcathinone (1), and 3-MMC (1). In the latter case, the sample was reported to contain 38.7% of the hydrochloride salt of 3-CMC. In one case it was detected in combination with caffeine (1).

3-CMC was sold as other cathinones in 3 cases – as 3-MMC in 1 case, and as 4-MMC in 2 cases, where it was detected in combination with 4-CMC. In view of this, it is possible that some users might consume the substance inadvertently when purchasing other cathinones.

Information on where the samples were purchased, packaging and pricing is mostly unreported. When reported, the substance was bought online (3 cases).

The scientific literature has limited information regarding collected samples of 3-CMC. There is only one recorded instance where other substances were missold as 3-CMC – a sample bought as 3-CMC which contained 4-CMC (Grifell et al. 2017).

Information from biological samples

A total of 213 detections where 3-CMC was analytically confirmed in biological samples were reported by 4 Member States: Sweden (182), Hungary (18), Poland (12) and Spain (1).

Serious adverse events with confirmed exposure to 3-CMC from biological samples — 1 acute poisoning reported by Spain and 10 deaths reported by Poland (7) and Sweden (3) — are discussed in Section 4.1.2.

In addition to these, 202 detections of 3-CMC in biological samples were reported by Sweden (179), Hungary (18) and Poland (5). The biological samples were reported between 2015 and 2021 as follows: 2015 (18 samples), 2016 (1), 2017 (48), 2018 (13), 2019 (17), 2020 (36), 2021 (69). Detections included:

- 4 samples associated with deaths, reported by Sweden ([14]);
- 2 samples associated with non-fatal poisonings, reported by Hungary ([15]);
- 27 samples associated with petty drug offences, reported by Sweden;
- 21 cases of persons suspected of driving under the influence of drugs, reported by Sweden (16), Poland (3) and Hungary (2);
- 15 samples analysed for criminal justice purposes, reported by Hungary (14) and Poland (1);
- 15 samples associated with abuse cases, reported by Sweden;
- 6 samples analysed for drug treatment purposes, reported by Sweden; and
- 112 samples reported as aggregated data associated with forensic case work (details not specified), reported by Sweden (111) and Poland (1).

4.1.2 Health problems

Acute poisonings

One acute non-fatal poisoning with confirmed exposure to 3-CMC was reported by Spain and was related to chemsex ([16]). Other substances were identified in biological samples, including 3-MMC, GHB/GBL, cocaine, sildenafil, and methamphetamine.

In addition, France and Sweden reported cases of serious adverse events without analytical confirmation from biological samples. These include one case of drug dependence reported by France and 47 acute poisonings with suspected exposure to 3-CMC reported to the Swedish Poisons Information Centre between 2015 and 2021: 2015 (7 cases), 2016 (4), 2017 (8), 2018 (8), 2019 (6), 2020 (7), and 2021 (7). These cases are not discussed further in this report.

Deaths

A total of 10 deaths with confirmed exposure to 3-CMC were reported by Poland (7) and Sweden (3). The cases occurred between November 2019 and June 2021 (one case in 2019; three cases in 2020; six cases in 2021). Of the deaths, eight were male and two were female. Where reported, the males were aged between 17 and 47 (mean: 30.5; median: 39.5).

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

[14] 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.
[15] 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.
[16] Chemsex is a term used to describe an intentional sex under the influence of psychoactive drugs, mostly among men who have sex with men.

Of note is that in two of the cases where other substances where identified, the only additional finding was alcohol. In at least three of the cases, the individuals were found dead. A cause of death was reported in nine cases. In five cases, 3-CMC was the cause of death or contributed to the death; in the remaining cases, the reported causes of death were multi-organ trauma as a result of a traffic accident (in two cases), intoxication with oxycodone and benzodiazepines (in one case), and gunshot wound to the chest (in one case).

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

4.1.3 Social problems

While there is limited data on the social risks related to the use of 3-CMC, it is possible that they share some similarities with those associated with other synthetic cathinones like 4-MMC. Depending on the user group, these might include changes in the social and economic conditions of the individual, impact their family structure and employment situation, as well as confer increased vulnerability (Brookman et al. 2016).

4.1.4 Patterns of use

The limited information suggests that 3-CMC is 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-CMC, it is likely that 3-CMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It is expected that the substance is 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 likely includes recreational use, and, in some cases high risk use, such as injecting. Although specific information is lacking, similar to other cathinones, it is likely that 3-CMC is used in private spaces (such as homes and domestic parties) as well as recreational settings (such as nightclubs, bars/pubs, music festivals).

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-CMC is a synthetic derivative of the naturally occurring substance cathinone, which is internationally controlled ([17]), and one of the psychoactive principles in khat (*Catha edulis* Forsk). 3-CMC was described in the scientific literature in the months prior to its first detection on the drug market in Europe in September 2014 (Blough et al., 2014).

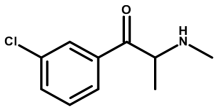
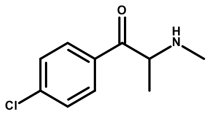
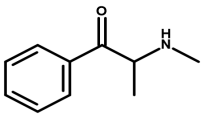
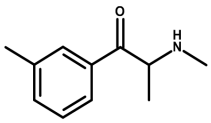
As with many other synthetic cathinone derivatives monitored by EMCDDA through the EU Early Warning System, 3-CMC is an *N*-alkylated and ring-substituted cathinone.

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

The common name 3-CMC is derived from 3-chloromethcathinone ([18]). 3-CMC is the 3-chloro derivative of methcathinone ([19]) and a positional isomer ([20]) of 4-CMC (4-chloromethcathinone) ([21]), which are both internationally controlled. 3-CMC is structurally related to 3-MMC (3-methylmethcathinone) ([22]), differing on the substituent present at the 3-position of the phenyl ring. Higher and lower homologues of 3-CMC monitored by the EMCDDA are: 3-CEC (3-chloroethcathinone) ([23]) and 3-chlorocathinone ([24]), respectively.

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

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

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

Common name(s):

3-CMC

3-Chloromethcathinone

Systematic (IUPAC) name:

1-(3-Chlorophenyl)-2-(methylamino)propan-1-one

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

Other chemical names:

1-(3-Chlorophenyl)-2-(methylamino)-1-propanone

[18] The origin for the abbreviated common name is indicated by underlining the relevant letters in the common name.
[19] 2-(methylamino)-1-phenyl-propan-1-one; listed in Schedule I of the 1971 United Nations Single Convention on Psychotropic Substances.
[20] 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.
[21] 1-(4-Chlorophenyl)-2-(methylamino)propan-1-one; formally notified by the EMCDDA in August 2014; and listed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.
[22] 2-(Methylamino)-1-(3-methylphenyl)propan-1-one; formally notified by the EMCDDA in September 2012.
[23] 1-(3-Chlorophenyl)-2-(ethylamino)propan-1-one; formally notified by the EMCDDA in March 2016.
[24] 2-Amino-1-(3-chlorophenyl)propan-1-one; formally notified by the EMCDDA in November 2020.

1-(3-Chloro-phenyl)-2-methylamino-propan-1-one

3′-Chloro-2-methylaminopropiophenone

2-(Methylamino)-1-(3’-chlorophenyl)-1-oxopropane

Other names:

3-Chloro-methcathinone

3-Cl-methcathinone

3-Cl-MCAT

Clophedrone

Metaclephedrone

Meta-chloro-*N*-methyl-cathinone

Meta-chloromethcathinone

PAL-434

Chemical Abstracts Service (CAS) registry numbers:

1049677-59-9 (base)

1607439-32-6 (hydrochloride salt)

2291021-63-9 (*R*-isomer)

2107425-89-6 (*S*-isomer)

IUPAC International Chemical Identifier Key (InCHI Key):

VOEFELLSAAJCHJ-UHFFFAOYSA-N (base)

QXEPSICDXPPHTO-UHFFFAOYSA-N (hydrochloride salt)

VOEFELLSAAJCHJ-SSDOTTSWSA-N (*R*–isomer)

VOEFELLSAAJCHJ-ZETCQYMHSA-N (*S*–iomer)

IUPAC International Chemical Identifier String (InchI string):

InChI=1S/C10H12ClNO/c1-7(12-2)10(13)8-4-3-5-9(11)6-8/h3-7,12H,1-2H3 (base)

InChI=1S/C10H12ClNO.ClH/c1-7(12-2)10(13)8-4-3-5-9(11)6-8;/h3-7,12H,1-2H3;1H (hydrochloride salt)

InChI=1S/C10H12ClNO/c1-7(12-2)10(13)8-4-3-5-9(11)6-8/h3-7,12H,1-2H3/t7-/m1/s1 (*R*-isomer)

InChI=1S/C10H12ClNO/c1-7(12-2)10(13)8-4-3-5-9(11)6-8/h3-7,12H,1-2H3/t7-/m0/s1 (*S*-isomer)

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

O=C(c1cc(Cl)ccc1)C(C)NC (base)

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

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

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

4.2.2 Physical description

There is limited information available on the solubility, lipophilicity, melting and boiling points or other physico-chemical properties of 3-CMC.

The hydrochloride salt of 3-CMC has been described in the literature as a grey solid (Blough, 2014), a white solid (Shalabi et al., 2017) and a white powder (SWGDRUG, 2017; RESPONSE, 2015), with melting points of 181 – 183 °C (Blough et al., 2014) and 193 °C (Shalabi et al., 2017) reported. Shalabi et al., noted that due to the 10 °C discrepancy in the melting point they obtained relative to the literature, the hydrochloride salt was submitted for microanalysis (Shalabi et al., 2017).

Due to its similarity to 4-CMC, 3-CMC is expected to be soluble in organic solvents such as dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) or solvents such as ethanol (ECDD, 2019; Cayman Chemical, 2014).

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

3-CMC has been identified in combination with other cathinones, including but not limited to: 2-MMC ([25]), 3-MMC, 3-CEC ([26]), 4-CEC ([27]), 4-CMC, 4-MEC ([28]), α-PVT ([29]), eutylone ([30]), mexedrone ([31]) and *N*-ethylhexedrone ([32]). 3-CMC 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) ([33]) and internationally controlled substances such as cocaine, MDMA, amphetamine and metamphetamine.

In at least some of the detections, the hydrochloride salt form of 3-CMC was identified.

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

[25] 2-(Methylamino)-1-(2-methylphenyl)propan-1-one
[26] 1-(3-Chlorophenyl)-2-(ethylamino)propan-1-one
[27] 1-(4-Chlorophenyl)-2-(ethylamino)propan-1-one
[28] 2-(Ethylamino)-1-(4-methylphenyl)propan-1-one
[29] 2-(Pyrrolidin-1-yl)-1-(thiophen-2-yl)pentan-1-one
[30] 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one
[31] 3-Methoxy-2-(methylamino)-1-(4-methylphenyl)propan-1-one
[32] 2-(Ethylamino)-1-phenylhexan-1-one
[33] Methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate

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-CMC which has been identified within Europe. General methods for the synthesis of cathinones, including 3-CMC are described below.

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

Cathinones may be prepared using several synthetic approaches. For ring-substituted cathinones, such as 3-CMC and 3-MMC, 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 (IV) (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 with propionyl chloride in the presence of aluminium chloride (Wrzesień, 2018). A standard Grignard reaction with the corresponding ring-substituted benzene is also possible.

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 ones 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 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).

A general synthesis scheme for methcathinone derivatives, including 3-CMC, has been described by Blough et al., (Blough et al., 2019). Two specific methods for the synthesis of

the hydrochloride salt of 3-CMC have been described in the literature by Blough et al., (*compound 9*) and by Shalabi et al., (*compound 6*) (Blough et al., 2014; Shalabi, 2017).

For 3-CMC, Blough et al., treated 3-chloropropiophenone with bromine to yield 2-bromo-1-(3'-chlorophenyl)-1-oxopropane, which was then reacted with *N*-benzylmethylamine to produce 2-(*N*-benzyl-*N*-methylamino)-1-(3'-chlorophenyl)-1-oxopropane. This was then mixed with 1-chloroethyl chloroformate in dichloroethane to afford 3-CMC hydrochloride as a grey solid (Blough et al., 2014). Shalabi et al., reacted 2-bromo-1-(3-chlorophenyl)propan-1-one with methylamine, in the presence of ethanol to yield 3-CMC hydrochloride as a white solid (Shalabi et al., 2017).

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-CMC

Information on the synthetic pathways used to produce the 3-CMC 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.

Limited information exists on the synthetic impurities present in 3-CMC samples. Approximately 400 kg of 3-CMC powders, also containing iso-3-CMC, were seized by Dutch Customs in 2021. Isocathinones such as iso-3-CMC, can be by-products of cathinone synthesis (Westphal et al.; 2012; Wrzesień, 2018), occurring when the amino moiety and the keto group change place in the molecule. Their occurrence is attributed to the first synthetic pathway (bromination/amination), which, as already explained above, is the most ''industrially efficient'' method to fabricate these compounds.

Seizures of precursors reported to the European Commission do not contain information on specific chemicals needed for the synthesis of 3-CMC. 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').

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 involved in the production of 3-CMC: one seized in Slovakia in 2017, and 2 seized in Poland in 2020.

4.2.4 Detection and analysis

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

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

Physical samples	
Method	**References**
Gas chromatography–mass spectrometry (GC-MS)	Blough et al., 2014 SWGDRUG, 2017 Cayman Chemical, 2015 RESPONSE, 2015
Fourier transform infrared spectroscopy (FTIR)	SWGDRUG, 2017 RESPONSE, 2015 Piorunska-Sedlak et al., 2020
High-performance liquid chromatography-ultraviolet (HPLC-UV)	Hägele et al., 2020 Kadkhodaei et al., 2018 Kadkhodaei et al., 2020
Raman spectroscopy	Kranenburg et al., 2021
Chiral capillary electrophoresis (CEC)	Hägele et al., 2019
^{1}H nuclear magnetic resonance spectroscopy (NMR)	Blough et al., 2014 SWGDRUG, 2017 RESPONSE, 2015
^{13}C NMR	RESPONSE 2015
Biological samples	
Method	**References**
HPLC and supercritical fluid chromatography tandem mass spectrometry (SFC-MS/MS)	Lajtai et al., 2020
Gas chromatography tandem mass spectrometry (GC-MS/MS)	Woźniak et al., 2020

Quantification of 3-CMC in physical samples can be carried out according to the general procedure described by the UNODC (UNODC, 2020). Due to its structural similarity to 4-CMC, quantification of 3-CMC in blood samples could be carried out according to the procedure described by Wiergowski et al., using UPLC–MS/MS (Wiergowski et al., 2017).

Discrimination of 3-CMC from its positional isomers

3-CMC has two positional isomers, 2-CMC ([34]) and 4-CMC, differing only in the position of the chlorine atom on the phenyl ring. Reference standards of the hydrochloride salt of 3-CMC (Cayman Chemical, 2015), 2-CMC (Cayman Chemical, 2017), and 4-CMC (Cayman Chemical, 2014) are commercially available. Reference standards are also commercially available for the base form and the *S*-isomer of 3-CMC (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-CMC poses analytical challenges, as techniques solely relying on mass will not allow an unequivocal identification. The positional isomers of 3-CMC, 2-CMC and 4-CMC, 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 by GC-MS will result in very similar mass spectrometry fragmentation patterns. Hägele et al. highlighted that discrimination by GC-MS is particularly challenging when using common achiral columns (Hägele et al., 2019; Hägele et al., 2020). The ability to distinguish between these isomers requires the use of analytical reference standards, access to reference spectra for both substances, and/or additional analytical methods, such as FTIR or NMR.

Hägele et al. demonstrated that positional isomers can be discriminated by use of capillary electrochromatography (CEC), providing the example of the discrimination of three different fluorinated methcathinone derivatives, 2-FMC ([35]), 3-FMC ([36]) and 4-FMC ([37]), 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 CSP could discriminate between the three positional isomers of mephedrone (2-MMC, 3-MMC and 4-MMC) (Kadkhodaei et al., 2020). It could be expected that the discrimination of 2-CMC, 3-CMC and 4-CMC is possible using these methods.

Piorunska-Sedlak et al., demonstrated that 3-CMC could be discriminated from 4-CMC using ATR-IR, as the spectra are sufficiently different (Piorunska-Sedlak et al., 2020). 2-CMC was not included in the analysis as it was not identified in the 45 samples studied (Piorunska-Sedlak et al., 2020).

[34] 1-(2-Chlorophenyl)-2-(methylamino)-1-propanone
[35] 1-(2-Fluorophenyl)-2-(methylamino)propan-1-one
[36] 1-(3-Fluorophenyl)-2-(methylamino)propan-1-one
[37] 1-(4-Fluorophenyl)-2-(methylamino)propan-1-one

A validated GC–MS/MS method for the determination of NPS in blood samples from forensic cases has been described by Woźniak et al. (Woźniak et al., 2020). The authors explained that while 3-CMC and 4-CMC had close retention times and shared the same multiple reaction monitoring (MRM) transitions, the identification of these compounds was facilitated by the use of internal standards and by calculation of their relative retention times. It was highlighted by the authors that the method is limited to screening, with quantification only possible when only one of these analytes is present in a sample (Woźniak et al., 2020).

3-CMC is also a structural isomer of iso-3-CMC ([38]). Iso-3-CMC is not currently monitored by the EMCDDA but other iso-cathinones monitored by the EMCDDA are: 3-fluoro-isomethcathinone (3-FiMC) ([39]) iso-pentedrone ([40]) and iso-ethcathinone ([41]). Iso-3-CMC has been recently identified, alongside 3-CMC, in two significant seizures reported by Customs in the Netherlands, amounting to 400 kilograms of powder, that occurred in the first half of 2021. The presence of iso-3-CMC in these seizures could be as a result of dimerisation due to the reaction of the alpha-haloketone and the amine. The detection of iso-cathinones in seized samples has been discussed in the literature (McDermott et al. 2011). Based on the authors hypotheses in their study of iso-mephedrone and iso-ethcathinone, the detection of iso-3-CMC could be due to the starting material for 3-CMC having been contaminated with the starting material for the iso-3-CMC, or from the use of liquid amine rather than amine in solution during synthesis, or possibly as a result of rearrangement of 3-CMC directly to iso-3-CMC through an imino-amine intermediate (McDermott et al. 2011). The authors suggested that, based on their findings, the use of liquid amine was the likely factor in the presence of the iso-cathinone compounds identified in seized samples and as these were not commonly identified in samples this 'could be used to compare batches of material and suggest a common origin' (McDermott et al. 2011).

Differentiation of enantiomers

Cathinones such as 3-CMC contain a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*R*)- and (*S*)-3-CMC. There is no information on the enantiomeric composition of the samples of 3-CMC 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.

Hägele et al., reported the use of an isocratic HPLC method with a specific chiral stationary phase (CSP), developed for the enantioresolution of synthetic chiral drugs, to successfully separate enantiomers of a range of new psychoactive substances, including 3-CMC (Hägele et al., 2020). Kadkhodaei et al., also demonstrated the separation of a range of NPS enantiomers using an isocratic HPLC method with a specific CSP (Kadkhodaei et al., 2018). The authors highlighted that in general 'for a successful chiral separation, the position and

[38] 1-(3-Chlorophenyl)-1-(methylamino)propan-2-one

[39] 1-(3-Fluorophenyl)-1-(methylamino)propan-2-one; formally notified by the EMCDDA in February 2012

[40] 1-(Methylamino)-1-phenylpentan-2-one; formally notified by the EMCDDA in September 2011

[41] 1-(Ethylamino)-1-phenylpropan-2-one; formally notified by the EMCDDA in June 2010

the atomic mass of halogen substituents play a crucial role', with substitution in the *ortho* position considered to produce less satisfactory results than in the *para* position. This was demonstrated by the successful chiral separation of 3-CMC and 4-CMC compared with 2-CMC (Kadkhodaei et al., 2018).

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

3-CMC is a ring-substituted synthetic cathinone. Similar to closely related cathinones such as 4-chloromethcathinone (clephedrone, 4-CMC), 3-CMC has been shown to interact with the monoamine transporter system in a number of in vitro studies, which suggest that 3-CMC acts as a psychostimulant. For example, 3-CMC was reported to act as a monoamine (dopamine, noradrenaline and serotonin) transporter substrate that induces release in rat brain synaptosomes (Kohut et al. 2013, Blough et al. 2014, Shalabi et al. 2017, Blough et al. 2019, Walther et al. 2019). This mechanistic principle is also found in other closely related ring-substituted synthetic cathinones such as 4-MMC, methcathinone, and 4-CMC (Walther et al. 2019). 3-CMC was also observed to produce sustained and selective decreases in cocaine self-administration in rhesus monkeys and produced fewer side effects than methcathinone (Kohut et al. 2013). 3-CMC was also 3–8 fold less potent than cocaine or methcathinone in eliciting cocaine-like discriminative stimulus effects in rhesus monkeys (Kohut et al. 2013). Consistent with a locomotor stimulant profile, 3-CMC was observed to increase spontaneous horizontal locomotor activity in mice in a dose-dependent manner (Wojcieszak et al. 2020). Taken together, these results suggest that 3-CMC 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-CMC are likely to share some similarities with other substituted cathinones such as 4-CMC. These might include general stimulation, euphoria, sociability, increased heart rate and elevated blood pressure (Abdulrahim and Bowden-Jones, 2015; 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).

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

Similar to other stimulant cathinones, the use of 3-CMC 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-CMC, the chronic health risks might share some similarities to those seen with other synthetic cathinones such as 4-CMC. This may include dependence.

ECHA reported to the EMCDDA that according to the Classification and Labelling (C&L) Inventory, 3-CMC hydrochloride salt is classified as an eye irritant category 2. EFSA reported to the EMCDDA that they do not currently have any information on 3-CMC.

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

Europol received replies from 13 Member States (Austria, Bulgaria, Croatia, Cyprus, Denmark, Finland, France, Germany, Greece, Luxembourg, Poland, Slovakia and Slovenia) and Norway.

Replies were also received from Iceland ([42]), the United Kingdom (UK) ([43]) and the United States Drug Enforcement Administration (DEA) ([44]).

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

Poland reported the seizure of two clandestine laboratories producing 3-CMC, in the last year. They reported that they do not currently have accurate data on the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of 3-CMC.

Slovakia reported a significant decrease in the activities of foreign criminal groups, dealing with the production of 3-CMC, according to information from the police. This decrease is considered to be a result of Covid-19 restrictions.

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

Information on seizures of 3-CMC

In general, seizures of 3-CMC reported to Europol occurred between 2015 and 2021.

- Austria reported a slight increase in cases involving 3-CMC in recent years. 3-CMC has been seized as a white powder, and as a brown liquid which was also found to contain cocaine and/or 4-MMC.

[42] Iceland reported that no information was available on 3-CMC.
[43] The UK reported that according to records from the Border Force on the INCB IONICS system, there were ten incidents involving 3-CMC so far in 2021. The UK was the destination country for seven of the ten shipments, while Poland (2) and Ukraine (1) were the other destinations. The Netherlands was the origin country for all ten shipments. In the case of the shipment destined for the Ukraine, it appears to have transited through the UK, where it was seized. In total, they reported that there have been 82 incidents worldwide associated with 3-CMC, which have been recorded in the system since March 2015.
[44] The DEA reported that information on seizures of 3-CMC 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-CMC 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, which they believe could have been purchased from chemical supply companies. A total of three detections of 3-CMC were identified in the DEA LIMS in 2016, in crystalline, rock and powder form, ranging in quantity from 0.96 to 54.463 grams. In one case, the hydrochloride salt form of 3-CMC was identified and, in the other two cases, 3-CMC was identified with alpha-PVP and an unidentified substance. A total of 16 detections of 3-CMC were registered in the Diversion Control Division's NFLIS database, recorded between 2015 and 2019.

- Denmark reported that most seizures of 3-CMC, approximately ten, 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-CMC, by police and customs, also reported to the EMCDDA.

- France reported that 3-CMC has been identified in detections since 2014 and according to information available to French police and OFDT ([45]) is available to purchase online, at a reported price of 14 to 18 euro per gram. Information from analysis by OFDT indicates that 3-CMC has been identified in products sold online as 3-MMC. They also reported that while some seizures of 3-MMC have been reported by French law enforcement services, no 3-CMC seizures have been reported.

- Germany reported that all information has been sent to the EMCDDA by the DBDD ([46]).

- Greece reported generally on 3-CMC, in the context of more specific information provided on 3-MMC.Norway reported that 3-CMC was seized for the first time in Norway in 2015, with tens of seizures reported between 2015 and 2017, followed by a decrease in seizures from 2017. From 2020, an increase in seizures was observed with more than 15 seizures of 3-CMC in crystal form reported; the largest individual seizure during this timeframe was 2.5 kilograms.

- Slovakia reported two seizures of 3-CMC made by the police during four raids in 2019 (148.2 grams; and 0.76 grams also containing 3-CEC (3-chloroethcatinone).

- Slovenia reported that a total of 30 grams of 3-CMC was identified in seizures in 2019, from individuals who mostly purchased the substance online.

Austria, Bulgaria, Denmark and Greece reported information on the national control measures applied to 3-CMC and/or 4-CMC. Croatia, Cyprus and Luxembourg reported that no information is 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 ([47]), it appears that 3-CMC 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

[45] The French Observatory for Drugs and Drug Addiction (OFDT)
[46] The German Monitoring Centre for Drugs and Drug Addiction (DBDD)
[47] 26 Member States, as well as Norway and Iceland provided a response to the EMA's request regarding human and/or veterinary medicinal products.

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-CMC 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.

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-CMC 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-CMC is used for other legitimate purposes.

ECHA reported that there are no registrations or classification and labelling (C&L) notifications for 3-CMC in the C&L Inventory database ([48]).

ECHA reported a C&L notification for the hydrochloride salt of 3-CMC that classifies the substance as an eye irritant category 2, and labels it with hazard statement H319 (‘causes serious eye irritation’) (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-CMC 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-CMC is not subject to restrictive measures at national level.

[48] 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

When reporting whether 3-CMC is subjected to restrictive measures, 11 Member States (Austria, Belgium, Croatia, Denmark, France, Germany, Hungary, Ireland, Latvia, Lithuania, and Malta) and Turkey mentioned that this substance is covered by the generic definition of cathinones.

Drug control legislation

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

- Croatia reported that 3-CMC is controlled by generic definition since 2014;
- Czechia reported that 3-CMC is controlled since 2017;
- Denmark reported that 3-CMC is covered by generic cathinone classification since 2012;
- Estonia reported that 3-CMC is controlled under the Act on Narcotic Drugs and Psychotropic Substances and Precursors thereof, List VI, since 2016;
- France reported that 3-CMC is controlled by a generic approach since 2012;
- Ireland reported that 3-CMC is covered by the generic cathinone definition under Statutory Instrument 551/2011, in force since November 2011;
- Italy reported that 3-CMC was included in the list of new psychoactive substances in the update of 6 August 2021 of the decree of the President of the Republic n. 309;
- Latvia reported that 3-CMC 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-CMC is controlled by a regulation of the Minister of Health since 2018;
- Portugal reported that 3-CMC is included in Law No. 25/2021 of 11 May which amends for the twentieth-seventh time the Decree-Law No. 15/93 of 22th January, as of 11 May 2021.
- Slovenia reported that 3-CMC is controlled by the Regulation on the Classification of Illicit Drugs since 2016;
- Slovakia reported that 3-CMC is controlled by Act No. 139/1998 Coll. on Narcotics and Psychotropic Substances and Preparations since 1 January 2020;
- Sweden reported that 3-CMC was regulated as goods dangerous to health as of 18 August 2015 and was re-scheduled as a narcotic drug in 2019;
- Turkey reported that 3-CMC was controlled by generic legislation in the context of Law on Control of Drugs numbered 2313, since 2016;

- Norway reported that 3-CMC 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-CMC. 3-CMC is also classified as a 'forbidden' narcotic, meaning even stricter regulations regarding licenses for import/export/manufacture.

New psychoactive substance legislation

Seven Member States (Austria, Belgium, Cyprus, Germany, Finland, Hungary, and Malta) reported that 3-CMC is controlled under new psychoactive substance legislation.

- Austria reported that 3-CMC is covered by generic definition by the Austrian Act on New Psychoactive Substances of 2012;
- Belgium reported that 3-CMC is covered by generic definition;
- Cyprus reported that 3-CMC is controlled since 2011;
- Germany reported that 3-CMC is covered by the New Psychoactive Substances Act since 2016;
- Finland reported that 3-CMC is banned by a government decree on psychoactive substances since 2015;
- Hungary reported that 3-CMC 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-CMC 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-CMC is controlled under medicines legislation (included in the group of cathinone derivatives) since 10 March 2015.

Other information

3-CMC 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 17 September 2021, the World Health Organization informed the EMCDDA that 3-CMC is not currently under assessment nor has it been under assessment by the United Nations system.

4.9 Other relevant information

Austria

In Austria, the drug checking service CheckIt reported two samples containing 3-CMC and 4-CMC in January 2020. Both samples were submitted as mephedrone (CheckIt, 2021).

Switzerland

In Switzerland, the drug checking service SaferParty reported 8 samples containing 3-CMC between May 2019 and October 2021. In all cases 3-CMC was sold as other substance: 3-MMC (in 4 cases) ([49]), MDMA (2), methamphetamine (1), and mephedrone (1). Three samples contained other substances such as MDMA, 4-CEC, 3-MMC, 4-MMC, and ketamine (SaferParty, 2021).

[49] In one of these cases, the sample was sold as '5-MMC', which would be equivalent to 3-MMC.

5. Analysis and assessment

1-(3-Chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) 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-CMC and (*S*)-3-CMC. It is a derivative of cathinone, the naturally occurring stimulant and main psychoactive substance in the khat plant *Catha edulis*. 3-CMC is also closely related to and shares similar stimulant effects with methcathinone (ephedrone) and 4-chloromethcathinone (4-CMC; clephedrone). Cathinone, methcathinone, and 4-CMC are controlled under the 1971 United Nations Convention on Psychotropic Substances because of the public health and social risks that they pose.

3-CMC was first identified in Europe in September 2014 based on a police seizure made in Sweden. Despite appearing on the drug market at around the same time as 4-CMC, until 2020, the detection of 3-CMC in law enforcement seizures remained relatively low in comparison to 4-CMC. However, during 2020 and 2021 there has been a large increase in seizures of 3-CMC. Although the reasons for this are unclear, it does coincide with the recent control of 4-CMC under the United Nations system in 2020. At least in part, it appears that 3-CMC is being used as a 'legal' replacement to 4-CMC.

The limited information suggests that 3-CMC is 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-CMC, it is likely that 3-CMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It is expected that the substance is 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 likely includes recreational use, and, in some cases high risk use, such as injecting. Although specific information is lacking, similar to other cathinones, it is likely that 3-CMC is used in private spaces (such as homes and domestic parties) as well as recreational settings (such as nightclubs, bars/pubs, music festivals).

Since 2014, 3-CMC has been identified in 23 Member States and Norway. In total, approximately 2 720 kg of 3-CMC powder has been seized, including at least 2240 kg by customs and 320 kg by police. However, of this, approximately 2 500 kg (92%) was seized between 2020 and 2021. During 2021, 3-CMC continues to be imported, distributed, and used in parts of Europe; this includes the seizure of a total of 1 400 kg of powder at the external EU border.

The available information suggests that 3-CMC is currently imported into Europe in bulk quantities mainly from India, with approximately 700 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. In addition, three illicit laboratories producing 3-CMC have been seized in Europe, with the two most recent laboratories 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-CMC which accounted for just over a quarter of the quantity of powders seized during 2020. In addition, 3-methylmethcathinone (3-MMC), which is also currently the subject of an initial report following its re-emergence in Europe, accounted for a similar quantity.

One acute non-fatal poisoning with confirmed exposure to 3-CMC has been reported by one Member State: Spain. Other substances were identified.

A total of 10 deaths with confirmed exposure to 3-CMC have been reported by two Member States: Poland and Sweden. In six cases, other substances were identified. The cases occurred between November 2019 and June 2021; three of the deaths occurred in 2020 and six in 2021. In five cases, 3-CMC was the cause of death or contributed to the death.

Currently, there is limited information on the involvement of criminal groups in the manufacture, trafficking, and distribution of 3-CMC 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-CMC.

The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution and use of 3-CMC is currently unknown. However, seizures of more than of 2 170 kg of bulk powders by customs agencies during the pandemic suggest that 3-CMC continues to be imported and distributed in Europe. It is possible that, in case of a reduced availability of controlled stimulants (such as 4-CMC and MDMA) in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including 3-CMC.

Based on the available information, it appears that 3-CMC 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-CMC 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-CMC is used for other legitimate purposes.

3-CMC is subject to restrictive measures in 21 Member States, Turkey, and Norway. 3-CMC is controlled in China. It is unknown if 3-CMC is controlled in India, from where bulk quantities of pure powder have originated and recently been seized by customs agencies in Europe.

3-CMC has not been subject to assessment nor is it currently under assessment by the United Nations system.

The EMCDDA will continue to intensively monitor 3-CMC 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 the recent emergence of 3-CMC, the EMCDDA considers that there are indications that 3-CMC 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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