



3-CMC

Report on the risk assessment of
1-(3-chlorophenyl)-2-(methylamino)propan-1-one
(3-chloromethcathinone, 3-CMC) in accordance
with Article 5c of Regulation (EC) No 1920/2006
(as amended)

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of Regulation (EC) 1920/2006 (as amended by Regulation (EU) 2017/2101).

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Foreword

This publication presents the data and findings of the risk assessment on 3-CMC (3-chloromethcathinone; 1-(3-chlorophenyl)-2-(methylamino)propan-1-one), carried out by the extended Scientific Committee of the EMCDDA on 19 November 2021.

The Risk Assessment Report, which was submitted to the European Commission on 25 November 2021, examines the health and social risks of the drug, information on international trafficking and the involvement of organised crime, as well as a consideration of the potential implications of subjecting the drug to control measures.

On the basis of the Risk Assessment Report, the Commission adopted delegated act in order to add 3-CMC in to the definition of a drug in the Annex of the Council Framework Decision 2004/757/JHA (as amended by Directive (EU) 2017/2103). This decision was adopted in the final stage of the three-step process — early warning, risk assessment and control of new psychoactive substances — established by Regulation (EC) 1920/2006 (as amended) and Council Framework Decision 2004/757/JHA (as amended).

Regulation (EC) 1920/2006 (as amended) and Council Framework Decision 2004/757/JHA (as amended) allow the EU institutions and Member States to act on all new and potentially threatening narcotic and psychotropic drugs which appear on the European drug scene, with the EMCDDA and Europol, in collaboration with their respective networks playing a central role in the early detection of such substances as well as the harms caused by their use — information that underpins risk assessment, and, ultimately, decision-making.

In this respect we would like to acknowledge the essential role played by the respective networks in the Member States — the Reitox national focal points — in collecting and providing national data. We would also like to acknowledge the role of Europol and Europol National Units, the European Medicines Agency (EMA) and the national competent authorities responsible for medicinal products, the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) that provided valuable input to the report, thus guaranteeing its truly multidisciplinary nature.

Finally, we would like to thank all the participants in the risk assessment process for the high quality of work carried out. This procedure occurred under challenging circumstances, amidst the coronavirus (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The resulting report is a valuable contribution at European level, and provides clear support to political decision-making.

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EMCDDA Initial Report on 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC)

On 9 September 2021, the EMCDDA assessed the existing information on 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (commonly known as 3-chloromethcathinone or 3-CMC), based on the following criteria: (1) reports of health problems; (2) reports of social problems; (3) reports of seized material; (4) pharmacological and toxicological properties and analogy with better-studied substances; and, (5) 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.

On 18 October 2021, the EMCDDA submitted to the Commission and Member States an initial report on the new psychoactive substance 3-CMC, in accordance with Article 5b of the Regulation (EC) 1920/2006 (as amended). The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in 3-CMC, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 5c of the Regulation (EC) 1920/2006 (as amended).

The full text of the Initial Report can be found at:

https://www.emcdda.europa.eu/publications/initial-reports/initial-report-3-cmc_en

Risk assessment report on a new psychoactive substance: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC)

Introduction

New psychoactive substances can cause serious cross-border threats to health. In Europe, 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) (hereafter the 'Regulation') and 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, sets up a three-step legal framework of early warning, risk assessment and control measures that allows the European Union (EU) to rapidly detect, assess and respond to the public health and social risks caused by new psychoactive substances. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is responsible for the first two steps in this system, namely operating the EU Early Warning System on new psychoactive substances (EWS) in close cooperation with Europol, and conducting risk assessments. The European Commission is responsible for proposing control measures. Thus, the legal framework allows the institutions of the EU and the Member States to act on all new psychoactive substances (NPS) that appear on the European drug market.

In accordance with Article 5a of the Regulation, 1-(3-chlorophenyl)-2-(methylamino)propan-1-one, commonly known as 3-chloromethcathinone (3-CMC), was formally notified as an NPS 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.

On 9 September 2021, based on signals suggesting a large, significant, increase in seizures at the EU external border by customs agencies during 2020 and 2021, the EMCDDA assessed the existing information on 3-CMC. The EMCDDA concluded that the assessment gave rise to concerns that 3-CMC may pose health or social risks at EU level, and, consequently, determined that an initial report should be produced in accordance with Article 5b of the Regulation. The initial report was submitted to the Commission and Member States on 18 October 2021. Based on the findings of the initial report, on 27 October 2021, the Commission requested that the EMCDDA carry out a risk assessment on 3-CMC in accordance with Article 5c of the Regulation.

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the Scientific Committee of the EMCDDA on 3-CMC. The report is intended for policymakers and decision-makers in the institutions of the EU.

The report has been prepared and drafted in accordance with the requirements of Article 5c of the Regulation as well as the conceptual framework and the procedure set out in the EMCDDA risk assessment operating guidelines. It is written as a stand-alone document, which presents a summary of the information considered during the detailed assessment of the scientific and law enforcement information available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on 3-CMC prepared by the EMCDDA (Annex 1), is provided below.

In accordance with Article 5c of the Regulation, the meeting to assess the risks of 3-CMC was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of six additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a list of experts approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented or not sufficiently represented in the Scientific Committee, and whose contribution was necessary for the balanced assessment of the risks posed by 3-CMC. A further six experts were observers to the risk assessment: two experts from the Commission, two experts from the EMCDDA, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 19 November 2021. Owing to the on-going response to the coronavirus (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the meeting was conducted both in person at the EMCDDA and by videoconference.

The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, the EMA, the European Centre for Disease Prevention and Control (ECDC), the European Chemicals Agency (ECHA), and the European Food Safety Authority (EFSA). A list of the Scientific Committee members, observers, and other participants attending the risk assessment meeting is annexed to this report (Annex 2).

For the risk assessment, the Scientific Committee considered the following information resources:

- the EMCDDA technical report on 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) (Annex 1);
- the EMCDDA initial report on the new psychoactive substance 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC);
- open source information, including scientific articles, official reports, grey literature, Internet drug discussion forums and related websites;
- additional information provided during the course of the risk assessment meeting by the participants;
- EMCDDA operating guidelines for the risk assessment of new psychoactive substances;

- 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); and
- 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.

Background

1-(3-Chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) is a synthetic cathinone with psychostimulant effects. It is monitored as a new psychoactive substance by the EMCDDA in accordance with Regulation (EC) No 1920/2006. The substance was first identified on the European drug market in September 2014 based on a police seizure made in Sweden.

3-CMC 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 psychostimulant 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.

Synthetic cathinones are the second largest group of new psychoactive substances monitored by the EMCDDA through the EWS, with 161 notified since the first synthetic cathinone, methylone, was identified on the European drug market in 2005.

3-CMC has two positional isomers, 2-chloromethcathinone (2-CMC) and 4-chloromethcathinone (clephedrone; 4-CMC). 4-CMC, also known as clephedrone, was first identified on the drug market in Europe in June 2014, at around the same time that 3-CMC was identified. Although now under international control, 4-CMC continues to be encountered regularly on the drug market in Europe, with at least some of the substance produced in illicit laboratories in Europe in recent years. Conversely, although some reports indicate that 2-CMC has been available on the drug market in at least two Member States since 2016, with small amounts seized in 2016, the substance has not been formally reported to the EMCDDA.

The differentiation of 3-CMC from 2-CMC and 4-CMC requires the use of appropriate analytical techniques. Due to differences in reporting practices across Europe, the differentiation of 3-CMC from its positional isomers is done in many, but not all, forensic and toxicology laboratories. For the purposes of the risk assessment, 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.

Despite appearing on the drug market at around the same time as 4-CMC in 2014, the detection of 3-CMC in law enforcement seizures remained relatively low in comparison to 4-CMC until 2020. However, during 2020 and 2021 there has been a large, significant, 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 international drug control system in 2020. At least in part, it appears that 3-CMC is being manufactured, imported, distributed, sold, and used as a 'legal' replacement to 4-CMC as well as other controlled psychostimulants.

Chemical and physical properties and the methods and precursors used for manufacture

Chemical and physical properties

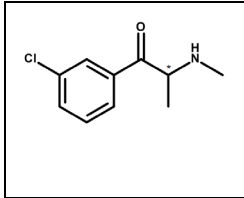
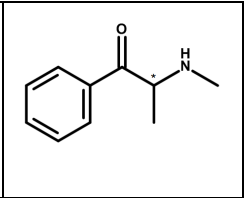
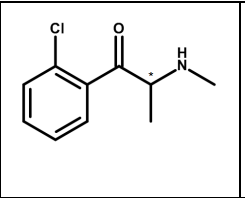
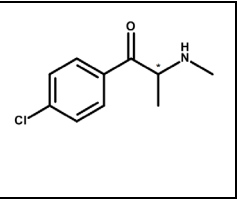
1-(3-Chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) is an *N*-alkylated and ring-substituted cathinone. 3-CMC contains a chiral centre so two enantiomers may exist: (*R*)-3-CMC and (*S*)-3-CMC. No information is available on the enantiomeric composition of 3-CMC on the drug market in Europe, which may in part reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Based on the likely synthetic routes used, and available precursors, it is most probably available as a racemic mixture of the (*R*)- and (*S*)- enantiomers.

There is limited information on the physicochemical properties of 3-CMC. In its pure form, 3-CMC has the appearance of a fine white powder or small white crystals. The hydrochloride salt of 3-CMC is described as a white powder or grey solid. The hydrochloride salt is readily soluble in water and can be dissolved for oral use or for injection.

3-CMC shares structural features with methcathinone, to an extent, and its two positional isomers, 2-CMC and 4-CMC. Methcathinone and 4-CMC are controlled under the United Nations Convention on Psychotropic Substances of 1971.

The molecular structure, molecular formula, molecular mass, and monoisotopic mass of 3-CMC are provided in Figure 1.

FIGURE 1
Molecular structure, molecular formula, molecular mass, and monoisotopic mass of 3-CMC

				
	3-CMC (clophedrone)	Methcathinone	2-CMC	4-CMC (clephedrone)
Molecular formula	C ₁₀ H ₁₂ ClNO	C ₁₀ H ₁₃ NO	C ₁₀ H ₁₂ ClNO	C ₁₀ H ₁₂ ClNO
Molecular mass	197.66	163.22	197.66	197.66
Monoisotopic mass	197.060741	163.099714	197.060741	197.060741

Note: Information on methcathinone, 2-CMC, and 4-CMC are provided for comparison. Chiral centres are denoted by an asterisk on the molecular structures.

The analytical identification and quantification of 3-CMC in physical and biological samples is possible using standard analytical techniques. These have been extensively described in the scientific literature and include methods for the differentiation of 3-CMC from its positional isomers, 2-CMC and 4-CMC. These include chromatographic and mass spectrometric methods.

There is some evidence in the literature about 4-CMC being particularly unstable and it is likely that the same applies to 3-CMC. As a result, it is possible that instability in biological samples may influence the number of detections reported to the EMCDDA.

The availability of analytical reference material is important for correct identification and for facilitating the quantification of 3-CMC in physical and biological samples. Such reference materials are commercially available.

It is important to note that, due to differences in reporting practices, the differentiation between 3-CMC and its two positional isomers may not be undertaken during routine forensic and toxicological analysis in Europe. Detections where the positional isomer of 3-CMC is not specified have been excluded from the report.

Methods and precursors used for manufacture

Currently, there is no information on the specific methods or precursors used for the manufacture of the 3-CMC that has been identified on the European drug market. A number of methods for the production of cathinones, including 3-CMC, have been described in the scientific and patent literature. Some of these allow manufacture on an industrial-scale; others allow production at a much smaller-scale, including homemade production in kitchen laboratories.

Equipment and knowledge similar to that needed for the synthesis of other synthetic cathinones that have been produced in illicit laboratories in Europe, such as methcathinone, 4-CMC, 4-methylmethcathionone (4-MMC; mephedrone), and 3-methylmethcathionone (3-MMC), as well as more established drugs such as amphetamine and MDMA, are required. Production is relatively straightforward, does not require a high-level of technical expertise, nor complex laboratory equipment.

Based on the number of large-scale seizures reported by customs agencies, much of the 3-CMC appears to have been manufactured and imported into Europe on an industrial-scale. In particular, from 2020 onwards, where reported, most consignments seized at the EU external border have originated in India. In addition, limited information indicates that some production has taken place in illicit laboratories in Europe.

One of most efficient methods suitable for the manufacture of cathinones on an industrial-scale, including 3-CMC, includes a two-step procedure that involves the α -bromination of a suitable arylketone (commonly called a 'propiophenone'), followed by the reaction with an amine to obtain the desired cathinone. Brominated intermediates 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. This allows the production of several cathinones using the same route, the same equipment, and most of the same chemicals.

The precursors that can be used for the manufacture of 3-CMC using this method, such as 3-chloropropiophenone, being a key starting material of the synthesis of bupropion, is manufactured on a large scale, are typically commercially available in bulk quantities or can be easily synthesised. They are not controlled under by the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988. Several other synthetic routes are possible to produce cathinones depending on the available precursor.

In addition to the standard organic synthesis methods referred to above, chemically masked derivatives of 3-CMC, as well as synthetic cathinones in general, can also be produced in order to circumvent legal controls and/or avoid detection by law enforcement, such as customs agencies. Here, the cathinone is chemically masked to produce a non-controlled substance which can then be converted back into the parent drug through relatively simple steps. Although no cases of masked 3-CMC have been reported so far, during 2019, Dutch Police seized 350 kilograms of

chemically masked 3-MMC ⁽¹⁾ at a site linked to a producer/distributor that had apparently imported the substance from India. The 3-MMC was masked as *N*-acetyl-3-MMC. It is presumed that this derivative was intended to be converted to 3-MMC, for example by acid hydrolysis using hydrochloric acid. Approximately 150 kilograms of 3-MMC were also seized at the site.

Detailed information on the presence of impurities, such as side-products or by-products, as well as other contaminants arising from the manufacture of 3-CMC is not available, though the presence of route-specific impurities is possible. In a large-scale seizure of 400 kilograms of 3-CMC powder at the external EU border in 2021, the structural isomer, iso-3-CMC ⁽²⁾, was also identified in the powder. Potentially, iso-3-CMC is a side-product from synthesis. There is no information on the pharmacological nor toxicological properties of iso-3-CMC.

The use of ephedrine-type precursors for the synthesis of 3-CMC with the use of potassium permanganate as an oxidising agent can lead to residual manganese which poses a risk of poisoning that can cause neurotoxicity with Parkinsonian-like clinical features.

Pharmaceutical forms

Information provided from seizures and collected samples reported to the EMCDDA show that 3-CMC is typically available on the drug market as a powder. Other physical forms, such as tablets and capsules, have also been reported, but to a much smaller extent. Occasionally liquids, herbal material, and blotters containing 3-CMC have also been reported. These findings are consistent with recent reports from people who use similar synthetic cathinones, such as 4-CMC and 3-MMC, and who typically report the use as a powder.

In at least some of the detections reported in Europe, the free base form and the hydrochloride salt form of 3-CMC has been identified. The hydrochloride salt of 3-CMC is readily soluble in water and can be dissolved for oral use or for injection.

Similar to other drugs, the purity of 3-CMC, as well as the presence of adulterants and diluents, depends on factors such as when and where in the supply chain the substance is obtained. Limited information is currently available for 3-CMC, which in part reflects the relatively low-level of seizures until recently as well as differences in both the level of analyses conducted on physical samples and reporting practices in Europe.

Seizures of 3-CMC by customs at the EU external border are almost exclusively powders and, where reported, have been described as 'white' in colour and 'pure'; 'crystals' or 'rocks' have also been reported. As discussed above, a single seizure of 400 kilograms of 3-CMC powder at the external EU border in 2021, which originated from India, also contained iso-3-CMC. Seizures by

⁽¹⁾ It is unknown whether *N*-acetyl-3-MMC is hydrolysed to 3-MMC in human stomach acid. No information is available on the pharmacology or toxicology of this masked derivative.

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

police are typically powders. Where reported, they have been described as crystals ranging from 'colourless' to 'white' to 'light-yellow'; the purity of 3-CMC is rarely reported. Collected samples, typically submissions from clients of drug-checking services, are mostly powders; the purity of 3-CMC is rarely reported. Typically, 3-CMC is the only psychoactive substance identified in police seizures and collected samples, but again, this may vary according to the time and place of when the sample is obtained. Other substances, particularly 4-CMC as well as other synthetic cathinones, and established stimulants such as amphetamine, cocaine, and MDMA, have been identified to some extent. Adulterants and/or diluents typical of the stimulant market have also been reported occasionally, such as caffeine, benzocaine, paracetamol, and mannitol.

Pharmacological and toxicological properties

Pharmacological properties

There is limited information on the pharmacological properties of 3-CMC. Similar to closely related cathinones such as 4-CMC, 3-CMC has been shown to interact with the monoamine transporter system in a number of *in vitro* studies. For example, 3-CMC inhibits the reuptake of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) at their respective transporters DAT, NET and SERT. Furthermore, it has also been shown that 3-CMC is able to act as a substrate-type releaser, a feature also found in synthetic cathinones such as methcathinone and 4-CMC. In addition, limited animal studies suggest that 3-CMC can elicit a cocaine-like discriminative stimulus and increase spontaneous locomotor activity in a dose-dependant manner. Taken together, these results suggest that 3-CMC is likely to act as a psychostimulant in humans and might also show abuse liability.

Information about the pharmacology of the individual enantiomers of 3-CMC is limited. The biological properties of the individual enantiomers may differ, as has been shown for a number of synthetic cathinones.

Information on whether 3-CMC affects other pharmacological targets is limited. Currently, it is unclear from the available data whether activity at such targets by 3-CMC might have any influence on the overall effects of the substance in humans.

There are currently no pharmacokinetic studies of 3-CMC. A recent analysis found 3-chloroephedrine as a possible human metabolite of 3-CMC. A similar metabolic fate was also found for 3-MMC and some fluorinated cathinones, which metabolised into their ephedrine-like counterparts. The pharmacological and toxicological properties of these metabolites are unknown.

Currently, there is no information on the pharmacokinetic interaction of 3-CMC with other substances, including other psychoactive substances and medicinal products.

Toxicological properties

There is limited information on the toxicological properties of 3-CMC. Currently, data are limited to exploratory cytotoxicity studies. Further study is required in order to determine the relevance of these findings in humans.

Health risks

Based on the available information, the health risks associated with 3-CMC are likely to share some similarities with other closely related synthetic cathinones and psychostimulants under international control, although this requires further study.

While no specific information is available, it is likely that while some individuals report only using 3-CMC, the substance may also be commonly used in combination with a range of other drugs (polydrug use). These include other stimulants as well as depressants, such as alcohol. This combined use may either be intentional or unintentional. As such, it is important to take this polydrug use into account when assessing the health risks of 3-CMC as the presence of and/or interaction with other substances may contribute to the effects reported, and ultimately the public health risks.

Some factors related to use of 3-CMC, including the route of administration (such as intravenous injection) or context of use (for example chemsex practices), might carry additional health risks, including injection site infections and the transmission of blood-borne viruses.

Acute toxicity

There is limited information on the acute toxicity of 3-CMC. Based on the available information, the adverse effects associated with the acute toxicity of 3-CMC are likely to share some similarities with other closely related synthetic cathinones and psychostimulants under international control. In the case of poisoning, these similarities include the sympathomimetic toxidrome, the features of which includes cardiovascular, neurological, psychiatric, and other adverse effects. These include clinical symptoms such as: diaphoresis, tachycardia, hypertension, hyperthermia, tachypnoea, hyperactivity, mydriasis (dilated pupils), and agitation; altered mental status, aggression, hallucinations, and psychotic episodes; seizures may also occur.

Acute poisonings

Acute poisonings reported by the Member States

One acute non-fatal poisoning with confirmed exposure to 3-CMC has been reported to the EMCDDA by Spain. The case involved a male and was related to chemsex practices. Other substances were identified in the biological samples.

Acute poisonings identified from other sources

Currently, no cases of acute poisonings involving 3-CMC have been published in the scientific literature.

Deaths

Deaths reported by the Member States

A total of 10 deaths with confirmed exposure to 3-CMC were reported to the EMCDDA by two Member States: 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).

In six of the cases, other substances were identified, including stimulants (such as amphetamine and synthetic cathinones) and depressants (such as alcohol, opioids, synthetic cannabinoids, and benzodiazepines). Of note is that in two of the cases where other substances were identified, the only additional finding was alcohol. In four of the cases no other substances were identified in biological samples. In at least three of the cases, the individuals were found dead.

A cause of death was reported in nine cases and in one case the cause of death was unknown:

- In the cases reported by Poland, the reported causes of death were: multi-organ trauma as a result of a traffic accident (2 cases), toxic effect of 3-CMC in a person with cardiac hypertrophy (1), acute poisoning with 3-CMC and ethyl alcohol (1), acute intoxication with 3-CMC (1), and gunshot wound to the chest (1 case).
- In the cases reported by Sweden, the reported causes of death were: intoxication with 3-CMC (1 case), unintentional intoxication with 3-CMC, 4-CMC, 5F-MDMB-PICA and amphetamine (1 case), and intoxication with oxycodone and benzodiazepines (1 case).

There was a general lack of information regarding the amount of 3-CMC used, the route of administration, and any clinical features experienced prior to death.

Deaths identified from other sources

Currently, no death cases involving 3-CMC have been published in the scientific literature.

Chronic toxicity

The chronic toxicity of 3-CMC has not been studied. Based on the limited information related to its stimulant pharmacological properties, the chronic toxicity of 3-CMC may share some similarities with other closely related synthetic cathinones and psychostimulants under international control, although this requires further study.

Physical, mental and behavioural effects

The physical, mental, and behavioural effects of 3-CMC have not been studied. Based on the limited information related to its psychostimulant pharmacological properties, as well as self-reported experiences, the effects of 3-CMC is expected to share some similarities with other closely related synthetic cathinones and psychostimulants under international control.

For physical effects, these may include: elevated heart rate, elevated blood pressure, peripheral vasoconstriction, bruxism (grinding of the teeth), dilated pupils, sweating, and increased body temperature.

For psychological and behavioural effects, these may include: general stimulation, elevated mood, euphoria, increased energy, sociability, and increased libido. It may also include insomnia, anxiety, and psychosis.

The effects of 3-CMC on the ability to drive and operate machinery have not been studied. However, data suggests that stimulants in general can have detrimental effects on self-perception, critical judgement and risk-taking, and while the stimulating effects are wearing off the driver may suffer fatigue, anxiety, and irritability. These effects are likely to extend to 3-CMC. Three Member States (Hungary, Poland, and Sweden) reported 21 cases of suspected driving under the influence of drugs with confirmed exposure to 3-CMC. In addition, two death cases in which the individuals were involved in traffic accidents have been reported to the EMCDDA. In one of these cases the individual caused the accident.

There is some evidence in the scientific literature about cathinones in general having been linked to suicides.

Abuse liability and dependence-producing potential

The abuse liability and dependence potential of 3-CMC have not been studied. Data from *in vitro* studies on the pharmacological mechanism of action of 3-CMC and animal studies are insufficient to conclude on the abuse liability and possibly a dependence potential in humans, although this requires further study.

Social risks

Currently, there is limited information on the social risks related to 3-CMC. In general, the social risks of 3-CMC may share some similarities with other closely related synthetic cathinones and psychostimulants under international control, although this requires further study.

For individuals, these might include impacts on education or career, family, economic situation, or on other personal and social relationships, and may result in marginalisation and increased vulnerability.

The identification of 3-CMC in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

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 information to suggest criminal acts, such as trafficking, illicit production, and supply offences, involving 3-CMC.

At least three sites related to the illicit production of 3-CMC have been seized in Europe between 2017 and 2020. The production of synthetic cathinones in illicit laboratories can result in the uncontrolled storage, use, generation, and disposal of a wide range of chemicals, many of which are hazardous, and, in some cases, highly toxic, as well as the deposition of hazardous waste within the laboratory building. Overall, this may pose risks to both individual health, and, through contamination of the broader environment, to public health.

Extent and patterns of use, availability and potential for diffusion

The limited information suggests that 3-CMC is typically sold and sought after as a stimulant drug in its own right, but it may also be mis-sold as other drugs. In the latter case, this includes both 4-CMC and 3-MMC.

Currently, information on the extent and patterns of use, availability, and potential for diffusion of 3-CMC is very limited. The available information is largely derived from law enforcement seizures

and from collected samples as well as serious adverse events (discussed above). No formal epidemiological studies have been conducted.

Since 3-CMC was first detected on the drug market in September 2014, the substance has been identified in 23 Member States as well as Norway. While 3-CMC has been available on the European drug market since 2014, it appears that the availability of 3-CMC has increased significantly in around 2020, leading to its emergence in parts of Europe.

Availability

3-CMC was first identified on the European drug market 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 in 2014, the detection of 3-CMC in law enforcement seizures remained relatively low in comparison to 4-CMC until 2020. However, during 2020 and 2021 there has been a large, significant, 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 international drug control system in 2020. At least in part, it appears that 3-CMC is being manufactured, imported, distributed, sold, and used as a 'legal' replacement to 4-CMC as well as other controlled psychostimulants.

Since 2014, approximately 2720 kilograms of 3-CMC powder has been seized in Europe. This includes at least 2260 kilograms by customs and just over 320 kilograms by police, in more than 9000 seizures. Approximately 2500 kilograms (92%) has been seized during 2020 and 2021, including 1600 kilograms in 2021 alone. Other physical forms, such as tablets and capsules, have also been seized, but to a much smaller extent.

The available information suggests that 3-CMC is currently imported into Europe in bulk quantities mainly from India, with approximately 2100 kilograms of pure powders that originated from the country seized in 2020 and 2021. It is then processed, packaged, and then distributed in wholesale and retail amounts in Europe either online (typically on the surface web) or by street dealers.

In this respect, it is notable that following the recent control of 3-MMC in the Netherlands on 28 October 2021, there are indications that some online vendors have started to offer 3-CMC as a 'legal' replacement to 3-MMC (alongside already offering 3-CMC as a replacement to 4-CMC). However, it is not possible to draw any firm conclusions at this stage on the potential for 3-CMC to emerge as a replacement for 3-MMC.

Of particular note, is that while the quantities of synthetic cathinone powders seized in Europe have been decreasing since they peaked in 2015 and 2016, at around 1800 kilograms per year, and falling to 750 kilograms by 2019, during 2020 there was a significant increase, with approximately 3300 kilograms of powders seized. 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 (just under 880 kilograms). In addition, 3-methylmethcathinone (3-MMC), which is also currently the

subject of a risk assessment following its re-emergence in Europe, accounted for a similar quantity (just under 750 kilograms).

This increase in seizures of synthetic cathinones, especially by customs, coincides with a recent increase in reports of consignments originating from India. This may mark an important change in the synthetic cathinone market, where previously most of the manufacture of these substances was reported to be based in China. This may add greater resilience to the supply chains of synthetic cathinones in Europe.

Extent and patterns of use

Similar to other cathinones, such as 4-CMC, the available information suggests that 3-CMC is likely to be typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. Other routes may also be reported. 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 is likely to include recreational use, and, in some cases high risk use, such as injecting. In addition, due to high availability it is also possible that it will be used by inexperienced users.

Although there is no specific information, 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).

Limited information from self-reported experiences user experiences suggests that a range of doses may be used and that these may depend on the length of the session, the setting, route of administration, the desired effects, tolerance, and the use of other substances at the same time. Related to this, the use of 3-CMC with other drugs may be intentional or unintentional.

Similar to other synthetic cathinones, it is possible that 3-CMC may be used in chemsex, including by those who inject the substance and other drugs. Drug injection is associated with health risks which include transmission of blood-borne diseases. Injection of stimulant drugs has been associated with elevated levels of drug and sexual risk taking behaviours.

Potential for diffusion

The available information suggests that while 3-CMC is typically sold and sought after as a stimulant drug in its own right, at least in part it appears that the substance is being manufactured, imported, distributed, sold, and used as a 'legal' replacement to controlled stimulants such as 4-CMC, amphetamine, cocaine, and MDMA. In addition, it may also be missold as other drugs, including 4-CMC and 3-MMC.

Information on the current price of 3-CMC is limited. Based on prices advertised by online vendors, information reported by France noted that 1 gram of 3-CMC costs 14–18 Euros. Similar to other cathinones, such as 3-MMC, the price is likely to vary depending on the type of vendor and the amount purchased.

Reports of the mis-selling of 3-CMC as other drugs have so far been limited. Despite this, the potential for 3-CMC to be mis-sold as other drugs, particularly 3-MMC, as well as controlled stimulants such as 4-CMC and MDMA, exists.

The further diffusion of 3-CMC is likely to be influenced by many factors. These include the control of the substance in countries involved in the manufacture and distribution, as well as the availability and quality of other stimulant drugs, including other possible legal replacements. In the latter case, the EMCDDA monitors a large number of synthetic cathinones with similar effects to 3-CMC. This includes the positional isomer 2-CMC that appears to have been detected on the drug market in 2016, but rarely encountered since. In addition, as mentioned above, the recent control of 3-MMC in the Netherlands appears to have already led to some suppliers offering 3-CMC as a replacement substance.

Commercial and industrial uses, the extent of such use and its use for scientific research and developmental purposes

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, although unlikely, 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.

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.

Other relevant information

Restrictive measures

International restrictive measures

At international level, 3-CMC is not controlled under the United Nations Single Convention on Narcotic Drugs, 1961, nor under the Convention on Psychotropic Substances of 1971.

National restrictive measures

Europe

3-CMC is subject to restrictive measures in 21 Member States. Thirteen Member States reported that 3-CMC is controlled under drug control legislation: Croatia, Czechia, Denmark, Estonia, France, Italy, Ireland, Latvia, Poland, Portugal, Slovenia, Slovakia, and Sweden. Seven Member States reported that 3-CMC is controlled under new psychoactive substance legislation: Austria, Belgium, Cyprus, Germany, Finland, Hungary, and Malta. Lithuania reported that 3-CMC is controlled under medicines legislation.

Turkey and Norway also reported that 3-CMC is controlled under drug control legislation.

Six Member States (Bulgaria, Greece, Luxembourg, the Netherlands, Romania, and Spain) reported that 3-CMC is not subject to restrictive measures at national level.

Other countries

3-CMC has been controlled in China since October 2015. It is unknown if 3-CMC is controlled in India.

COVID-19 pandemic

In some settings, the on-going COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events 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 2170 kilograms of bulk powders by customs agencies and just over 190 kilograms by police between 2020 and 2021 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, 4-MMC, and MDMA) in Europe, criminal groups, as well as people who use drugs, may use a range of replacement substances, including 3-CMC.

Conclusion

1-(3-Chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) is a synthetic cathinone with psychostimulant effects in humans. It is monitored as a new psychoactive substance by the EMCDDA in accordance with Regulation (EC) No 1920/2006.

3-CMC 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 psychostimulant effects with methcathinone 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 has been available on the drug market in the European Union since at least September 2014 and has been identified in 23 Member States as well as Norway. While 3-CMC has been available on the European drug market since 2014, it appears that the availability of 3-CMC has increased significantly in around 2020, leading to its spread in parts of Europe. Although the reasons for this are unclear, it does coincide with the recent control of 4-CMC under the international drug control system in 2020. At least in part, it appears that 3-CMC is being manufactured, traded, imported, and used as a 'legal' replacement to 4-CMC and other controlled psychostimulants.

It is likely that 3-CMC 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-CMC, it is likely that 3-CMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It appears likely that it may 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 the latter case, this may be part of chemsex practices including men who have sex with men. Among other settings, 3-CMC is likely to be 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 practices. In addition, due to high availability it is also possible that it will be used by inexperienced users.

Since 2014, approximately 2720 kilograms of 3-CMC powder has been seized, including at least 2260 kilograms by customs and 320 kilograms by police, in more than 9000 seizures. During 2020 and 2021, approximately 2500 kilograms of powder was seized, including 2170 kilograms by customs (of which approximately 2100 kilograms (97%) originated from India) and just over 190 kilograms by police. This represents just over 90% of the total quantity of 3-CMC powders seized since monitoring of the substance began in Europe in 2014.

The available information suggests that 3-CMC is currently imported into Europe in bulk quantities mainly from India, with almost 700 kilograms and 2100 kilograms of powders that originated from

the country seized in 2020 and 2021, respectively. It is then processed, packaged, and then distributed in wholesale and retail amounts in Europe either online or by street dealers. In addition, at least three illicit sites, including some directly involved in the production of 3-CMC, have been seized in Europe, with the most recent sites seized in 2020.

Of particular note, is that while the quantities of synthetic cathinone powders seized in Europe have been decreasing since they peaked in 2015 and 2016, at around 1800 kilograms per year, and falling to 750 kilograms by 2019, during 2020 there was a significant increase, with approximately 3300 kilograms of powders seized. 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 (just under 880 kilograms). In addition, 3-methylmethcathinone (3-MMC), which is also currently the subject of a risk assessment following its emergence in Europe, accounted for a similar quantity (just under 750 kilograms).

One acute poisoning with confirmed exposure to 3-CMC has been reported by Spain.

A total of 10 deaths with confirmed exposure to 3-CMC have been reported by two Member States: Poland and Sweden. In at least 4 of the cases, no other substances were identified. Where reported, the cases occurred between late 2019 and 2021. In at least five cases, 3-CMC was the cause of death or contributed to the death.

The chronic health effects of 3-CMC, including abuse liability and dependence producing potential in humans, have not been studied. Overall, the chronic health effects may share some similarities with other closely related synthetic cathinones and psychostimulants under international control, although this requires further study.

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 information to suggest 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 2170 kilograms of bulk powders by customs agencies and just over 190 kilograms by police between 2020 and 2021 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 people who use drugs, 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, although unlikely, 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. 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 as well as Turkey and Norway. 3-CMC has been controlled in China since October 2015. 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 is not controlled under the United Nations Single Convention on Narcotic Drugs, 1961, nor under the Convention on Psychotropic Substances of 1971.

There is currently very limited information on the extent or patterns of use of 3-CMC in Europe, that reflects the recent emergence of the substance. Information from law enforcement seizures that took place in 2020 and 2021 indicates that its availability and potential for diffusion within the Union has recently increased and may be significant. In addition, the available information suggests that the use of 3-CMC causes harm to health associated with its acute toxicity. Due to lack of studies, there is uncertainty on the dependence potential and abuse liability of 3-CMC. The harm to health is considered life-threatening because it may cause death or lethal injury, severe disease, severe physical or mental impairment or a spread of diseases, including the transmission of blood-borne viruses, such as hepatitis C and HIV. These effects are comparable with other closely related synthetic cathinones and psychostimulants under international control, although this requires further study.

As for any new psychoactive substance, many of the questions related to 3-CMC that are posed by the lack of data on the risks could be answered through further research. Considering the apparent emergence and use of 3-CMC and adverse effects associated with its use, there is an urgent need for complementary information on the dependence potential and abuse liability of 3-CMC. Other areas where additional information would be important include studies on: epidemiology; the market; chemical profiling; extended pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between 3-CMC and other substances; and the public health and social risks associated with its use.

The Committee considers that to prevent diffusion of 3-CMC and to limit associated health and social risks, communication including prevention and harm reduction messages needs to be strengthened in Europe. The Committee notes that a decision to control 3-CMC has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks arising from the use of 3-CMC. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, pharmacologically analogous substances that may replace 3-CMC are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those

who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation.

Finally, the Committee notes that it is important to continue to collect accurate information on 3-CMC and to disseminate it to people who use the substance, as well as to practitioners, policymakers and decision-makers.

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

Purpose

The purpose of this technical report is to provide an analysis of the available information on 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC), a synthetic cathinone that has recently emerged on the drug market in Europe, in order to support the risk assessment of the substance which has been requested by the European Commission in accordance with Article 5c of Regulation (EC) No 1920/2006.

Parts of this report were prepared under EMCDDA contracts (ref. CT.21.SAS.0072.1.0 and CT.21.SAS.0076.1.0).

Information sources

The following information sources are included in this technical report:

- Information reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with the requirements of Article 5a and Article 5b of Regulation (EC) No 1920/2006 (EMCDDA, 2021).
- Information reported by the European Medicines Agency (EMA), the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), and the European Food Safety Authority (EFSA) to the EMCDDA in accordance with the requirements of Article 5b of Regulation (EC) No 1920/2006.
- Information collected by the EMCDDA through searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, online drug discussion forums and related websites, and online vendors selling 3-CMC.

Literature search and review

Literature searches used both chemical structure and textual queries in online databases; searches were conducted in September 2021. The retrieved publications were then scanned for additional relevant references (snowballing technique) including Crossref, Scopus and Web of Science.

SciFinder[®] and Reaxys were searched by exact structure-based search. PubMed and Google Scholar was searched for '3-chloromethcathinone', '3-CMC' and the IUPAC name '1-(3-

chlorophenyl)-2-(methylamino)propan-1-one'. The references were screened for relevance and included in the review where appropriate.

Terminology and definitions

The terminology and definitions used in this technical report are based on those used for the operation of the EU Early Warning System on new psychoactive substances, including those related to relevant internal EMCDDA processes. They can be accessed on the EMCDDA website (EMCDDA, 2019 and EMCDDA, 2020a).

Unless otherwise indicated, the terms and definitions are for operational use only and do not have legal meaning. They may differ from those used in other settings and by other organisations (EMCDDA, 2019).

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 can pose 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 purpose 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. Iso-3-CMC is a structural isomer of 3-CMC (and 4-CMC). The identification and discrimination of structural isomers can also pose analytical challenges.

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 Technical Report:

- For the period comprised between 1 January 2014 and 31 December 2020, annual aggregated seizure data which are systematically reported to the EMCDDA have 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. These data are not comparable to aggregated seizure data.
- Open source information has also been used in 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’.

Since the preparation of the initial report on 3-CMC (EMCDDA, 2021), additional clarifications on the information initially reported and updates have been received. These have been included in this technical report.

It is also important to note that, in some settings, the on-going COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ECDC, 2020; EMCDDA, 2020b; WHO, 2020) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving 3-CMC.

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1. Summary

Ring-substituted synthetic cathinones, such as 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) are a group of substances with stimulant effects that are derivatives of cathinone, the naturally occurring stimulant and main psychoactive substance in the khat plant *Catha edulis*.

Since 2005, more than 160 synthetic cathinones have been identified on the European drug market. They are the second largest category of substances monitored by the EMCDDA through the European Union Early Warning System on New Psychoactive Substances (EU Early Warning System). Seizures of cathinone powders in Europe peaked in 2015 and 2016, when around 1 800 kg were seized per year, and fell to 750 kg by 2019. During 2020, there was a significant increase in the quantities of cathinone powders seized in Europe, 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.

3-CMC is monitored as a new psychoactive substance by the EMCDDA in accordance with Regulation (EC) No 1920/2006. The substance is a halogenated, *N*-alkylated and ring-substituted cathinone and contains a chiral centre, so two enantiomers may exist: (*R*)-3-CMC and (*S*)-3-CMC. 3-CMC is 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.

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 under international control, 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 people who use stimulant drugs such as cocaine, amphetamines, ecstasy, and other synthetic 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).

On the drug market, cathinones are typically found in powders and tablets. To date, seizures and collected samples containing 3-CMC reported to the EMCDDA have been mostly in powder form, although there are reports of other physical formats such as tablets, capsules, liquids (some of which branded legal-high type products), herbal material and blotters. Information on the

enantiomeric composition of seized and collected samples has not been reported. 3-CMC has been identified in combination with other synthetic cathinones, including but not limited to 4-methylmethcathinone (mephedrone, 4-MMC) and 3-methylmethcathinone (metaphedrone, 3-MMC), and a variety of other substances including synthetic cannabinoids and other internationally controlled substances such as cocaine and MDMA.

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 2 260 kg by customs and 320 kg by police. 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 seizures of a total of 1 400 kg of powder at the external EU border, originating in India.

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 seized in 2020 and 1 400 kg, which also originated from India, seized in 2021. It is then processed, packaged, and 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.

In general, halogenated cathinones interact with monoamine transporters in the brain, i.e. with dopamine, serotonin and norepinephrine transporters. The pharmacodynamic effects of 3-CMC have been tested *in vitro* and initial findings have also been obtained *in vivo* which suggest that 3-CMC shows a psychostimulant profile comparable to some other synthetic cathinones under international control. Pharmacokinetic properties of 3-CMC in humans and animals are currently unknown.

There is limited information on the acute toxicity of 3-CMC. Based on the available information, the health risks are likely to be similar to those observed with other synthetic cathinones under international control. 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 clinical features. 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 toxicity.

One acute non-fatal poisoning with confirmed exposure to 3-CMC has been reported by one Member State (Spain) with other substances being identified as well.

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.

To date, no instances of acute poisonings, driving under the influence, or death investigations with confirmed exposure to 3-CMC have been reported in the scientific or medical literature.

There is no information on the chronic health effects of 3-CMC in humans, including abuse liability and dependence potential. The chronic health risks might share some similarities to those seen

with other synthetic cathinones under international control. It has been suggested that many synthetic cathinones have been associated with abuse liability and dependence potential, and that consumption of synthetic cathinones can produce withdrawal-like symptoms when use is discontinued following a regular use.

Psychological and behavioural effects of 3-CMC have not been formally studied, but are likely to share some similarities with those commonly reported for other synthetic cathinones under international control, including general stimulation, euphoria, increased energy, sociability, increased libido, insomnia, and anxiety.

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 on-going COVID-19 pandemic on the manufacture, trafficking, distribution and use of 3-CMC is currently unknown. However, seizures of more than of 2 tonnes 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 people who are using drugs, 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. 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.

2. Chemical and physical properties, methods and the precursors used for manufacture or extraction

2.1 Background

1-(3-Chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC, also known as chlophedrone) is an N-alkylated and ring-substituted synthetic cathinone. 3-CMC was first described in the scientific literature in the months prior to its first detection on the drug market in Europe in September 2014 (Kohut et al., 2013).

Synthetic cathinones are analogues and derivatives of the naturally occurring substance cathinone, which is internationally controlled ⁽¹⁾, and the main psychoactive ingredient of the khat plant (*Catha edulis*). Cathinone is also structurally related to amphetamine, differing from it by the presence of a β -keto group, which means that it is an amino ketone. Similarly, all synthetic cathinones contain a β -keto moiety as a structural prerequisite. Some synthetic cathinones are (or were) available as medicines (e.g., diethylpropion ⁽²⁾ and bupropion ⁽³⁾), whereas others are controlled substances with history of abuse and examples include methcathinone and 4-methylmethcathinone (4-MMC, mephedrone).

3-CMC is the 3-chloro derivative of methcathinone ⁽⁴⁾ and a positional isomer ⁽⁵⁾ of 4-CMC (4-chloromethcathinone) ⁽⁶⁾, which are both internationally controlled and listed in Schedules I and II, respectively. 3-CMC is also structurally related to 3-MMC (3-methylmethcathinone) ⁽⁷⁾, differing on the substituent present at the 3-position of the phenyl ring. Iso-3-CMC ⁽⁸⁾, an isocathinone, is also a structural isomer of 3-CMC and 4-CMC. Higher and lower homologues of 3-CMC monitored by the EMCDDA are: 3-CEC (3-chloroethcathinone) ⁽⁹⁾ and 3-chlorocathinone ⁽¹⁰⁾, respectively.

3-CMC has a chiral centre at the C₂ carbon of the propanone side chain thus the two possible enantiomers are (*R*)-3-CMC and (*S*)-3-CMC.

2.2 Names and chemical structure

The common name 3-CMC is derived from 3-chloromethcathinone ⁽¹¹⁾. The molecular structure, molecular formula, molecular mass and monoisotopic mass of 3-CMC are provided in Figure 1.

⁽¹⁾ Listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances.

⁽²⁾ Diethylpropion, also known as amfepramone (2-(diethylamino)propiofenone), is listed in Schedule IV of the 1971 United Nations Single Convention on Psychotropic Substances.

⁽³⁾ 2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one.; formally notified by the EMCDDA in 2014.

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

⁽⁵⁾ 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.

⁽⁶⁾ 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.

⁽⁷⁾ 2-(Methylamino)-1-(3-methylphenyl)propan-1-one; formally notified by the EMCDDA in September 2012.

⁽⁸⁾ 1-(3-Chlorophenyl)-1-(methylamino)propan-2-one; formally notified by the EMCDDA in October 2021.

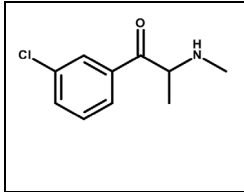
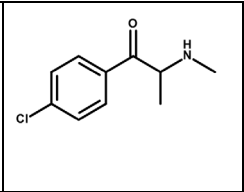
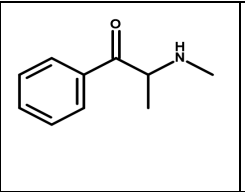
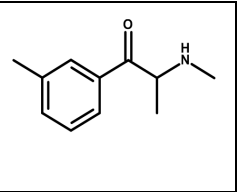
⁽⁹⁾ 1-(3-Chlorophenyl)-2-(ethylamino)propan-1-one; formally notified by the EMCDDA in March 2016.

⁽¹⁰⁾ 2-Amino-1-(3-chlorophenyl)propan-1-one; formally notified by the EMCDDA in November 2020.

⁽¹¹⁾ The origin for the abbreviated common name is indicated by underlining the relevant letters in the common name.

FIGURE 1

Molecular structure, molecular formula, molecular mass and monoisotopic mass of 3-CMC

				
	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
Monoisotopic mass	197.060742	197.060742	163.099714	177.115364

Note: Information on 4-CMC, methcathinone and 3-MMC is provided for comparison.

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

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*-isomer)

IUPAC International Chemical Identifier String (Inchl string):

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

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)

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)

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)

CC(C(=O)C1=CC(=CC=C1)Cl)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)

EC / List no.

814-937-5

Other identifiers

PubChem CID 50999285

ChEMBL3305871

DTXSID501014162

MFCD11053592

AKOS006309213

2.3 Physical properties

There is limited information available on the solubility, lipophilicity, melting and boiling points or other physicochemical 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). Shalabi et al. (2017) 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 to confirm elemental composition.

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 or phosphate-buffered saline (PBS) (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.

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

3-CMC has been identified in combination with other cathinones, including but not limited to: 2-MMC ⁽¹²⁾, 3-MMC, 3-CEC ⁽¹³⁾, 4-CEC ⁽¹⁴⁾, 4-CMC, 4-MEC ⁽¹⁵⁾, α -PVT ⁽¹⁶⁾, eutylone ⁽¹⁷⁾, mexedrone ⁽¹⁸⁾ and *N*-ethylhexedrone ⁽¹⁹⁾. 3-CMC has also been identified in combination with a variety of other categories of substances including synthetic cannabinoids, such as the

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

⁽¹³⁾ 1-(3-Chlorophenyl)-2-(ethylamino)propan-1-one

⁽¹⁴⁾ 1-(4-Chlorophenyl)-2-(ethylamino)propan-1-one

⁽¹⁵⁾ 2-(Ethylamino)-1-(4-methylphenyl)propan-1-one

⁽¹⁶⁾ 2-(Pyrrolidin-1-yl)-1-(thiophen-2-yl)pentan-1-one

⁽¹⁷⁾ 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one

⁽¹⁸⁾ 3-Methoxy-2-(methylamino)-1-(4-methylphenyl)propan-1-one

⁽¹⁹⁾ 2-(Ethylamino)-1-phenylhexan-1-one

internationally controlled 4F-MDMB-BINACA (4F-MDMB-BUTINACA) ⁽²⁰⁾, and other internationally controlled substances, such as cocaine, MDMA, amphetamine and methamphetamine.

2.4 Methods and chemical precursors used for the manufacture or extraction

Limited information is available on 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 the specific methods for the preparation of 3-CMC (Blough et al., 2014; Shalabi et al., 2017), are described below.

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

The interest in cathinones (and α -aminoketones in general) has motivated significant work aimed at developing efficient synthetic approaches to produce them. Some of this work is related to the synthesis of bupropion (Mehta, 1974; see also Perrine et al., 2000), an atypical antidepressant authorised in a number of Member States as an aid to smoking cessation and treatment of major depressive disorder.

Many of the published synthetic approaches occur *via* a propiophenone precursor (i.e. an aryl ketone), which can be synthesised in a variety of ways, some of which generic and applicable to all ring substituted cathinones, others specific to some derivatives ⁽²¹⁾. The propiophenone precursor ((I), see Scheme 1) needed to afford 3-CMC and its *N*-alkyl-homologues can be synthesized from:

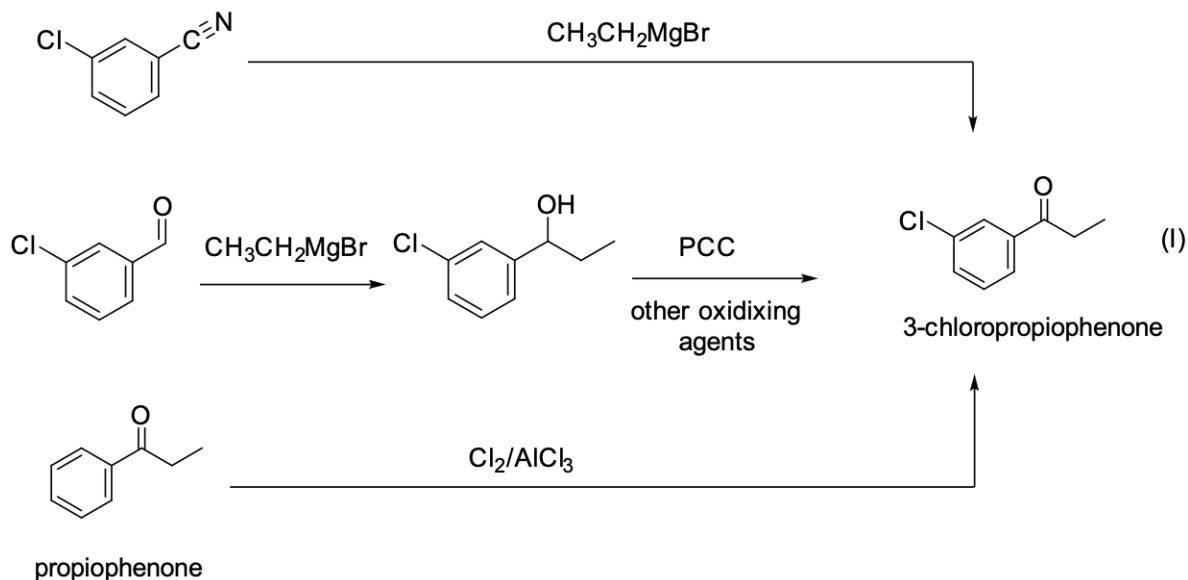
- 3-chlorobenzonitrile, using a Grignard reaction (with ethylmagnesium bromide) as described in the original patent for bupropion (after Mehta, 1974; Carroll et al., 2009; Li et al., 2017) (Scheme 1),
- 3-chlorobenzaldehyde, using a Grignard reaction to afford an alcohol intermediate which is then oxidised with pyridinium chlorochromate (or other oxidizing reagents) (based on Power et al., 2011) (Scheme 1)
- propiophenone, by regioselective chlorination, in the presence of AlCl₃ (Nair et al., 2002)
- 3-chloropropiophenone, by reacting it with sulfonyl chloride, resulting in the corresponding α -chloropropiophenone precursor (not represented in Scheme 1) (Kavanagh et al., 2012).

⁽²⁰⁾ Methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate; listed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.

⁽²¹⁾ In the case of mephedrone (4-MMC) and some of its analogous compounds, including 4-CMC, the starting propiophenone can be produced *via* a Friedel-Crafts acylation between a substituted benzene ring and, typically, an acyl chloride (such as propionyl chloride).

SCHEME 1

Preparation of 3-chloropropiophenone (I), a precursor of 3-CMC from 3-chlorobenzonitrile (after Mehta, 1974; Carroll et al., 2009; Li et al., 2017), **from 3-chlorobenzaldehyde** (based on Power et al., 2011) **or from propiophenone** (Nair et al., 2002).

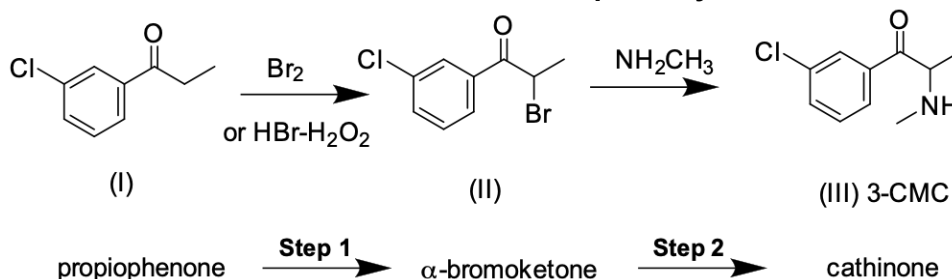


Importantly, propiophenone precursors like (I) can also be purchased from chemical suppliers and imported in bulk. 3-Chloropropiophenone (I), being a key starting material of the synthesis of bupropion, is manufactured on a large scale.

Once available, it can be transformed into many *N*-alkylated cathinones, such as 3-CMC, using a number of approaches. One of the most straightforward is described in Scheme 2. It uses equipment and knowledge similar to those required for the synthesis of other synthetic drugs like MDMA or amphetamine (EMCDDA, 2011).

SCHEME 2

Preparation of 3-CMC via the 'bromination-amination' pathway



Note: Shalabi et al., 2017; Blough et al., 2014; for related compounds, see Carroll et al., 2009; Reddy et al., 2010; Power et al., 2011; Wojcieszak et al., 2021.

This 2-step bromination-amination procedure starts with the α -bromination of the propiophenone (I) to produce the corresponding α -bromoketone (II). The product is then reacted with an amine ⁽²²⁾ to afford a free cathinone base (III) (EMCDDA, 2011; Wrzesień, 2018). Here lies one of the biggest advantages of the approach, in that a number of different *N*-substituted cathinones can be produced in series, by obtaining intermediate (II) at a large scale, subdividing it into lots and reacting each lot with a different amine to produce a number of different cathinones (Collins, 2016), making it an 'industrially efficient' method. Unless steps are taken to resolve the reaction products, this synthesis produces racemic mixtures.

Due to the instability of the free base, the product (III) is converted into suitable salts (hydrochlorides or hydrobromides), which are then recrystallised (EMCDDA, 2011; Wrzesień, 2018).

Similar to the propiophenone precursor (I), the α -bromoketone (II) intermediate is also available from chemical suppliers. Data reported to the European Commission (unpublished) indicates that between 2017 and 2019, at least 2.1 tonnes of α -bromoketone (II) intermediates were seized in Europe, most of which were 2-bromo-4-chloropropiophenone (an intermediate for the synthesis of 4-CMC) and 2-bromo-4-methylpropiophenone (an intermediate for the synthesis of 4-MMC).

For the production of cathinones, importing the bromoketone derivatives reduces the number of steps needed to obtain the final product and avoids the use of bromine. Bromine ⁽²³⁾, which is required for step 1 (in Scheme 2), is a fuming liquid which is toxic by inhalation, may accelerate the burning of combustible materials, and is very corrosive to metals and to human tissue and dangerous for the environment.

Alternatively, using *N*-bromosuccinimide (NBS) in the presence of an acid catalyst avoids the hazardous reagent bromine, which might be the preferred approach for an industrial-scale production of precursor (II) (Reddy et al., 2010; see also Guha et al., 2015). Methods that avoid the use or the isolation of the lacrimatory α -bromoketone (II) have also been developed (Allen et al., 2021).

Other than the 'bromination-amination' procedure as depicted in Scheme 2 (Shalabi et al., 2017) there are several published syntheses of 3-CMC:

- An early patent on α -(alkylamino)propiophenones describes a one-pot synthesis of the α -chloro analogue of α -bromoketone (II) in which propiophenone reacted with excess of sulfuryl chloride in the presence of AlCl_3 to afford the key intermediate ' α,m -dichloropropiophenone' ⁽²⁴⁾ which was then reacted with *t*-butylamine to afford bupropion (Mehta, 1971).
- A method circumventing the use of methylamine and using *N*-benzyl-*N*-methylamine instead was developed for 3-CMC, and a wide range of ring-monosubstituted

⁽²²⁾ This step promotes the nucleophilic substitution of the bromine to obtain the α -bromoketone. For ring substituted cathinones, the amine is typically methylamine hydrochloride and triethylamine in an acidic scavenger.

⁽²³⁾ Bromine 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).

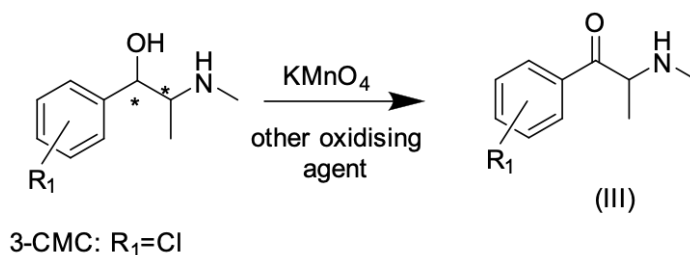
⁽²⁴⁾ Systematic name: 2-chloro-1-(3-chlorophenyl)propan-1-one

methcathinones (Blough et al., 2014). The *N*-benzyl protective group in (III) could readily be removed using 1-chloroethyl chloroformate.

Other than those described in the literature for 3-CMC, more generic methods of preparation of cathinones exist and one example is the so-called ‘permanganate process’ (Scheme 3), which involves the direct oxidation of a suitable ephedrine analogue (I) with a strong oxidant (e.g. potassium permanganate) to yield the desired cathinone (II). If (I) is obtained in a specific enantiomeric form, the synthesis is stereoselective and the resulting cathinone (II) will be enantiopure, which may be of interest if one of the forms is more active than the other. Although this method can yield chiral 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).

SCHEME 3

"Permanganate process" for the preparation of ring substituted cathinones



Note: For 3-CMC, the process would start with 3-chloroephedrine (1-(3-chlorophenyl)-2-(methylamino)propan-1-ol). Asterisk (*) indicates chiral centre.

The synthesis of the (*R*)- or the (*S*)-enantiomer of 3-CMC have not been reported in the literature at the time of writing. The optical isomers of related cathinones or metabolites have been obtained by specific, multistep synthetic routes (Blough et al., 2014; Niello et al., 2021).

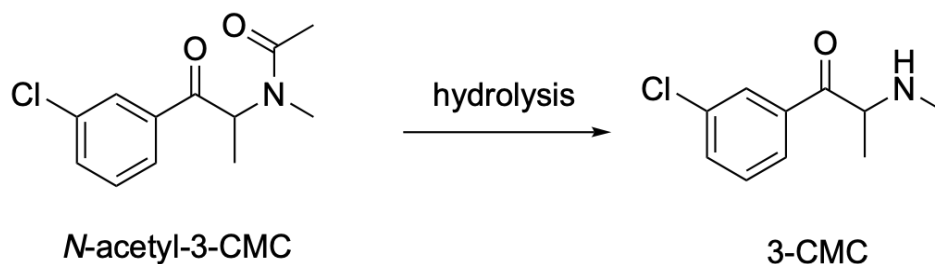
"Designer" precursors

Other than standard organic synthesis methods using known precursors, cathinones can be prepared using so-called "designer precursors" or "made-to-order" 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). Primary and secondary amine compounds, including cathinones, are especially suited for the latter approach, in that "masking" or "protecting" groups (such as acetyl groups, "Boc", 'Cbz' or "Tosyl" groups for example) since these can be easily introduced into the molecule (making it a different chemical entity) and then easily cleaved off, often in excellent yields to produce the controlled amine of choice. In Scheme 4, an example is provided for the *N*-acetyl protected cathinone 3-CMC.

It should be noted that approximately 350 kg of the structurally related *N*-acetyl-3-MMC imported from India were seized in the Netherlands in 2019, alongside 154 kg of 3-MMC at a 'dealer/producer' site (CAM 2021). This suggests that this alternative to the production of cathinones may be of interest to illicit manufacturers of cathinones.

SCHEME 4

Use of acetyl protecting groups to yield cathinones as exemplified for 3-CMC



Note: Hydrolysis may occur preferably via acid catalysed reaction.

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', ⁽²⁵⁾ were seized by Dutch Customs in 2021. Isocathinones such as 'iso-3-CMC', can be formed as side products during the synthesis that involves the bromination-amination pathway (McDermott et al., 2011; Westphal et al.; 2012; Wrzesień, 2018), which, as explained above, is the most "industrially efficient" method to manufacture 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 the amination step in the bromination-amination pathway (Step 2 in Scheme 2). This suggests that cathinone labs in Europe may be using the pathway in question 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 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.

⁽²⁵⁾ 1-(3-Chlorophenyl)-1-(methylamino)propan-2-one

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.

2.5 Methods for identification and analysis

The analysis of positional isomers of chloromethcathinones has been published in the scientific literature. Table 1 contains an overview of the literature involving the determination of 2-, 3-, and 4-CMC either alone or from mixtures with other NPS, from buffers or biological material (including whole blood and urine samples). Also, enantiomer-selective determinations have also been described.

The first description of analytical methodology has been provided by Blough et al. in 2014, through gas chromatography– mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR) (Blough et al., 2014). This combination of methodologies is currently the most frequently used, especially when analysing bulk material.

TABLE 1

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

Physical samples	
Analytical method	References
Gas chromatography–mass spectrometry (GC-MS)	Blough et al., 2014 SWGDRUG, 2017 Cayman Chemical, 2015 RESPONSE, 2015
Gas chromatography/electron ionisation-triple quadrupole energy-resolved mass spectrometry (GC/EI-QqQ-ERMS)	Murakami et al., 2021
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 (CE)	Hägele et al., 2019
¹ H Nuclear magnetic resonance spectroscopy (NMR)	Blough et al., 2014 Shalabi et al., 2017 SWGDRUG, 2017 RESPONSE, 2015
¹³ C NMR	RESPONSE, 2015
Ultraviolet spectroscopy	Zuba and Adamowicz, 2018
Biological samples	
Analytical method	References
High-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS)	Adamowicz and Tokarczyk, 2019
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 products can be carried out according to the general procedure described by the 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; Tomczak et al., 2018) but also other procedures that facilitate the separation between these positional isomers might be applicable.

Discrimination of 3-CMC from its positional isomers

3-CMC has two positional isomers, 2-CMC ⁽²⁶⁾ and 4-CMC, differing 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 can pose analytical challenges, as techniques solely relying on mass spectral data alone will not allow for 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, and their use involving suitable methods of separation, and/or additional analytical methods such as FTIR or NMR. The discrimination of these isomers is described in further detail below.

Analysis of 2-, 3- and 4-CMC by GC-MS will result in very similar mass spectra, which limits the ability to differentiate between them. Recently, the trifluoroacetyl derivatives of the three positional isomers could be discriminated by different relative abundances of certain fragments under energy-resolved GC/EI-QqQ-MS conditions. In addition, all three isomers could be differentiated by gas chromatography as well (Murakami et al., 2021).

Hägele et al. demonstrated that positional isomers could also be discriminated by use of capillary electrochromatography (CEC), providing the example of the discrimination of three different fluorinated methcathinone derivatives, 2-FMC ⁽²⁷⁾, 3-FMC ⁽²⁸⁾ and 4-FMC ⁽²⁹⁾, using a carboxymethyl-β-CD stationary phase 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 many isomeric cathinones including 2-, 3-, and 4-CMC (Kadkhodaei et al., 2020).

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

A validated GC-MS/MS method for the determination of NPS in blood samples from forensic cases has also been described (Woźniak et al., 2020) which included 3-CMC and 4-CMC as pentafluoropropionyl derivatives. The chromatographic and mass spectral differences however

⁽²⁶⁾ 1-(2-Chlorophenyl)-2-(methylamino)-1-propanone

⁽²⁷⁾ 1-(2-Fluorophenyl)-2-(methylamino)propan-1-one

⁽²⁸⁾ 1-(3-Fluorophenyl)-2-(methylamino)propan-1-one

⁽²⁹⁾ 1-(4-Fluorophenyl)-2-(methylamino)propan-1-one

were relatively minor which might limit the use of these specific conditions to the presence of only one of these analytes in a given sample (Woźniak et al., 2020).

Iso-3-CMC, a structural isomer of 3- and 4-CMC, has also 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 detection of iso-3-CMC reflects the presence of side products that can form during the bromination-amination reaction sequence and this phenomenon has been reported previous investigations involving other synthetic cathinones as well (McDermott et al. 2011; Westphal et al., 2012). In the study reported by McDermott et al. (2011) investigating the detection of iso-mephedrone and iso-ethcathinone, it was suggested that their formation could have originated from a number of sources, including contaminated starting material, the use of liquefied amines (e.g. neat *N*-methylamine in liquid form) instead of amine solutions, or as a consequence of rearrangement during the reaction. It is conceivable that either some or all of these phenomena could explain the detection of iso-3-CMC in the seized samples.

Differentiation of enantiomers

Cathinones, such as 3-CMC, contain a chiral centre that explains the existence of (*R*)- and (*S*)-3-CMC within a racemic mixture. 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. Nevertheless, it is assumed that, due to the high cost of producing the individual stereoisomers, the substance occurring on the illicit drug market is racemic.

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. (2020) reported the use of an isocratic HPLC method with a specific chiral stationary phase (CSP) to separate enantiomers of a range of new psychoactive substances, including 3-CMC. Kadkhodaei et al. (2018) also demonstrated the separation of a range of NPS enantiomers using an isocratic HPLC method with a specific CSP. The authors also noted a successful chiral separation of 3-CMC and 4-CMC enantiomers though 2-CMC enantiomers could not be separated under the conditions used (Kadkhodaei et al., 2018).

Stability of 3-CMC

There is very limited information available on the stability of 3-CMC. However, the salts of cathinones are generally considered to be more stable than the free base form and are more stable in acidic urine (pH 4) than in alkaline urine (pH 8) (Aldubayyan et al., 2021).

A recent study indicates that 4-CMC, the positional isomer of 3-CMC, was highly unstable in biological matrices exposed to a variety of temperature and pH conditions (Adamowicz and Malczyk, 2019). From a total number of 17 new psychoactive substances, 4-CMC was found to be the least stable compound which means that the drug concentrations determined during forensic toxicological investigations depend on the time of sampling. The extent to which the instability observed for 4-CMC applies to 3-CMC warrants further study.

2.6 Dosage regimens

Pharmaceutical and posological information

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.

Racemic 3-CMC is commercially available as analytical reference material ⁽³⁰⁾.

On the drug market, cathinones are typically found in powders and tablets. To date, seizures and collected samples containing 3-CMC reported to the EMCDDA have been mostly in powder form, although there are reports of other physical formats such as tablets, capsules, liquids (some of which branded legal-high type products), herbal material and blotters.

Powders were found to range from 'white/colorless crystals to white/off-white powders. 3-CMC may be sold under its own name ('3-CMC', 'Clophedrone'), or as other drugs.

Information on the enantiomeric composition of seized and collected samples has not been reported. 3-CMC has been identified in combination with other cathinones, including but not limited to 4-MMC and 3-MMC, and a variety of other substances including synthetic cannabinoids and internationally controlled substances such as cocaine and MDMA.

Apart from a recent detection of iso-3-CMC as an apparent contaminant in some 3-CMC seizures, no information available with regards to route-specific by-products produced during the synthesis of 3-CMC is currently not available.

No information on the purity of the compounds that are sold by online vendors is available.

Route of administration and dosage

Information on the dose and dosage regimens ⁽³¹⁾ for 3-CMC is limited. Most information available is from reports posted on Internet forums and surveys.

According to anecdotal information posted on Internet forums, the most common routes of 3-CMC administration involve oral ingestion, nasal insufflation (snorted) or intravenous injection. In the case of the 4-CMC isomer, and depending on the route of administration and the user's tolerance, the dose resulting in the desired effects have been reported to range from 100 to 300 mg for oral ingestion and 50 to 150 mg for snorting (Tomczak et al., 2018).

Risk-modifying factors

One possible risk-modifying factor would be a potential elevation of body temperature – which has not been reported in rigorous scientific studies on 3-CMC. For the closely related mephedrone (4-MMC), some studies in rodents suggest elevated body temperature (Baumann et al., 2012) though others reported a reduction in body temperature following administration (Wright et al., 2012;

⁽³⁰⁾ <https://www.lgcstandards.com/DE/de/3-Chloromethcathinone-hydrochloride-/p/CAY-17394-5MG> and <https://www.caymanchem.com/product/16436> accessed on October 24, 2021.

⁽³¹⁾ Dosage regimen: is information on the formulation (dosage form), route of exposure, as well as the schedule of doses of a new psychoactive substance, including the amount taken each time, time between doses, and the duration of use.

Aarde et al., 2013). Nevertheless, some users also described a cold sensation following mephedrone ingestion (Winstock et al., 2011).

Uncertainty analysis

The largest uncertainty comes from the relative instability of the compound in biological samples which has not been thoroughly established (Adamowicz and Malczyk, 2019; Aldubayyan et al., 2021). Although the stability studies of 3-CMC have not been conducted so far, it is known that 4-CMC is very unstable in biological material and decomposes very quickly (Nowak et al., 2019; 2020). Hence, it will be difficult to predict how the measured levels of 3-CMC may relate to poisonings, including clinical features.

3. Legitimate use

3.1 Summary

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, although highly unlikely, 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 (EMCDDA, 2021). There is currently no information that suggests 3-CMC is used for legitimate purposes other than research or forensic application.

3.2 Medical use

Based on information from the European Medicines Agency for the initial report (EMCDDA, 2021), it appears that 3-CMC is not an active substance in:

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

- 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;

- 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.

3.3 Industrial, commercial, and scientific use

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

As part of the initial report process, the European Chemical Agency (ECHA) reported that there are no registrations or classification and labelling (C&L) notifications for 3-CMC in the C&L Inventory database ⁽³²⁾. 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, no date). The identity of C&L notifiers is not published on the ECHA dissemination website, due to the sensitivity of this information.

As part of the initial report process, the European Food Safety Authority (EFSA) reported to the EMCDDA that they hold no information on 3-CMC and have not assessed this substance in any context.

Risk-modifying factors

At least some of the 3-CMC available on the European market originates from illegal manufacturing facilities. This might mean that its quality is unknown and different batches of product might have high variability in content.

Uncertainty analysis

While information on legitimate use originated from reliable sources, it is possible that the submitted information is incomplete due to under-reporting. Since data was collected from European agencies only, it is possible that 3-CMC might have legitimate uses outside EU.

4. Pharmacological and toxicological properties

4.1 Summary

In general, halogenated chlorocathinones interact with monoamine transporters, namely dopamine transporter (DAT), serotonin transporter (SERT) and norepinephrine transporter (NET) as transported substrates in the synapse (Blough et al., 2014; Eshleman et al., 2017; Luethi et al., 2019; Walther et al., 2019). This leads to (i) a competitive inhibition of re-uptake of physiological

⁽³²⁾ 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

substrate and (ii) transporter-mediated reverse transport of intracellular, cytosolic physiological substrate. The first point illustrates the distinct interaction between the compound and its clinically relevant target, while the second reveals its nature as an amphetamine-type stimulant which distinguishes such compounds from cocaine-like inhibitors (Sitte and Freissmuth, 2015). The pharmacodynamic effects of 3-CMC have been tested *in vitro* and initial findings have also been obtained *in vivo*, e.g., in experiments assessing spontaneous locomotor activity and other behavioural assays in rodents (Wojcieszak et al., 2020; 2021).

For 3-CMC, the *in vitro* DAT/SERT ratio, which is thought to predict the reinforcing or dependence producing properties associated with highly dopaminergic compounds (Glennon, 2014) was found to be below 10 which was inconsistent with other psychostimulants known to display abuse liability and dependence producing properties.

Pharmacokinetic properties of 3-CMC in humans and animals are currently unknown.

Although not formally studied, the psychological and behavioural effects of 3-CMC are likely to share some similarities with those commonly reported for other synthetic cathinones under international control, including general stimulation, euphoria, increased energy, sociability, increased libido, insomnia, and anxiety.

The abuse liability and dependence producing potential of 3-CMC have not been studied. However, it has been suggested that many synthetic cathinones display abuse liability and dependence potential, and that consumption of such substances can produce withdrawal-like symptoms when use is discontinued following regular use

4.2 Pharmacodynamics

Most of the few studies examining 3-CMC have been conducted *in vitro*. There are also a few animal studies on effects on spontaneous locomotor activity and motor performance.

4.2.1 *In vitro* data

4.2.1.1 Uptake inhibition studies

The monoamine transporter uptake inhibition of tritium-labeled dopamine (DA), norepinephrine (NE) and serotonin (5-HT) was investigated for a set synthetic cathinones using rat brain synaptosomes (Shalabi et al., 2017). Data for representative compounds, including 3-CMC, are shown in Table 2. Based on the DAT/SERT ratio, the antidepressant bupropion is an efficacious inhibitor at DAT and NET but weak at SERT, which might explain the sporadic misuse of bupropion. In this regard, bupropion is comparable to the stimulant and frequently used alkaloid (S)-cathinone found in the khat plant. 3-CMC, which can be considered a lower homologue with a less bulky amine moiety, has a more balanced effect on the three neurotransmitters, yet dopaminergic properties still dominate under the *in vitro* conditions studied. Interestingly, removal of the *N*-methyl group affording 3-chlorocathinone (or nor-3-CMC) did not seem to affect potency at the three transporters.

TABLE 2

Inhibition of DAT-, SERT- and NET-mediated monoamine uptake of DA, 5-HT and NE by cathinone analogues

Drug	DAT inhibition IC₅₀, nM	SERT inhibition IC₅₀, nM	NET inhibition IC₅₀, nM	DAT/SERT selectivity
Bupropion	305 ± 55	>10,000	3715 ± 545	>30
3-CMC	342 ± 46	1104 ± 79	290 ± 36	3.2
(-)-(S)-cathinone	357 ± 46	>10,000	224 ± 37	>30
3-Chlorocathinone	399 ± 87	2779 ± 454	551 ± 50	7

Note: Shalabi et al., 2017. All compounds are racemic unless otherwise noted. Experiments were carried out with male rat brain synaptosome preparations using appropriate radiolabeled ligands. EC₅₀ values are mean ± standard deviation; ratio of SERT-IC₅₀/DAT-IC₅₀ values.

4.2.1.2 *Transporter-mediated release*

The monoamine transporter-mediated release of tritium-labeled dopamine (DA), norepinephrine (NE) and serotonin (5-HT) has been investigated for a set of variously substituted synthetic cathinones using rat brain synaptosomes (Blough et al., 2014). The compounds studied were mostly ring-substituted *N*-cyclopropyl analogues of bupropion. The DA-releaser activity, reported as mean EC₅₀ values (± standard deviation), for 3-CMC (PAL-434) and 3-chloroamphetamine (PAL-304), its close structural variant, were 46.8 (±4.0) nM, and 11.8 (±0.7) nM, respectively. The 5-HT release EC₅₀ values for 3-CMC and 3-chloroamphetamine were 410 (±36) nM and 120 (±6) nM, respectively, indicating that dopaminergic effects dominate over serotonergic effects *in vitro*, with PAL-304 being a more potent releaser. No NE release data were reported for the compounds in this publication (but see, Kohut et al., 2013).

The same laboratory investigated the DA and 5-HT releasing activity of 28 cathinone analogues, including 3- and 4-CMC (Blough et al., 2019), and data for 3-CMC and for some structurally relevant substances are presented in Table 3. Also shown are results of other studies that involved 3-CMC and close analogues (Shalabi et al., 2017; Walther et al., 2019).

In addition to the observation of competitive inhibition at monoaminergic transporters, both 3-CMC and 4-CMC induce transporter-mediated release via all three monoamine transporters either in an approach utilising rat brain synaptosomes (Blough et al., 2014; Walther et al., 2019) or the human isoforms expressed in HEK293 cells (Eshleman et al., 2017) in a concentration-dependent manner. 3-CMC has initially been introduced as a SERT-releaser by Blough et al. (Blough et al., 2014) at an EC₅₀ value of 1328 nM. Stereoselective effects by the two enantiomers of 3-CMC

resulted in lower values, (-)-3-CMC at 562 ± 152 nM and (+)-3-CMC at 733 ± 163 nM (Blough et al., 2014). In an additional study utilizing the same technique, Blough et al. (2019) reported in vitro release EC₅₀ of 46.8 ± 4.0 nM for DAT and 410 ± 38 nM for SERT in case of 3-CMC and an EC₅₀ of 74.7 ± 15 nM for DAT and 71.1 ± 12 nM for 4-CMC. Using the same experimental approach, Walther et al. (Walther et al., 2019) examined the interaction of 3-CMC with DAT, NET and SERT in comparison to 4-CMC in vitro in a rat brain synaptosomes approach (Walther et al., 2019; Table 3). The EC₅₀ values obtained show a concentration-dependent effect of 3-CMC at DAT, NET and

TABLE 3
DAT-, SERT- and NET-mediated monoamine release activity of cathinone analogues ^a

Drug	DA release EC ₅₀ , nM	5-HT release EC ₅₀ , nM	NE release EC ₅₀ , nM (% at 10 μ M)	DA selectivity ^b
3-CMC	46.8 ± 4.0 ^c 26 ± 4 ^e 29 ± 3 ^f	410 ± 38 ^c 211 ± 33 ^e 212 ± 32 ^f	(94 %) ^c ; 54.4 ± 4.8 ^d 19 ± 3 ^e 40 ± 9 ^f	8.8 8.1 7.3
2-CMC	179 ± 22 ^e	2815 ± 620 ^e	93 ± 6 ^e	16
4-CMC	74.7 ± 15 ^c 42.2 ± 5.2 ^f	71.1 ± 12 ^c 144 ± 22 ^f	(102 %) ^c 44 ± 9 ^e	0.96 3.4
3-FMC	64.8 ± 8.6 ^c	1460 ± 640 ^c	(100 %) ^c	22
3-BMC	28.0 ± 4.1 ^c 21 ± 3 ^e	137 ± 75 ^c 136 ± 24 ^e	(112 %) ^c 25 ± 4 ^e	4.9 6.5
3-MMC	70.6 ± 22 ^c 28 ± 6 ^d	292 ± 39 ^c 268 ± 25 ^d	(94 %) ^c 27 ± 4 ^e	4.2 9.6
4-MMC	49.1 ± 8.3 ^g	118 ± 26 ^g	63 ± 16 ^e	2.4
Methcathinone	49.9 ± 3.1 ^c 12.5 ± 1.1 ^g	4270 ± 270 ^c 3860 ± 520 ^g	(100 %) ^c ; 22.4 ± 2.3 ^d 22 ± 4 ^e	85 309
Cathinone	83.1 ± 6.8 ^c 18 ± 4 ^{f,f}	6100 ± 750 ^c 4741 ± 1035 ^{f,h}	(100 %) ^c 28 ± 5 ^{f,h}	73 263
3-Chlorocathinone	64 ± 10 ^f	567 ± 75 ^f	105 ± 20 ^f	8.9

Note: All compounds are racemic unless otherwise noted. ^a Experiments were carried out with male rat brain synaptosome preparations using appropriate radiolabelled ligands. EC₅₀ values are mean \pm standard deviation; ^b Ratio of 5-HT-EC₅₀/DA-EC₅₀ values; ^c Blough et al., 2019; ^d Kohut et al., 2013; ^e Walther et al., 2019; ^f Shalabi et al., 2017; ^g Bonano et al., 2015; ^h Natural (-)-(*S*)-isomer.

SERT with EC₅₀-values of 26 ±4 nM, 19 ±3 nM and 211 ±33 nM, respectively (Walther et al., 2019) and for 4-CMC with EC₅₀-values of 42.2 nM, 44 ±9 nM and 144 nM, respectively (Walther et al., 2019), the DAT/SERT ratios are 8 and 3.4 for 3- and 4-CMC, respectively. In the same study, Walther and colleagues also examined 3- and 4-MMC with very similar results, also in absolute numbers and rank order of potencies. Also, for the methylated pair of methcathinone, the DAT/SERT ratios are 10 and 2.4 for 3- and 4-MMC, respectively (Walther et al., 2019).

It may be mentioned that bupropion was found to be inactive as a releaser of DA, 5-HT or NE but, as discussed above, inhibited the uptake of these neurotransmitter with respective DAT, SERT and NET IC₅₀ values of 305, >10,000 and 3715 nM (Shalabi et al., 2017).

It must finally be mentioned that the overall psychoactivity of any substance depends not only on pharmacodynamics but also on pharmacokinetics: the metabolic rate and the pharmacological properties of the metabolites as well as the route of administration may greatly influence the overall (psycho)pharmacotoxicological profile of the drug.

Eshleman et al. described the concentration-dependent effect of 4-CMC in HEK293 cells stably expressing the human DAT, NET and SERT with EC₅₀ values of 2890 ±990 nM, 1240 ±440 nM and 1980 ±420 nM, respectively (Eshleman et al., 2017). In this study, the DAT/SERT ratio is 0.42, and the release potency rank order in this study NET > SERT > DAT. In contrast, for 4-CMC the rank orders obtained in studies with rat brain synaptosomes were either DAT ≅ SERT (DAT/SERT ratio ~1) or DAT > NET > SERT (DAT/SERT ratio 3.4) (see Table 3). This discrepancy may be due to species differences or simple due to experimental variability. However, an important finding of the studies is that 3- and 4-CMC behave as substrates of DAT, NET and SERT and not only as uptake inhibitors. Nevertheless, this example illustrates the inherent difficulties of comparing or interpreting data obtained under different *in vitro* experimental conditions.

4.2.1.3 Receptor binding studies

No experiments on neurotransmitter receptor binding affinities have been reported for 3-CMC so far.

4.2.2 In vivo data

There is limited information on the activity of 3-CMC and also of 4-CMC in animals, and no study examined the effect of 3-CMC in humans.

The effects of 3-CMC and 4-CMC on the spontaneous locomotor activity and motor performance of adult male mice has recently been investigated (Wojcieszak et al., 2020) The two compounds were administered subcutaneously at 5, 10 and 20 mg/kg doses. Both drugs stimulated horizontal locomotor activity of mice in a dose-dependent manner. No elevation of vertical locomotor activity (rearing behaviour) could be detected nor did the compounds affect the motoric functions on the accelerating rotarod, pointing to the lack of impairment of motor coordination in mice after acute drug exposure. In a follow-up study employing 4-CMC only, Wojcieszak et al. (2021) examined its behavioural effects related to psychostimulant properties, abuse and dependence potential in DBA/2J mice. Similar to the earlier study, 4-CMC increased spontaneous locomotor activity after acute treatment. Furthermore, 4-CMC produced behavioural sensitisation after 7-day intermittent

treatment, a common feature of other drugs of abuse. Interestingly, 4-CMC did not induce conditioned place preference after 4 days, normally an indication for rewarding properties of drugs of abuse. Finally, the ability of 4-CMC to induce withdrawal symptoms after discontinuation from 14-day treatment was assessed using a battery of tests for behavioural markers of depression in mice: a tail suspension test, a forced swim test, measuring despair, and a sucrose preference test, measuring anhedonia. None of the three tests revealed increased depressive symptoms. Moreover, neither spontaneous locomotor activity nor motor performance on a rotarod was impaired after 14-day treatment with 4-CMC, as shown earlier. These results indicate that 14-day treatment of mice with 4-CMC does not induce significant withdrawal symptoms after cessation, nor significant impairment of dopaminergic circuitry resulting in motor impairment. The authors concluded that 4-CMC did not produce abuse-related behavioural changes in mice in a very pronounced manner (Wojcieszak et al., 2021). 4-CMC was also examined in assays of intracranial self-stimulation (ICSS) that are usually the gold standard behavioural procedure to study abuse potential of monoamine releasers and other classes of drugs (Bonano et al., 2015). The data point to a slightly lower abuse potential of 4-CMC compared to methcathinone and other related compounds with a smaller steric bulk in the *para*-position which are more DAT-selective and less SERT-selective (Bonano et al., 2015). Whether the results of these latter observations with 4-CMC extend to 3-CMC remains to be studied.

Since methcathinone and 3-CMC display equal potency for the induction of dopamine release but 3-CMC has a 10-fold higher potency for serotonin release (Table 3), Kohut and colleagues studied these drugs in drug discrimination studies (Kohut et al., 2013). Monkeys were trained to discriminate cocaine from saline then methcathinone or 3-CMC (PAL-434) was intravenously administered chronically for 7–10 days. 3-CMC was about 4-fold and methcathinone about 1.6-fold more potent at decreasing cocaine- over food-maintained responding. Hourly injections of 3-CMC at 0.56 or 1.0 mg/kg intravenous doses produced sustained and selective decreases of cocaine self-administration with fewer side effects than methcathinone. It was concluded that compounds with moderate (8–15-fold) selectivity for dopamine vs. serotonin release might be effective for the treatment of cocaine dependence.

In an *in vivo* microdialysis study in the awake rat, Suyama and colleagues determined that 4-CMC produced dose- and time-dependent increases in nucleus accumbens dopamine and serotonin levels (Suyama et al., 2016), which reflects the dopaminergic effect of this compound *in vitro* (see Tables 2 and 3 above). In the related 4-MMC, release of dopamine and serotonin was measured similarly by *in vivo* microdialysis in the awake rat, resulting in an increase in locomotor activity (Kehr et al., 2011).

4.3 Psychological and behavioural effects

To date, no published formal studies assessing the psychological and/or behavioural effects of 3-CMC are available in humans. In case of 4-CMC, depending on the route of administration and the user's tolerance, the dose of 4-CMC resulting in the desired effects is thought to range from 100 to 300 mg for oral ingestion and 50 to 150 mg for snorting (Tomczak et al., 2018). One study reports the 4-CMC effects described in online forums, such as Bluelight or Erowid (Griffell et al., 2017).

Interestingly, there was quite substantial description of the dose-dependent effects of 4-CMC: At a dose up to 20 mg 4-CMC, users describe no clear effects, called “under threshold” dose; at a dose of 50 mg 4-CMC, comparable to 75-90 mg of MDMA, experimenting euphoria, increased energy, sociability and sexuality, visual and auditory hallucinations, and strong empathogenic feelings; one user ingested 1 gram over a 24 h period, in combination with MDPPP⁽³³⁾ and MDPHP⁽³⁴⁾ and reported intense tremor, bruxism, and nearly blacking out. It was described as a stimulating empathogen and weaker than 3-MMC. The recommended dose for “an experienced ketone user” was 150 mg; another user reported the dose for a first-time user as 100 to 200 mg orally and 50 to 100 mg nasally, but warned about painful sensation upon insufflation; upon insufflation of 80 mg, another user reports light-headedness, dizziness, and feelings of warmth. Injection of 80 and 250 mg 20 min later: User describes increase in body heat, nystagmus, euphoria, and extreme feelings of ecstasy for about 30 min, and then a gradual decrease of effects (Grifell et al., 2017).

Many ring-substituted synthetic cathinones have been reported to exert similar effects comparable to other amphetamine-type stimulant drugs (Karinen et al., 2014). In user forums, it has been described that adverse events after using 4-CMC can occur: extreme pain when snorted which suggests that this might function as a limiting factor when using this route of administration. Most users describe headaches the following day. Users also reported anxiety, apathy, jaw tension and involuntary eye movements. One user reported consuming one gram of 4-CMC intravenously. By mistake and surviving, he reportedly required assistance in an emergency department and received beta blockers for treatment. He also reported an intense MDMA-like hangover lasting at least 1 week (Grifell et al., 2017).

4.4 Safety pharmacology

Apart from observations during a drug discrimination study discussed in Section 4.2.2 (Kohut et al., 2013), there have no studies been published on safety pharmacology of 3-CMC.

4.5 Pharmacokinetics

Detailed data on the metabolic transformation of 3-CMC in humans are not available to date. However, a recent analysis of the surface water of Lake Balaton, Hungary, using solid-phase extraction followed by SFC-MS/MS method reported the detection of ‘3-chloroephedrine’ (3-chloroephedrine)⁽³⁵⁾ at 0.2 ng/L concentration on a sample taken in April 2018 (Maasz et al., 2019). This unique halogenated amino alcohol may be considered a reductive metabolite of 3-CMC indicating (human) consumption of the cathinone. Similar ephedrine-like human metabolites were detected forensic urine samples formed from fluoromethcathinones (Ularets et al., 2014), and in pubic hair samples (Frison et al., 2016).

⁽³³⁾ 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)propan-1-one

⁽³⁴⁾ 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)hexan-1-one

⁽³⁵⁾ 1-(3-Chlorophenyl)-2-(methylamino)propan-1-ol

4.5.1 Pharmacokinetic parameters of 3-CMC in comparison to 4-CMC

To date, no detailed studies on pharmacokinetics of 3-CMC and 4-CMC have been performed. In self-reports, users reported that the effects of 4-CMC can be felt more rapidly after nasal insufflation (already within 2 to 3 min) than after peroral administration (onset of effects takes between 30–60 min), but the duration of the effect is longer with peroral administration (Grifell et al., 2016).

4.6 Toxicology

The cytotoxicity of 3-CMC and 4-CMC was evaluated by assessing viability, as measured by mitochondrial activity, and membrane integrity of human neuroblastoma SH-SY5Y cell line upon drug exposure *in vitro* (Wojcieszak et al., 2020). Incubation of SH-SY5Y cells with 3-CMC in concentrations range of 50–300 μM for 24 hours did not affect cell viability; upon 72-hour exposure, however, cell viability declined: maximal 51% cell death was observed for the 300 μM concentration. After 48 h, 3-CMC dose-dependently affected membrane integrity, as reflected by the activity of lactate dehydrogenase (LDH) released from damaged cells: at the 300 μM concentration 3-CMC increased LDH-activity by 21% relative to untreated control. The effect of 4-CMC on neuroblastoma cell viability and membrane integrity was similar to that of 3-CMC upon 24-hour exposure. However, after prolonged incubation, 3-CMC was more potent in disrupting cell membranes than 4-CMC. This difference in cytotoxicity might be due to 4-CMC being less stable than 3-CMC under the assay conditions. Whether this concentration is relevant to real-life conditions involving ingestion of 3-CMC is difficult to estimate. It is of note that in 4-CMC-related fatalities, 4-CMC concentrations in blood were in the 0.28–9 μM range (Tomczak et al., 2018).

No systematic clinical studies have been conducted to examine the adverse events of 3-CMC *in vivo*. During a drug discrimination study and cocaine-self-administration in rhesus monkeys, which was discussed in Section 4.2.2, the most prominent side effects noted during chronic intravenous 3-CMC treatment were facial flushing and reduced food intake (Kohut et al., 2013)

Some published (and partially anecdotal) evidence for 4-CMC and/or related cathinones is presented below.

Luethi and co-workers (Luethi et al., 2019) examined 4-CMC and other *para*-halogenated methcathinone derivatives for some toxicological features: They report that all substances depleted the cellular ATP content at lower concentrations (0.25–2 mM) than cell membrane integrity loss occurred (≥ 0.5 mM), suggesting mitochondrial toxicity which was confirmed for 4-CMC, since it additionally impaired the mitochondrial respiratory chain. The toxicity rank order for the *para*-substituents was the following: chlorine > fluorine > hydrogen. It was concluded that *para*-halogenation of methcathinones may increase the risk for serotonergic neurotoxicity and hepatic toxicity mediated by mitochondrial impairment in susceptible users. Whether this applies to cathinones with halogens at the *meta*-position is not known.

In addition, there have been observations on the methylated analogues related to the chlorinated cathinones in that 3- and 4-MMC-related toxicity occurs with an impact on specific organ systems: neurotoxicity, hyperthermia and significant effects on the cardiovascular system (Davidson et al.,

2001; Levi et al., 2012; Docherty et al., 2021). However, in the studies dealing with the effects of 3- and 4-CMC, there are only possible neurotoxic and hepatotoxic effects described so far.

From the Netherlands, two cases of excited delirium lasting for over 24 h was recently described (van Wonderen et al., 2020). The patients had used 'chloromethcathinone' which was identified by GC-MS and HPLC-UV methods in their urine as well as in the powder samples they provided; caffeine was also detected in the powders. Myoclonus, elevated heart rate (>110 beats per minute), and urine retention were common symptoms for both cases. One of the patients required supplemental oxygen therapy due to respiratory depression. Initial treatment included midazolam, followed, if needed, by intravenous benzodiazepines (actual medicine not specified) for the treatment of psychosis. However, as the authors pointed out, analytical methods used had not been able to make a distinction between 4-CMC and 3-CMC; nevertheless, it was suggested that since the treatment aim for both CMC variants was symptom control, this had no clinical implications.

Between January 2016 and July 2019, 61 poisonings involving synthetic cathinones were reported to the Dutch Poisons Information Centre. 3-CMC was one of the substances recorded though more detailed information specifically about this substance could not be identified based on the published information. The most common routes of administration were (oral) ingestion (36%), snorting (23%), and injection (21%). In 38% of cases followed up, multiple doses were used in one session (Nugteren-van Lonkhuyzen et al., 2021).

Risk-modifying factors

A major risk-modifying factor in terms of toxic effects on various organ systems is represented by drug-drug interactions. Other concomitantly applied drugs may also exert pharmacokinetically relevant effects, in terms of interactions at metabolically relevant enzymes or at efflux transporters that guard the blood-brain barrier from xenobiotics. In addition, the circumstances under which the drugs are used may also be accounted for as risk-modifying factors.

Uncertainty analysis

To date, there are no data available that detail the stability of 3-CMC. However, the positional isomer 4-CMC has been shown to be particularly unstable, especially if the biological material is stored under improper conditions (Adamowicz and Malczyk, 2019; Nowak et al., 2019; 2020). Further studies are needed to assess this for 3-CMC.

4.7 Abuse liability and dependence producing potential

Many synthetic cathinones have been associated with abuse liability (Baumann et al., 2018). However, limited information is available on 3- and 4-CMC as outlined above (section on "Pharmacological and toxicological properties").

4.7.1 *In vitro* data

The *in vitro* data on 3-CMC obtained in cultured cell lines expressing DAT, NET and SERT all point to the fact that it readily interacts with these transporters to inhibit the reuptake of their cognate substrates. Furthermore, 3-CMC acts as a typical stimulant in terms of inducing release of the neurotransmitters dopamine, norepinephrine and serotonin via DAT, NET and SERT in a way similar to 4-CMC though differences in the extent and selectivity of the activities have been noted between the results reported by different laboratories (Luethi et al., 2019; Eshleman et al., 2017). In addition, experiments performed in rat brain synaptosomes came to the same conclusion in an *ex vivo* paradigm, thus substantiating the findings over different animal species (Blough et al., 2014; Blough et al., 2019; Walther et al., 2019). Yet, experiments with cells expressing human monoamine transporters revealed a somewhat different picture (see Section 4.2.1).

Mechanistically, the pharmacodynamic data reported above suggest that 3-CMC behaves as an amphetamine-type stimulant but the currently available information obtained from these investigations makes the estimation in relation to dependence potential more challenging.

4.7.2 *Animal data*

Behavioural assessments have predominantly been reported for 4-CMC whereas less information appears to be available for 3-CMC. Suyama et al. (2016) reported their findings from an *in vivo* microdialysis study in the conscious rat that showed that the response to 4-CMC administration was delayed for dopamine release whereas the extracellular increase of serotonin rapidly initiated. Another study examined the effect of employing 3- and 4-CMC on spontaneous locomotor activity and motor performance of mice (Wojcieszak et al., 2020).

In studies in mice employing 4-CMC, the behavioural effects related to psychostimulant properties, abuse potential, and dependence were examined (Gatch et al., 2019; Gatch et al., 2021; see also Wojcieszak et al., 2021). The locomotor stimulant effects of 4-CMC displayed a time course resembling the administration of MDMA in this assay, with a slow onset and long-lasting effects. 4-CMC, however, did not produce the initial depressant effects on locomotion produced by low-dose MDMA (Gatch et al., 2019). In drug discrimination assays, 4-CMC was able to substitute for cocaine, metamphetamine and MDMA though, and 4-CMC mimicked MDMA-like discriminative stimulus effects more than it did for cocaine- or methamphetamine-like discriminative stimulus effects since it was 10-times more potent at producing MDMA-like discriminative stimulus effects (Gatch et al., 2019). This observation resembles the results obtained in the locomotor studies where 4-CMC induced locomotor stimulant effects more similar to MDMA than to cocaine or methamphetamine (Gatch et al., 2019).

4-CMC was also examined in the study by Bonano et al. (2015) in an approach employing intracranial self-stimulation (ICSS; see Section 4.2.2) which suggested that a low DAT/SERT ratio correlated with mixed effects on ICSS consisting of both facilitation of low ICSS rates and depression of high ICSS rates. This differed from cathinones with a high DAT-to-SERT selectivity that resulted in exclusive facilitation of ICSS. Information related to the 3-CMC isomer however is currently not available.

3-CMC, along with methcathinone, was studied in a drug discrimination paradigm with rhesus monkeys trained to discriminate cocaine from saline (Kohut et al., 2013). Upon chronic intravenous administration 3-CMC was about 4-fold and methcathinone about 1.6-fold more potent at decreasing cocaine- over food-maintained responding (for experimental conditions, see Section 4.2.2). It was concluded that compounds with moderate selectivity for dopamine vs. serotonin release may be effective for the treatment of cocaine dependence.

4.7.3 Human data

To date, there are no relevant studies examining the abuse potential of 3-CMC or 4-CMC in humans.

Risk-modifying factors

As with other synthetic cathinones, including 3-MMC described to be frequently combined with other drugs intentionally to enhance the recreational experience (Ameline et al., 2019). It can be expected that this is also the case for 3-CMC.

Socioeconomic conditions, for example poor living circumstances or unemployment, may increase the likelihood of abuse liability for 3-CMC. In case of young people, groups that are particularly vulnerable include young offenders, young people in institutional care, early school leavers and students with social or academic problems, and young people who live in disadvantaged families or neighbourhoods where multiple risk factors and problems associated with drug use are concentrated. On the other hand, favourable relationships with family and family support are likely to decrease the likelihood of abuse liability.

Other factors such as easy availability, low price, social acceptability, peer pressure, and legal status may increase the likelihood of abuse liability for 3-CMC and other recreational substances.

Finally, it is possible that to some extent the ongoing COVID-19 pandemic could lead to localised or more broader changes in use and patterns of use of drugs, including 3-CMC. Boredom, anxiety, reduced availability of other controlled stimulants could increase the likelihood of 3-CMC use.

Uncertainty analysis

Like the above described risk-modifying factors, uncertainty related to the use of 3-CMC can be ascribed to be combination with other drugs; here, users describe and exchange on positive, neutral or negative experiences with different drugs combined with 3-CMC on various internet drug forums (e.g., bluelight.org; erowid.org; reddit.com).

Also, the effects seen in experiment *in vitro* and in animals have to be viewed with caution as animal experiments cannot always simply be extrapolated to humans.

5. Extent and patterns of use, availability, and potential for diffusion

5.1 Summary

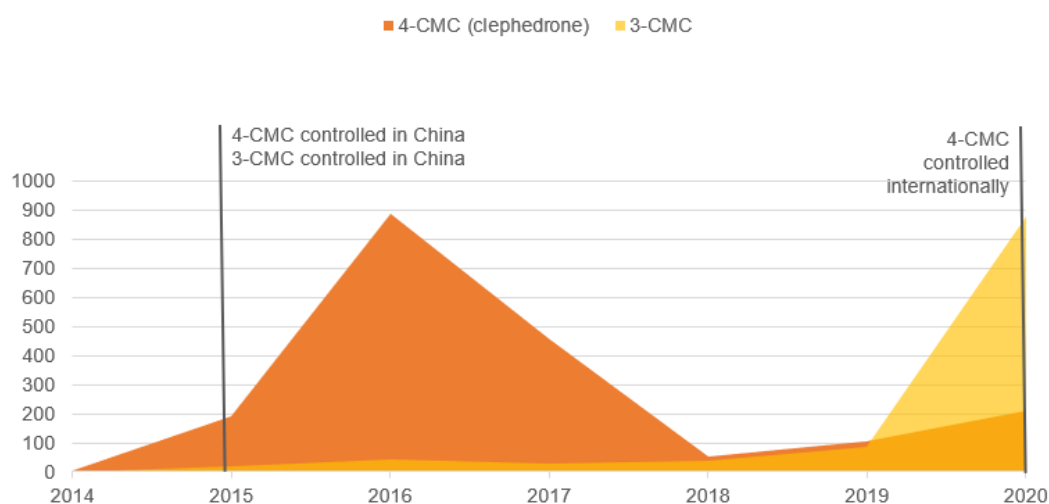
There is limited information on the extent and patterns of use of 3-CMC in Europe. The available evidence suggests that the substance is available in the majority of Member States and that its availability may have increased recently, at least in some Member States.

3-CMC has been present on the European drugs market since at least September 2014. As of October 2021, the substance has been detected in 23 Member States and Norway. These detections relate to 9 607 seizures (amounting to 2.73 tonnes of seized material in all physical forms), 67 collected samples and 213 biological samples. Most reports related to the first identification of 3-CMC in a country occurred around the date of its first identification in Europe between 2014 and 2016 (n=16; 67%).

The appearance of 3-CMC in Europe occurred at around the same time as 4-CMC, but until 2020, the detection of 3-CMC in law enforcement seizures remained relatively low in comparison to 4-CMC. The latter was subject to international controls in 2020 ⁽³⁶⁾. At least in part, it appears that 3-CMC may be used as a ‘legal’ replacement to 4-CMC (Figure 2).

FIGURE 2

Quantity of powders (kg) containing 4-CMC (clephedrone) and 3-CMC seized in Europe 2014–2020



⁽³⁶⁾ Decision 63/9; Inclusion of 4-CMC (4-chloromethcathinone, clephedrone) in Schedule II of the Convention on Psychotropic Substances of 1971

Since it first emerged on the market, approximately 2.72 tonnes of 3-CMC powders have been seized, including at least 2.26 tonnes by customs and 322 kg by police. Importantly, around 2.5 tonnes of 3-CMC powders (92% of all powders seized) were reported in 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.

In part, seizures of 3-CMC, alongside seizures of 3-MMC (also currently the subject of a risk assessment) and *N*-ethylhexedrone (internationally controlled ⁽³⁷⁾) have driven a sharp increase in the quantity of cathinone powders seized in Europe in 2020. Following a peak in 2015 and 2016, when around 1 800 kg of cathinone powders were seized per year, reports steadily decreased, reaching 750 kg by 2019. In 2020, seizures of approximately 3 300 kg of cathinone powders were reported in Europe, over a quarter of which contained 3-CMC. 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 originating from India, including those relating to seizures of 3-CMC (and 3-MMC which is subject to a separate EMCDDA risk assessment at this time). Additionally, as shown in Section 2.4, part of the cathinone powders available in Europe are produced within the European Union.

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 nasal 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, and/or 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).

The effect of the ongoing COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020b; WHO, 2020) on the manufacture, trafficking, distribution and use of 3-CMC is currently unknown. However, seizures of more than of 2170 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.

5.2 Information from seizures

Between 1 January 2014 and 30 September 2021, a total of 9 607 seizures, amounting to 2.73 tonnes of material (in all physical forms) were reported by 23 countries. Of these, 222 kg were reported in the period of 2014 to 2019, and 877 kg were reported in 2020. The remaining 1.63 tonnes were reported in 2021 (60% of all material seized) since monitoring began.

⁽³⁷⁾ *N*-Ethylhexedrone was internationally controlled in 2020. Decision 63/10; Inclusion of *N*-ethylhexedrone in Schedule II of the Convention on Psychotropic Substances of 1971

The large majority of the cases reported (n= 9 375; 98%) were seizures of powders, amounting to 2.72 tonnes. To a much lesser extent, seizures of other forms were also reported: tablets and capsules (196 cases), other or unknown physical forms (21), herbal material (7), liquids (7) and blotters (1). For this reason, the following analysis is focused on seizures of powders.

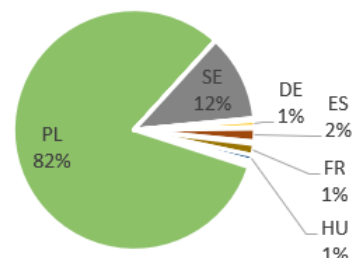
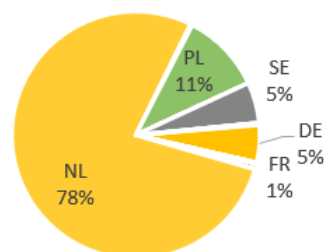
The number of seizures of powders and the quantity of powders seized reported to the EMCDDA are shown in Table 4. These values include seizures reported in the period of 1 January 2014 to 30 September 2021. The majority of cases were reported by Poland (7 663 cases; 82%). The country reporting the largest quantities of seized powders was the Netherlands (2.12 tonnes; 78% of all powders seized).

A total of 9 375 seizures of powders were reported by police (6 702 cases; 71%), customs (639; 7%) and other authorities (2 034; 22%). A summary of the information reported is provided.

TABLE 4

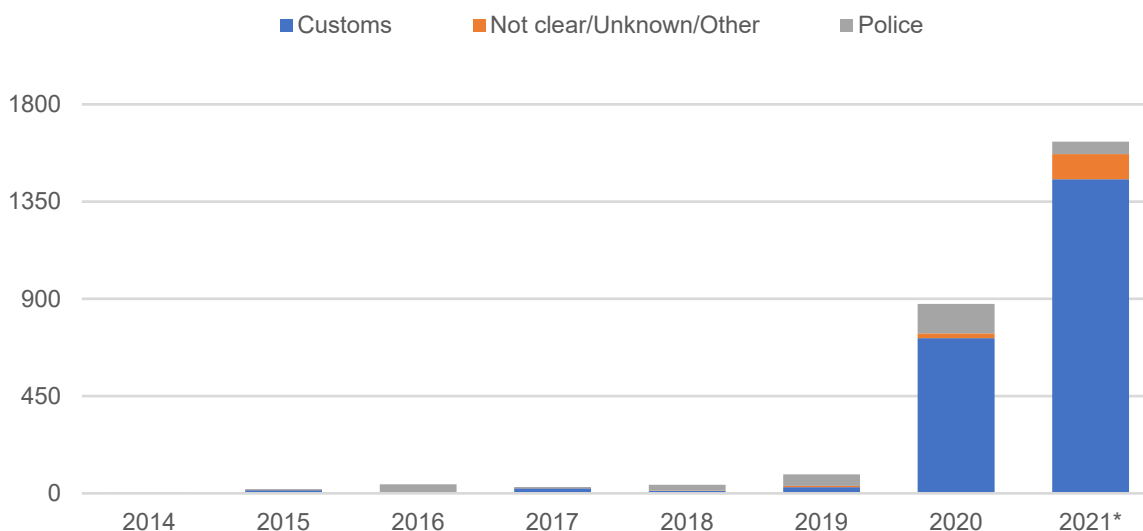
Number of seizures of powders containing 3-CMC and quantity seized (in kg), by country

Country	Number of seizures (powders)	Quantity powders (kg)
Poland	7663	287.3
Sweden	1091	144.8
Spain	162	5.5
France	140	17.5
Germany	78	133.4
Hungary	74	0.4
Netherlands	43	2119.8
Finland	30	0.0
Norway	21	7.1
Estonia	13	0.0
Belgium	11	1.1
Slovakia	10	5.3
Lithuania	6	0.0
Slovenia	7	0.1
Czechia	6	0.9
Ireland	4	0.5
Portugal	4	0.0
Denmark	3	0.0
Italy	3	0.0
Greece	2	0.0
Romania	2	0.0
Bulgaria	1	0.0
Malta	1	0.1
Total	9375	2723.9

Seizures of powders (n)
2014 - 2021Quantity of powders seized (kg)
2014 - 2021

Note: The values include all seizures reported to the EMCDDA between 1 January 2014 and 30 September 2021. Quantities are expressed in kilograms and, in some cases, for quantities below 100 grams, they appear as '0' due to rounding conventions. Pie charts. Seizures and quantities of powders seized by country in Europe 2014–2021. 2021 Data are not comparable to data from previous years.

FIGURE 3
Quantity of 3-CMC powders seized (kg), by reporting authority



Note: The values include all seizures reported to the EMCDDA between 01 January 2014 and 30 September 2021. *See methodological note for further details.

5.2.1 Customs seizures

Since 2014, customs authorities have reported 639 seizures of 3-CMC amounting to 2.26 tonnes of powders. Of these, 135 seizures (718 kg; 32%) occurred in 2020 and 165 seizures (1.45 tonnes; 64%) occurred in 2021. While most seizures were reported by Sweden (199 cases; 31%), the largest quantities of powders were seized in the Netherlands (2.12 tonnes; 94% of customs seizures).

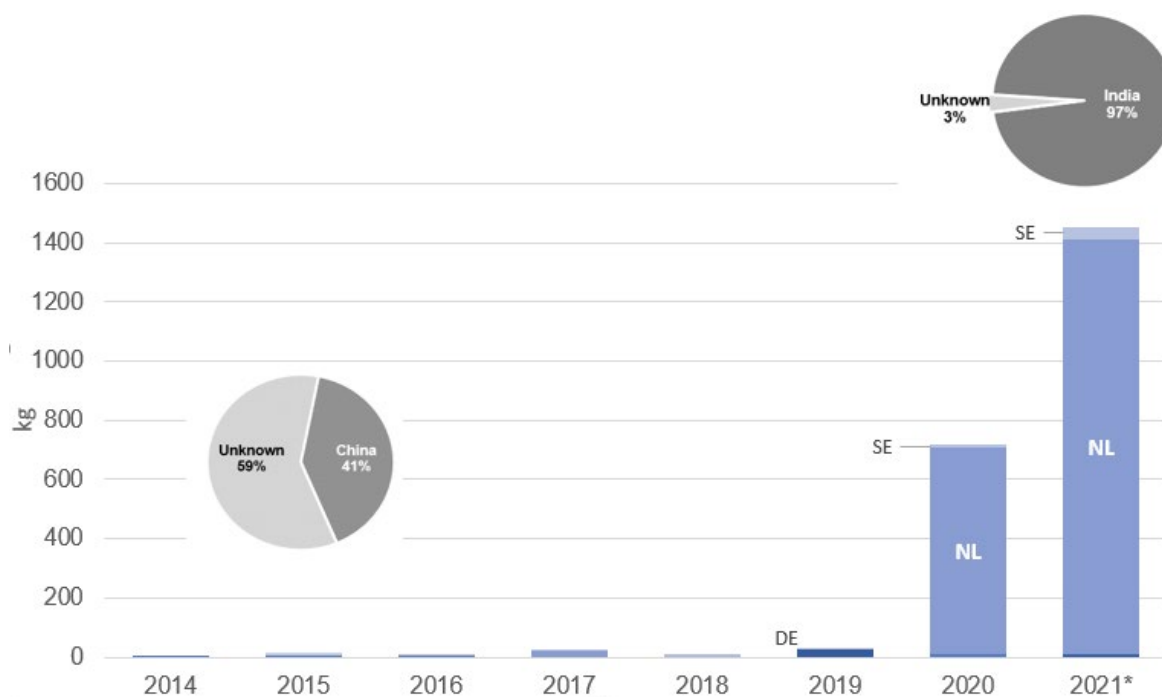
Individual seizures reported by Customs were typically larger in quantity than those reported by police and provide some evidence of attempts to import large amounts of 3-CMC powders to Europe.

For the majority of customs seizures, the origin of the consignment was not reported (626 cases; 1.55 tonnes). For the 13 cases where the origin of the consignment is known, the powders originated in China (2 seizures, 6 kg; all of which in 2015), India (6 seizures pure powder amounting to 695 kg; all of which made by Dutch customs in 2020), and Europe (n=5). Additional information submitted after the data collection period indicated that 5 seizures totalling 1.4 tonnes of powder by Dutch Customs in 2021 also originated in India.

Whenever European countries were mentioned as the country of origin, the consignments were typically small (less than 5 g). Belgium and the Netherlands were the only countries of origin mentioned in those cases.

The largest single seizure was reported by Dutch customs and occurred in 2021. The seizure comprised of 400 kg of 3-CMC powders, also containing iso-3-CMC ⁽³⁸⁾, which may be an impurity from synthesis. The powders were imported from India.

FIGURE 4
Quantity of 3-CMC powders seized (kg), by customs



Note: The values include all seizures reported to the EMCDDA between 1 January 2014 and 30 September 2021. The country reporting the seizure is indicated in the bars; the origin of the consignment by % weight (pie charts). *See methodological note for further details.

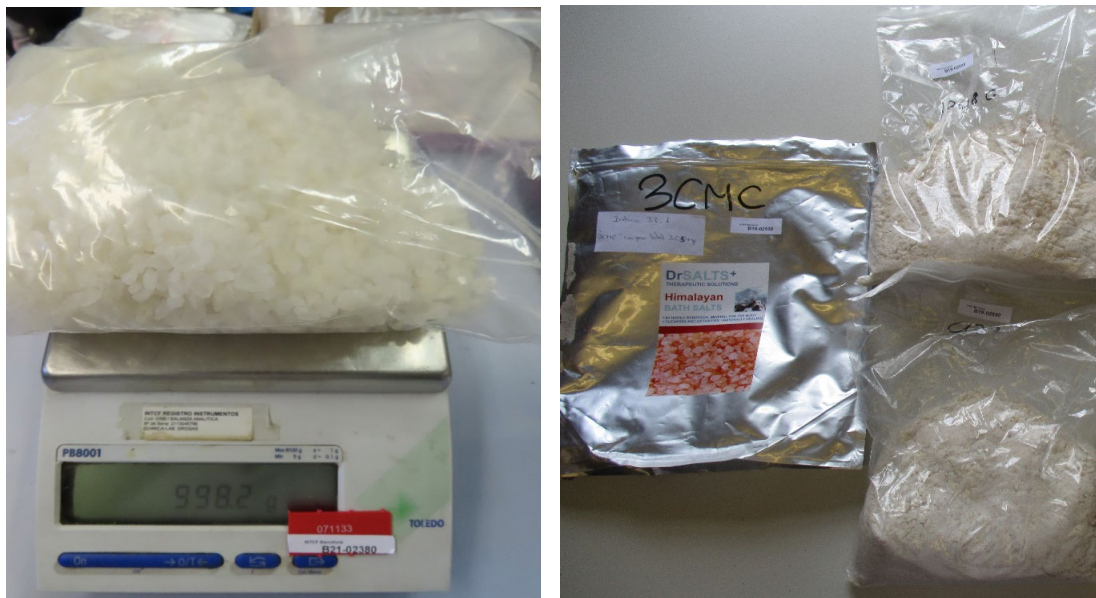
The purity of 3-CMC detected was rarely reported. In the seizures that originated in India during 2020, 3-CMC consisted of pure white powders. In other cases, the powders were sometimes reported as 'crystals' or 'rocks' (Figure 5). When reported, labels referred to '3-CMC' or 'Clophedrone'.

For the small number of cases where other substances were reported, the powders typically contained other stimulants such as other cathinones (including 3-MMC) and/or amphetamine (in 8 cases). One noteworthy case was the large-scale seizure of 400 kg, mentioned above, where iso-3-CMC was detected in 3-CMC powders. Adulterants and diluents reported included caffeine, benzocaine, menthol, and mannitol.

⁽³⁸⁾ At the time of drafting the initial report for 3-CMC, iso-3-CMC was not monitored as an NPS by the EMCDDA. Iso-3-CMC is monitored as an NPS since 25 October 2021, following the analytical confirmation of the substance in 252 grams of beige powder seized by Swedish Customs on 14 June 2021. 3-CMC was also identified in the seized powder.

FIGURE 5

Seizure made by Customs at the International Mail Centre in Barcelona, Spain, in March 2021 (left). Origin not reported. 3-CMC was identified in 998.2 g of white powder rock (pictured); Seizure of approximately 3 kg of 3-CMC powders within a large-scale seizure of 25 NPS (total weight 57 kg), by the Spanish National Police in April 2019 in Barcelona, Spain (right).

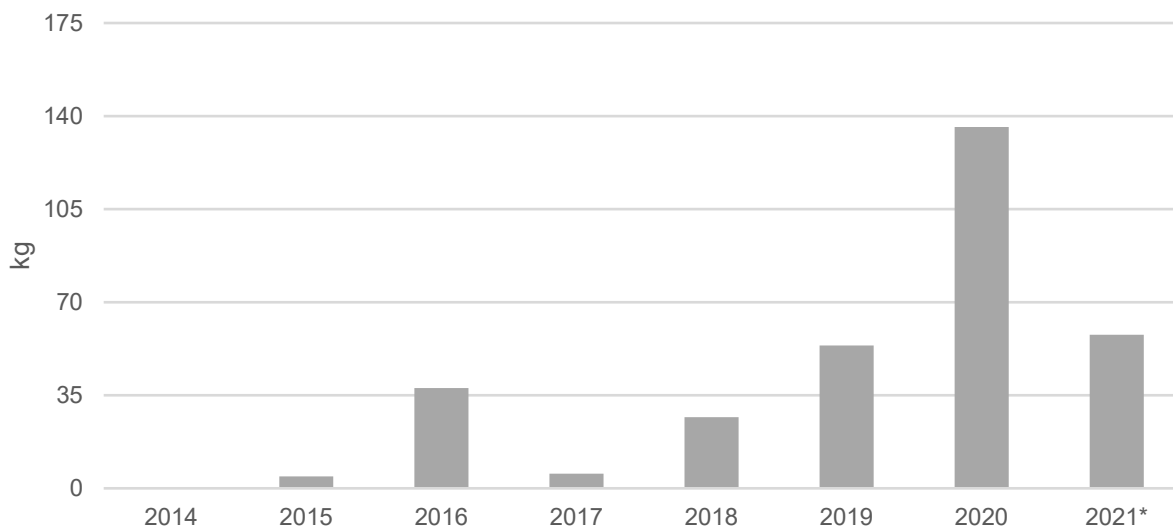


Note: Pictures courtesy of the of the National Institute of Toxicology and Forensic Sciences, Barcelona and Spanish national focal point.

5.2.2 Police seizures

Since 2014, police authorities have reported 6 702 seizures of powders containing 3-CMC, amounting to 322 kg (Figure 6). Poland reported 94% of all Police seizures (6 329 cases) and half of the quantity of powders seized by police (160 kg). German Police reported 28 seizures (102 kg). Swedish police reported 267 seizures (57 kg powders) all of which occurred in 2021. The remaining countries reported considerably smaller amounts.

FIGURE 6
Quantity of 3-CMC powders seized (kg) by police



Note: The values include all seizures reported to the EMCDDA between 1 January 2012 and 30 September 2021. *See methodological note for further details.

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

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

Other substances detected in police seizures (not quantified) included other cathinones (including 4-CMC, 191 cases) and, to a lesser extent, controlled 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.

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

5.3.3 Other seizures

In 2 034 cases, the reporting authority was not reported or unknown. These cases amounted to 147 kg of powders. Of these, 116 kg (79%) 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.

5.4 Information from collected samples

Between 01 January 2015 and 27 January 2021, a total of 67 collected samples were reported to the EMCDDA by 7 Member States: Poland (55), Austria (6), France (2), Czechia (1), Portugal (1), Slovenia (1), and Spain (1). One sample was collected in 2015, 1 in 2016, 4 in 2017, 6 in 2018, 50 in 2019, 4 in 2020, and 1 in 2021. Of these, most samples (66) 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 (75%). In 17 cases, it was detected in combination with other substances, particularly cathinones (16 cases), namely 4-CMC (4 cases in 2019 and 2 in 2020); 4-CMC and 4-CEC (4 cases in 2019); 4-CMC, 4-FPD⁽³⁹⁾ and 4-CEC (2 cases in 2019), 4-CEC (1 case in 2018), methcathinone (1 case in 2018), *N*-methyl-*N,N*-dimethylcathinone (1 case in 2017), and 3-MMC (1 case in 2019). In the latter, the sample was reported to contain 38.7% of the hydrochloride salt of 3-CMC. In addition, in one case in 2020 3-CMC was detected in combination with caffeine.

3-CMC was sold as other cathinones in 3 cases – as 3-MMC in 1 case in 2021, and as 4-MMC in 2 cases in 2020, 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, in 2015, 2016 and 2021).

In addition to information from collected samples reported by the Member States, the following information was identified from Austria, Spain and Switzerland. It is possible that some of these samples have been reported to the EMCDDA and thus overlap might exist with the information presented above on collected samples reported to the EMCDDA.

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).

Spain

In Spain, a sample bought as 3-CMC which contained 4-CMC was reported (Grifell et al. 2017).

Switzerland

In Switzerland, the first sample of 3-CMC reported by the drug checking service SaferParty was in May 2019. A total of 8 samples containing 3-CMC have been reported by SaferParty with the most

⁽³⁹⁾ 1-(4-fluorophenyl)-2-(methylamino)pentan-1-one

recent one in October 2021. In all cases 3-CMC was sold as another substance: 3-MMC (in 4 cases) ⁽⁴⁰⁾, 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).

5.5 Information from biological samples

Between 1 January 2015 and 8 October 2021, 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 are discussed in Sections 6.2.4.1 and 6.2.5.1. These include: 1 acute poisoning reported by Spain and 10 deaths reported by Poland (7) and Sweden (3).

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 (EMCDDA, 2021):

- 4 samples associated with deaths, reported by Sweden ⁽⁴¹⁾;
- 2 samples associated with non-fatal poisonings, reported by Hungary ⁽⁴²⁾;
- 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).

⁽⁴⁰⁾ In one of these cases, the sample was sold as '5-MMC', which would be equivalent to 3-MMC.

⁽⁴¹⁾ 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 Sections 6.2.1 and 6.2.2.

⁽⁴²⁾ 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 Sections 6.2.1 and 6.2.2.

6. Health risks

6.1 Summary

There is limited information on the acute toxicity of 3-CMC. Based on the available information, the health risks appear to be similar to those observed with other synthetic cathinones under international control. 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 clinical features. Similar to other synthetic 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 toxicity including a sympathomimetic toxidrome.

One acute poisoning with confirmed exposure to 3-CMC has been reported by Spain. It was related to a chemsex ⁽⁴³⁾ context, and other central nervous system stimulants (i.e. 3-MMC, methamphetamine, cocaine), as well as GBL/GHB and sildenafil were detected in the biological sample.

A total of 10 deaths with confirmed exposure to 3-CMC were reported by Poland (7) and Sweden (3). In 4 of these cases, 3-CMC was the only substance detected, while in 2 other the only additional substance found was alcohol. In some of the cases, 3-CMC was reported to be the cause of death or to have contributed to the death.

To date, no instances of acute poisonings, driving under the influence, or death investigations with confirmed exposure to 3-CMC have been reported in the scientific or medical literature.

There is no information on the chronic health effects of 3-CMC in humans, including abuse liability and dependence potential. The chronic health risks might share some similarities to those seen with other synthetic cathinones under international control, which may include dependence.

6.2 Acute health effects

6.2.1 Animal data

No studies were identified that investigated the acute health effects of 3-CMC or 4-CMC in animals.

6.2.2 Human data

No clinical studies were identified that have examined the acute health effects of 3-CMC and/or its metabolites in humans. To date, most information about the biological effects of 3-CMC relates to (scarce) user experiences, epidemiological data, clinical cases, toxicological findings, and animal studies. There is one published study conducted to explore the users' perspectives regarding the

⁽⁴³⁾ Chemsex is a term used to describe an intentional sex under the influence of psychoactive drugs, mostly among men who have sex with men.

effects and toxicity of cathinones, including 4-CMC (Grifell et al., 2017; see above). Another publication describes two cases of prolonged excited delirium syndromes following ingestion of “chloromethcathionone” but the analytical method used was not able to distinguish between the isomeric 3- and 4-CMC (van Wonderen et al., 2020) (see also Section 4.6). Agitation, myoclonus, elevated heart rate of 110 beat per minute, and urine retention was common for both cases; one of the patients developed respiratory depression requiring supplemental oxygen therapy. Treatment of the aggressive behaviour was symptomatic, and involved midazolam, and/or morphine.

6.2.3 Interactions with other drugs

Drug-drug interactions, or investigations pertaining to possible negative effects thereof, have not been reported to date for 3-CMC; however, related to 4-CMC, one study examined co-ingested psychostimulants and/or their metabolites, and described the determination of amphetamine, MDMA, MDA and 3-MMC as well as ecgonine methyl ester and benzoylecgonine, several benzodiazepines, THC, THCCOOH and ethanol (Tomczak et al., 2018).

6.2.4 Acute poisonings

6.2.4.1. Acute poisonings reported by the Member States

Confirmed exposure

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

Suspected exposure

Two Member States, 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). Further details are available for the case of drug dependence reported by France. This case occurred in 2019 and involved a male in his thirties who reported heavy consumption of cathinones, mainly 3-CMC and 4-chloro-*N,N*-dimethylcathinone. The patient reported that the use of cathinones was, at least initially, related to chemsex practices.

6.2.4.2. Acute poisonings identified from other sources

User self-reports contain information about the dosage (see above), however, the paucity of data on unknown bioavailability of 3-CMC, and possible different routes of administration render it difficult to estimate the typical, toxic and lethal blood concentrations.

Other reports on analytically confirmed 3-CMC could not be identified, and only 9 cases of non-fatal and 6 fatal intoxications involving 4-CMC have been reported from Poland (Tomczak et al.,

2018). The cases included driving under the influence, and fatalities including overdoses, suicide, and traffic accidents between 2015 and 2017. The effects described on 4-CMC-related adverse events are similar to other cathinone-related NPS such as sympathomimetic toxicity, including hypertension, tachycardia and chest pain. Effects related to the central nervous system include fear, aggression, agitation, psychoses, hallucinations, and sleeplessness (Tomczak et al., 2018). In the non-fatal cases (n=9), the concentrations of 4-CMC in the blood ranged from 1.3 up to 75.3 ng/mL; these cases were predominantly driving under the influence of drugs (DUID) cases. Apart from 4-CMC, psychostimulants and/or their metabolites, including amphetamine, MDMA, MDA and 3-MMC as well as ecgonine methyl ester and benzoylecgonine were also detected in four cases under study whereas another case featured several benzodiazepines. 4-CMC as the only compound was found in one case, with a concentration of 4-CMC in the blood of 5.5 ng/mL; the following adverse effects were reported in this case: agitation, joyful expressions, increased drive, tachycardia, dilated pupils, and difficulty in picking up objects from the ground.

In Slovenia, a suicide was attempted by a male person using multiple drug-containing products such as AB-CHMINACA, AB-FUBINACA, alpha-PHP, alpha-PVP and 4-CMC and identified in drug bags found at the scene of investigation. However, 4-CMC was neither found in stomach content or urine and it remained unclear whether 4-CMC was actually consumed at all (Klavž et al., 2016). In Hungary, identification of 4-CMC peaked around 2015 and it was detected frequently (11 instances) in blood samples in Hungary; in three quarters of all cases, multi-drug use was found (with concentrations of 4-CMC of 33.4 to 67900 ng/mL) (Arok et al., 2017).

Overall, the demographic data showed that the age ranged from 18 up to 35, all intoxicated people were males (Tomczak et al., 2018).

6.2.5 Medico-legal death investigations

6.2.5.1. Deaths reported by the Member States

Confirmed exposure

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: 29.5).

In six of the cases, other substances were identified, including:

- central nervous system depressants: alcohol (2), alprazolam (2), 5F-MDMB-PICA (1), etizolam (1), oxycodone (1), metabolite of flunitrazepam (1), metabolite of clonazepam (1);
- central nervous system stimulants: 4-CMC (2), amphetamine (2);
- other drugs: alimemazine ⁽⁴⁴⁾ (1), THC (1).

⁽⁴⁴⁾ Alimemazine is used as an antipruritic agent

Of note is that in two of the cases where other substances were identified, the only additional finding was alcohol; in those two cases the reported concentrations of 3-CMC were 888 ng/ml (matrix not specified) in one case, and 2050 ng/ml in blood and 8100 ng/ml in urine in the second case.

In four of the cases no other substances were identified in biological samples; in those four cases the reported concentrations in blood samples varied from 42 to 275 ng/ml and in one case the reported concentration of 3-CMC in urine sample was 249 ng/ml.

In at least three of the cases, the individuals were found dead. A cause of death was reported in nine cases:

- In the cases reported by Poland, the reported causes of death were: multi-organ trauma as a result of a traffic accident (2 cases), toxic effect of 3-CMC in a person with cardiac hypertrophy (1), acute poisoning with 3-CMC and ethyl alcohol (1), acute intoxication with 3-CMC (1), and gunshot wound to the chest (1 case);
- In the cases reported by Sweden, the reported causes of death were: intoxication with 3-CMC (1 case), unintentional intoxication with 3-CMC, 4-CMC, 5F-MDMB-PICA and amphetamine (1 case), and intoxication with oxycodone and benzodiazepines (1 case).

Of particular note is that in two cases the individuals were involved in traffic accidents (in one of these cases the individual caused the accident).

6.2.5.2. Deaths identified from other sources

Six deaths involving 4-CMC have been published in a study from Poland (Tomczak et al., 2018), including overdoses, suicide and traffic accidents between 2015 and 2017. In the majority of the deaths, the concentration of 4-CMC was markedly higher than in the non-fatal cases (56.2–1870 ng/ml; mean concentration 547 ng/ml, median 288 ng/ml). However, it needs to be noted that 5 out of 6 deaths involved risky behaviour rather than from the drug overdose itself. Three fatalities involving 4-CMC in combination with 25B-NBOMe have been reported in Poland (Wiergowski et al., 2017).

The age range reported in the fatal intoxications reported by Tomczak et al. (2018) was 20–38, with a predominance in the twenties; out of 5 well documented fatal cases, only one was female.

6.2.6 Driving and operating machinery under influence

A study from Poland, on blood concentrations of 4-CMC in forensic cases (Tomczak et al., 2018), includes cases of intoxications of driving under the influence, and fatalities including overdoses, suicide and traffic accidents between 2015 and 2017.

6.3 Chronic health effects

No studies were identified that systematically investigated the chronic health effects of 3-CMC in animals. In a 10-day study on the impact of 3-CMC on abuse-related effects of cocaine in the

rhesus monkey, hourly intravenous administration of up to 1.8 mg/kg of the drug produced relatively mild and transient psychostimulant-type symptoms while effectively decreasing cocaine self-administration (Kohut et al., 2013).

No clinical studies were identified that have examined the chronic health effects of 3-CMC in humans.

6.4 Preliminary analysis of health risks

Risk modifying factors

There are many factors possibly affecting health risks related to use of 3-MMC. The health risks arising from 3-MMC use are predominantly stemming from the purity of the compound, the use frequency, the use pattern, the route of administration, ingestion of additional substances, and the circumstances/context under which the substances are used.

Inter-individual differences between users may impact the outcome of 3-CMC use. Such differences include, among others, genetic differences, developed tolerance, overall state of health, underlying medical conditions, medication, age, and gender. Tolerance to some of the effects of 3-CMC might develop with prolonged and repeated use. This results in decreased sensitivity and leads users to administer larger doses to achieve the same effects.

Individuals with pre-existing health conditions, in particular cardiovascular or respiratory diseases, or in overall ill health state might be at higher risk of experiencing adverse effects than healthy individuals.

The use of some synthetic cathinones with serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs) (the most commonly prescribed antidepressants), serotonin norepinephrine re-uptake inhibitors (SNRIs), or monoamine oxidase inhibitors (MAOIs) has been associated with serotonin toxicity (serotonin syndrome), a potentially life-threatening condition. It is not known whether this this specific type of toxicity has been seen with 3-CMC.

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 acute toxicity.

Similar to other stimulants, concurrent use of 3-CMC with central nervous depressants, such as alcohol, benzodiazepines, or opioids, is likely to increase wakefulness and mask the depressant effects. This might lead to consumption of larger amounts of CNS depressants and increase the risk of adverse effects such as loss of consciousness or respiratory depression once the stimulant effects subside.

A range of factors associated with patterns of use and dosage regimens might further impact health risks associated with 3-CMC use. Dose-effect and dose-time relationships affect the likelihood of harmful effects occurring.

The routes of administration of 3-CMC may include nasal insufflation, oral and intravenous route. In general, injecting drugs, especially with shared needles or syringes, might carry additional

health risks to users including transmission of blood-borne diseases, such as hepatitis B, hepatitis C, human immunodeficiency virus, and injection site infections. This risk might be decreased if needle exchange programmes are available for users. Snorting of drugs with shared equipment might lead to the transmission of blood borne viruses as shared banknotes, cards or straws might be contaminated.

Health risks might be also affected by the context and the settings where 3-CMC is used. For example, users involved in chemsex practices while being under the influence of drugs might not use a protection (e.g. condoms) which can put them at risk of HIV and other sexually transmitted infections. Use in hot environments such as clubs might exacerbate the risk of developing hyperthermia. The risk of poisoning might be also exacerbated by use in environments where it may be difficult to summon help (e.g. alone in a home environment).

Lack of awareness and experience of users with 3-CMC may further increase the risk of accidental overdose and cause poisoning.

Uncertainty analysis

In some of the cases of serious adverse events reported to the EMCDDA as well as information from literature and user websites, exposure to 3-CMC was not analytically confirmed from biological samples from patients. In most of these cases the information on exposure to 3-CMC was limited to the name of the substance that the case or someone else linked to the event believed that the case had consumed and/or from packages containing the drugs that the case was thought to have consumed.

In some of the cases, individuals may have used other substances in addition to 3-CMC. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the reported effects. Information on mono-intoxications with confirmed exposure to 3-CMC is limited.

It is important to note that when interpreting the information on self-reported user experiences, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly, it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, chemical analyses of substances and products that are claimed by vendors to contain specific substances have shown that the composition of these may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of 3-CMC. In general, given the difficulties of collecting accurate self-reported data, these should be interpreted with caution.

Some of the effects experienced by users might be attributed, at least partially, to the environment where the substance was used. In some cases, hyperthermia (or sensation of increased body temperature) might have been caused to some extent by hot temperature in club.

The information on the prevalence of use of 3-CMC is limited, thus it is difficult to predict how probable is experiencing adverse effects after the use of 3-CMC. Similarly, it is probable that cases of minor or moderate acute poisonings might be considered as not as significant and less likely to be reported as compared to severe acute poisonings.

7. Social risks

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-CMC, as well as other stimulant drugs under international control. 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).

The illicit manufacture of cathinones, including 3-CMC, in illicit laboratories may carry serious risks to individuals and the environment.

7.1 Individual social risks

While there is no specific information on whether the use of 3-CMC causes individual social risks, any such risks may have some similarities with those associated with other synthetic cathinones and other psychostimulants under international control. These may impact on education or career, family or other personal and social relationships and may result in marginalisation.

7.2 Possible effects on direct social environment

There is no information on the possible effects of 3-CMC on the direct social environment; however, any such risks may have some similarities with those associated with the use of synthetic cathinones and other psychostimulants.

7.3 Possible effects on society as a whole

While there is no specific information on the possible effects of 3-CMC on society as a whole, any such risks may have some similarities with those associated with other synthetic cathinones and other psychostimulants.

The detection of 3-CMC in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

Due to the lack of data, it is not possible at this time to estimate the social risk associated with the trafficking and distribution of 3-CMC.

The illicit manufacture of cathinones such as 3-CMC in illicit laboratories may carry serious risks to individuals and the environment. These can have an impact in the health and safety of the individuals operating the clandestine labs, on innocent people in the vicinity of the premises and any others who are exposed to volatile chemicals (Fletcher and Al-Obaidi, 2014). Subsequent inhabitants of abandoned premises can also be at risk of being exposed to harmful chemical residues.

Occupational exposure to some of the chemicals used in the manufacture of cathinones, may pose a risk of poisoning to those who come into contact with the substances - namely law enforcement and chemical rescue units 'personnel involved in seizures of cathinone labs. These chemicals include, but are not limited to, bromine, flammable liquids including solvents and concentrated acids and bases. Bromine in particular may be toxic by inhalation, accelerates the burning of combustible material, is very corrosive to tissue and metals and dangerous for the environment.

The explosion of at least one illicit cathinone lab has been reported in Europe, connected to "incompetent handling" and resulting "environmental damage". There are no reports of explosions in any of the three seized labs of 3-CMC reported in Europe. Generally speaking, the materials used for the synthesis of the drugs, which include hazardous waste, raw materials, toxic chemicals, carcinogens and phytotoxins may be discarded at on- and off-site locations, including household drains, large containers, backyards, soil, roads and creeks, which poses additional environmental risks (Fletcher and Al-Obaidi, 2014).

7.4 Economic costs

There is no information on the health and social costs related to 3-CMC. As 3-CMC is a synthetic cathinone, any such costs may have some similarities with those associated with the use of other synthetic cathinones and other psychostimulants under international control. These may include, among others, costs related to healthcare, such as emergency department visits, hospitalisations and substance dependence treatments, costs related to loss of productivity in workplaces, criminal justice costs, and cost of social services.

Costs associated with the chemical clean-up and recovery of the clandestine production/storage sites and surrounding areas may be required.

7.5 Possible effects related to the cultural context, for example marginalisation

There is no information on the possible effects of 3-CMC related to the cultural context. As 3-CMC a synthetic cathinone, any such effects may have some similarities with those associated with the use of other synthetic cathinones and other psychostimulants.

Cost associated with the chemical clean-up and recovery of the illicit production/storage sites and surrounding areas will be incurred.

7.6 Possible appeal to specific population groups within the general population

There is limited information on the possible appeal to specific population groups. 3-CMC appears to be used by existing stimulant users, such as those who use cocaine, amphetamines, ecstasy, and other synthetic cathinones, who either add it to their existing repertoire or use it as a

replacement substance. Although specific information is lacking, it is possible that 3-CMC is used by users involved in chemsex and/or slamming practices ⁽⁴⁵⁾.

Similar to other new psychoactive substances, it also appears that there is interest in 3-CMC by people who experiment with a range of substances (so-called psychonauts).

7.7 Involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking

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.

Three illicit laboratories producing 3-CMC have been seized in Europe, two of which were seized in Poland in 2020. Poland reported that, at present there are no 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.

The effect of the on-going COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020b; WHO, 2020) 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.

8. Other relevant information

8.1 Information on restrictive measures

8.1.1 International restrictive measures

At international level, 3-CMC is not controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, or the Convention on Psychotropic Substances of 1971 ('United Nations system') (UNODC, 2021a; UNODC, 2021b).

⁽⁴⁵⁾ Slam is a form of chemsex in which psychostimulant drugs are administered by injection.

8.1.2 National restrictive measures

Six Member States (Bulgaria, Greece, Luxembourg, the Netherlands, Romania, and Spain) reported that 3-CMC is not subject to restrictive measures at national level.

The remaining countries reported that 3-CMC is subjected to restrictive measures, as follows (Table 5) (EMCDDA, 2021):

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.

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

Lithuania reported that 3-CMC is controlled under medicines legislation (included in the group of cathinone derivatives) since 10 March 2015.

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.

3-CMC has been controlled in China since October 2015. It is unknown whether 3-CMC is controlled in India.

TABLE 5

Control measures reported under Article 5b(2) of Regulation (EC) No 1920/2006, during the preparation of the Initial Report (EMCDDA, 2021)

Country	Control status	Type of control	Generic	Entry into force
Austria	Controlled	NPS	Generic	01/01/2012
Belgium	Controlled	NPS	Generic	n/r
Bulgaria	Not controlled			
Croatia	Controlled	Drug	Generic	06/07/1905
Cyprus	Controlled	NPS		24/06/2011
Czechia	Controlled	Drug		01/03/2017
Denmark	Controlled	Drug	Generic	04/07/1905
Estonia	Controlled	Drug		10/2016
Finland	Controlled	NPS		28/09/2015
France	Controlled	Drug	Generic	02/08/2012

Country	Control status	Type of control	Generic	Entry into force
Germany	Controlled	NPS	Generic	26/11/2016
Greece	Not controlled			
Hungary	Controlled	NPS	Generic	03/05/2012
Ireland	Controlled	Drug	Generic	11/2011
Italy	Controlled	Drug		06/08/2021
Latvia	Controlled	Drug	Generic	n/r
Lithuania	Controlled	Medicines	Generic	10/03/2015
Luxembourg	Not controlled			
Malta	Controlled	NPS	Generic	n/r
Netherlands	Not controlled			
Norway	Controlled	Drug		n/r
Poland	Controlled	Drug		21/08/2018
Portugal	Controlled	Drug		11/05/2021
Romania	Not controlled			
Slovakia	Controlled	Drug		01/01/2020
Slovenia	Controlled	Drug		08/04/2016
Spain	Not controlled			
Sweden	Controlled	Drug		05/04/2019
Turkey	Controlled	Drug	Generic	25/10/2016
n/r: not reported				

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ANNEX 2

Participants of the risk assessment meeting, 19 November 2021

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* Following the procedure laid down in Article 5c(4) of Regulation (EC) No 1920/2006 (as amended), the Scientific Committee of the EMCDDA has been extended with five additional experts.

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About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 25 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

Related publications and websites

| [EMCDDA initial report on the new psychoactive substance 3-CMC, 2021](#)

| [EMCDDA operating guidelines for the risk assessment of new psychoactive substances, 2020](#)

| [EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, 2019](#)

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| [EMCDDA Early Warning System on NPS](#)

| [EMCDDA Risk assessment of NPS](#)

| [EMCDDA New psychoactive substances webpage](#)

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