



# 3-MMC

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

## 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-MMC (3-methylmethcathinone; 2-(methylamino)-1-(3-methylphenyl)propan-1-one), carried out by the extended Scientific Committee of the EMCDDA on 18 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-MMC 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 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC)**

On 9 September 2021, the EMCDDA assessed the existing information on 2-(methylamino)-1-(3-methylphenyl)propan-1-one (commonly known as 3-methylmethcathinone or 3-MMC), 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-MMC 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-MMC, 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-MMC, 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-mmc\\_en](https://www.emcdda.europa.eu/publications/initial-reports/initial-report-3-mmc_en)

# **Risk assessment report on a new psychoactive substance: 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC)**

## **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, 2-(methylamino)-1-(3-methylphenyl)propan-1-one, commonly known as 3-methylmethcathinone (3-MMC), was formally notified as an NPS by the EMCDDA on behalf of Sweden on 5 September 2012. The notification was based on the identification of the substance in a customs seizure of 51.1 grams of powder made on 27 June 2012 in Gothenburg.

On 2 March 2021, based on signals suggesting the re-emergence of 3-MMC – specifically increased availability and harms related to the substance in some parts of Europe – the EMCDDA added 3-MMC to the list of new psychoactive substances under intensive monitoring. On 9 September 2021, the EMCDDA assessed the existing information on 3-MMC. The EMCDDA concluded that the assessment gave rise to concerns that 3-MMC 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-MMC 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-MMC. 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-MMC 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-MMC 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-MMC. 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 18 November 2021. Owing to the ongoing 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 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) (Annex 1);
- the EMCDDA initial report on the new psychoactive substance 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC);

- 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

2-(Methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) is a synthetic cathinone with psychostimulant effects that 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 June 2012 based on a customs seizure made in Sweden.

3-MMC is a derivative of cathinone, the naturally occurring stimulant and main psychoactive substance in the khat plant, *Catha edulis*. 3-MMC is also closely related to and shares similar psychostimulant effects with methcathinone (ephedrone) and mephedrone (4-methylmethcathinone; 4-MMC). Cathinone, methcathinone, and mephedrone 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-MMC has two positional isomers, 2-methylmethcathinone (2-MMC) and mephedrone (4-MMC). Both positional isomers have been identified on the drug market in Europe. Mephedrone, was first identified in May 2008, and came to epitomise the modern legal highs market after it spread rapidly in Europe between 2009 and 2010 when it was produced, distributed, and sold openly as a 'legal' stimulant. Although now under international control, mephedrone continues to be encountered regularly on the drug market, with at least some of the substance produced in illicit laboratories in Europe in recent years. Conversely, 2-MMC has only occasionally been



encountered since it was first identified in March 2014, with just under 160 kilograms seized, almost all of which was seized in 2015.

The differentiation of 3-MMC from 2-MMC and mephedrone requires the use of appropriate analytical techniques. Due to differences in reporting practices across Europe, the differentiation of 3-MMC 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-MMC has not been specified to the EMCDDA have been excluded from the data analysis of physical and biological samples. However, due to different reporting practices across Europe, it remains possible that some detections reported as 3-MMC but that are actually a different positional isomer, have been included.

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

### Chemical and physical properties

2-(Methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) is an *N*-alkylated and ring-substituted cathinone. 3-MMC contains a chiral centre so two enantiomers may exist: (*R*)-3-MMC and (*S*)-3-MMC. No information is available on the enantiomeric composition of 3-MMC 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.

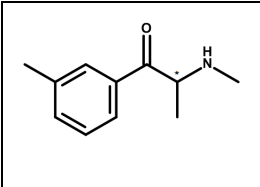
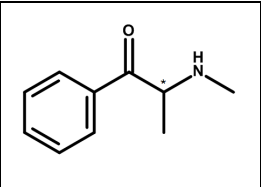
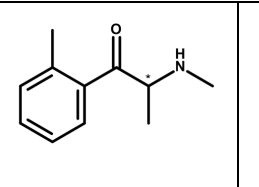
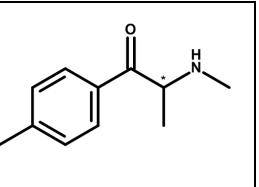
In its pure form, 3-MMC has the appearance of a fine white powder or small white crystals. The hydrochloride salt of 3-MMC is described as a white crystalline powder. The hydrochloride salt is readily soluble in water and can be dissolved for oral use or for injection.

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

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

FIGURE 1

**Molecular structure, molecular formula, molecular mass, and monoisotopic mass of 3-MMC**

				
	3-MMC (metaphedrone)	Methcathinone	2-MMC	Mephedrone (4-MMC)
Molecular formula	C <sub>11</sub> H <sub>15</sub> NO	C <sub>10</sub> H <sub>13</sub> NO	C <sub>11</sub> H <sub>15</sub> NO	C <sub>11</sub> H <sub>15</sub> NO
Molecular mass	177.24	163.22	177.24	177.24
Monoisotopic mass	177.115364	163.099714	177.115364	177.115364

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

The analytical identification and quantification of 3-MMC 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-MMC from its positional isomers, 2-MMC and mephedrone. These include chromatographic and mass spectrometric methods. The availability of analytical reference material is important for correct identification and for facilitating the quantification of 3-MMC 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-MMC and its two positional isomers may not be undertaken during routine forensic and toxicological analysis in Europe. Detections where the positional isomer of 3-MMC 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-MMC that has been identified on the European drug market. A number of methods for the production of cathinones, including 3-MMC, 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, mephedrone, 4-chloromethcathinone (4-CMC), and 3-chloromethcathinone (3-CMC), 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-MMC appears to have been manufactured and imported into Europe on an industrial-scale. In particular, from 2019 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-MMC, includes a two-step procedure that involves the  $\alpha$ -bromination of a suitable arylketone (commonly called a 'propiofenone'), followed by the reaction with an amine to obtain the desired cathinone. Brominated intermediates can be produced on a large-scale, subdivided 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-MMC using this method, such as 3-methylpropiofenone, 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-MMC, 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. For example, during 2019, Dutch Police seized 350 kilograms of chemically masked 3-MMC <sup>(1)</sup> 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

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<sup>(1)</sup> 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.

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-MMC is not available, though the presence of route-specific impurities is possible. Of particular note, is that, similar to the home-made production of methcathinone using ephedrine-type precursors, 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-MMC 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-MMC have also been reported. These findings are consistent with recent reports from people who use 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-MMC has been identified. The hydrochloride salt of 3-MMC is readily soluble in water and can be dissolved for oral use or for injection.

Similar to other drugs, the purity of 3-MMC, as well as the presence of adulterants and diluents, depends on factors such as the location in the supply chain where the substance is obtained, as well the point in time and the geographical area. Limited information is currently available for 3-MMC, which in part reflects the differences in the level of analyses conducted on physical samples as well as reporting practices in Europe. Seizures of 3-MMC by customs at the EU external border are almost exclusively powders and, where reported, have typically been described as 'white' in colour and 'pure'. Seizures by police are typically powders, and where reported, include 'white' and 'off-white' powders; the purity of 3-MMC is rarely reported. Collected samples, typically submissions from clients of drug-checking services, are mostly powders, and, where reported, the purity appears, at least in part, to vary according to the time and place of collection. Typically, 3-MMC is the only psychoactive substance identified in police seizures and collected samples, but again, these may vary according to the location in the supply chain from which the sample is obtained, as well as the point in time and the geographical area. Other substances, particularly other synthetic cathinones, as well as established stimulants such as cocaine and MDMA, have been identified to some extent. Adulterants and/or diluents typical of the stimulant market have also been reported very occasionally, such as caffeine and benzocaine.

## Pharmacological and toxicological properties

### Pharmacological properties

There is limited information on the pharmacological properties of 3-MMC. Similar to closely related cathinones such as mephedrone, 3-MMC has been shown to interact with the monoamine transporter system in a number of *in vitro* studies. For example, 3-MMC 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-MMC is able to act as a substrate-type releaser, a feature also found in synthetic cathinones such as methcathinone and mephedrone. Taken together, these results suggest that 3-MMC is likely to act as a psychostimulant in humans and might also show abuse liability. These findings are consistent with self-reported user experiences as well as reports from acute poisoning cases with confirmed exposure to 3-MMC which typically note stimulant-like effects and toxicity.

Information about the pharmacology of the individual enantiomers of 3-MMC has not been published. The biological properties of the individual enantiomers may differ, as has been shown for mephedrone.

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

While the pharmacokinetics of 3-MMC in humans has not been studied, animal studies indicate that 3-MMC has a low oral bioavailability and relatively rapid absorption. Distribution throughout body tissues and excretion are also fast, with a relatively short half-life. The metabolism of 3-MMC in animals appears to be similar to that of mephedrone, and the same 3-MMC metabolites observed in animal studies have been found in samples obtained from human poisoning cases. The pharmacological and toxicological properties of these metabolites are unknown. Furthermore, the available data suggests that 3-MMC is possibly metabolised in humans by the highly polymorphic cytochrome CYP2D6 isozyme. The significance of this in respect to the effects of 3-MMC is currently unknown.

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

### Toxicological properties

There is limited information on the toxicological properties of 3-MMC. Currently, aside from information from acute poisonings with confirmed exposure to the substance (discussed below), data are limited to exploratory *in vitro* studies, suggesting chromosome damaging properties

and a potential for liver toxicity. 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-MMC are likely to share some similarities with other closely related synthetic cathinones and psychostimulants under international control, although this requires further study.

The available information suggests that while some individuals report only using 3-MMC, the substance may also be commonly used in combination with a range of other drugs (polydrug use). These include psychostimulants 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-MMC as the presence of and/or interaction with other substances may contribute to the effects reported, and ultimately the public health risks.

In addition, information from one Member State shows that 3-MMC may also be used by vulnerable groups such as young people, including those who are inexperienced in drug use. This may increase the risk of accidental poisoning as well as other adverse effects in this group. Some factors related to use of 3-MMC, 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-MMC. Based on the available information, the adverse effects associated with the acute toxicity of 3-MMC 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*

A total of 14 acute poisonings with confirmed exposure to 3-MMC have been reported to the EMCDDA by four Member States: France (6), Germany (1), the Netherlands (6), and Spain (1).

Where known, the cases occurred between 2014 and 2021: 2014 (1 case), 2016 (2), 2017 (2), 2021 (2). Based on the available information, the majority of the cases are believed to be non-fatal poisonings.

Information on the clinical features of poisoning was available for 7 cases. These included: loss of consciousness, coma, respiratory arrest, respiratory insufficiency, epileptic seizure, uncontrolled movements of the hands, mouth, eyelids and nystagmus, and 'bad trip'. Three patients were hospitalised, two of them in intensive care. Based on the reported information, four of the cases could be classified as life-threatening (required admission to intensive care unit or involved life-threatening condition such as respiratory arrest or coma).

In 7 cases other substances were identified, including psychostimulants (such as synthetic cathinones, cocaine, amphetamine, methamphetamine) as well as depressants (such as GHB/GBL, benzodiazepines, and synthetic cannabinoids).

One case was related to a sexual assault. Two other cases were reported as related to sexual practice (chemsex or sadomasochism).

#### *Acute poisonings identified from other sources*

At least 291 cases of acute poisonings in Europe with confirmed exposure to 3-MMC have been published in the scientific literature. It is likely that these cases partially overlap with those reported by the Member States. Based on the available information, the majority of the cases are believed to be non-fatal poisonings. In most cases other substances were identified in the biological samples, including psychostimulants and depressants (alcohol, GHB, opioids, and benzodiazepines). Where reported, most of the patients presented with stimulant-type toxicity, especially sympathomimetic features. The patients were typically males and aged between twenty and thirty.

### **Deaths**

#### *Deaths reported by the Member States*

A total of 27 deaths with confirmed exposure to 3-MMC have been reported to the EMCDDA by five Member States: France (6), the Netherlands (8), Slovenia (1), Spain (3), and Sweden (9). Where known, the cases occurred between 2013 and 2021: 2013 (7 cases), 2016 (3), 2019 (5), 2020 (5), 2021 (1). Overall, 18 of the cases were either reported as mixed poisonings or other substances were identified in the biological samples, including stimulants (such as amphetamine, 4-fluoromethylphenidate and other synthetic cathinones) and depressants (such as alcohol, opioids, and benzodiazepines). Additional information on the type of poisonings (mixed- or mono-) or cause of death was reported in 18 cases:

- in one of the cases reported by France, the case was reported as accidental toxic death exclusively involving 3-MMC;
- in the cases reported by the Netherlands, the reported causes of deaths were: mono-intoxication with 3-MMC (2 cases), 1 mixed-intoxication in which 3-MMC contributed to the death (1 case), 1 mixed-intoxication in which 3-MMC did not contribute to the death (1 case), mixed intoxication with 3-MMC and other NPS (4-fluoromethylphenidate, 2-fluorodeschloroketamine, dimethocaine; analytical confirmation of other NPS not available) (1 case); intentional intoxication with 3-MMC, cocaine and caffeine in a person with no history of problematic drug use (1 case); intoxication with carbon monoxide following the use of 3-MMC (1 case);
- in the case reported by Slovenia, the reported cause of death was sudden cardiac death after ingestion of 3-MMC, THC and ethanol;
- in the cases reported by Sweden, seven of the cases were reported as mixed intoxications (three with buprenorphine, one with AH-7921, one case reported as hanging, in one case stick injuries were reported). In the two remaining cases, the reported causes of death were intoxication with buprenorphine, clonazepam, 3-MeO-PCP, and 3-MMC (1 case) and intoxication with several substances (pregabalin, tramadol) (1 case).

Three of the deaths were related to chemsex practices.

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

#### *Deaths identified from other sources*

At least 17 reports of deaths in Europe with confirmed exposure to 3-MMC have been published in the scientific literature. It is likely that these cases partially overlap with those reported by the Member States. In most cases, other substances were identified in the biological samples, including psychostimulants and depressants (such as alcohol and GHB). In three cases, 3-MMC was the only substance identified in the biological samples. The individuals were typically males and aged between twenty and thirty.

#### **Chronic toxicity**

The chronic toxicity of 3-MMC has not been studied. Based on the limited information related to its stimulant pharmacological properties, the chronic toxicity of 3-MMC 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-MMC have not been studied. Based on the limited information related to its stimulant pharmacological properties, information from acute poisonings with confirmed exposure to the substance, as well as self-reported experiences, the effects of 3-MMC 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-MMC 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-MMC. Four Member States (Denmark, France, Hungary, and Sweden) and Norway reported 45 cases of suspected driving under the influence of drugs with confirmed exposure to 3-MMC, including four traffic accidents. Similar cases, including from Europe, have been reported in the scientific literature. In some of the cases, 3-MMC was the only substance identified in the biological samples that were analysed. Where reported, the adverse effects attributed to 3-MMC were generally consistent with those seen in acute poisoning cases as well as stimulant-type toxicity in general.

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-MMC have not been studied. Data from *in vitro* studies on the pharmacological mechanism of action of 3-MMC suggest that it may have an abuse liability and possibly a dependence potential in humans, as demonstrated for mephedrone, although this requires further study.

France reported two cases of dependence associated with confirmed exposure to 3-MMC and three cases with suspected exposure. No further details are available on these cases.

## Social risks

Currently, there is limited information on the social risks related to 3-MMC. In general, the social risks of 3-MMC 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-MMC 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-MMC 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-MMC.

At least three sites related to the illicit production of 3-MMC have been seized in Europe between 2013 and 2020. In addition, information provided by Europol to the EMCDDA indicates that a number of abandoned illicit laboratories were seized in Slovakia in 2018 that were reported to be involved in the production of 'high volumes' of 3-MMC. One of the laboratories exploded resulting in environmental damage. 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-MMC is typically sold and sought after as a stimulant drug in its own right, but it may also be mis-sold as other drugs. In the latter case, this includes both mephedrone and MDMA (ecstasy).

Currently, information on the extent and patterns of use, availability, and potential for diffusion of 3-MMC is limited. The available information is largely derived from law enforcement seizures and from collected samples, targeted surveys with specific populations (such as young people and men who have sex with men who practice chemsex), as well as serious adverse events (discussed above).

Since 3-MMC was first detected on the drug market in June 2012, the substance has been identified in 23 Member States as well as Turkey and Norway. While 3-MMC has been available

on the European drug market since 2012, it appears that the availability of 3-MMC has increased significantly in around 2020, leading to its re-emergence in parts of Europe.

## Availability

3-MMC was first identified on the European drug market in June 2012 based on a customs seizure made in Sweden. The appearance of 3-MMC on the drug market followed the increasing control of mephedrone across Europe as well as in China, which, at the time, was identified as a source of bulk quantities of mephedrone that were being seized by customs agencies in Europe. At least in part, it appears that 3-MMC is being used as a 'legal' replacement to mephedrone.

Since 2012, approximately 2 790 kilograms of 3-MMC powder has been seized in Europe. This includes at least 2 360 kilograms by customs and just over 340 kilograms by police, in more than 8000 seizures. Other physical forms, such as tablets and capsules, have also been seized, but to a much smaller extent.

Following a decline in seizures of 3-MMC in Europe between 2016 and 2018, which coincides with the control of 3-MMC in China in October 2015, the substance appears to have re-emerged during 2019, and particularly from 2020 onwards. During that year, approximately 740 kilograms of powder was seized, including 630 kilograms by customs (of which approximately 600 kilograms (95 %) originated from India) and 110 kilograms by police. This represents just over a quarter of the total quantity of 3-MMC powders seized since monitoring of the substance began in Europe in 2012. During 2021, 3-MMC continues to be imported, distributed, and used in parts of Europe; this includes a single large-scale seizure of just over 120 kilograms of powder at the external EU border, originating in India.

The available information suggests that 3-MMC is currently imported into Europe in bulk quantities mainly from India, with approximately 600 kilograms of pure powders that originated from the country seized in 2020. It is then processed, packaged, and then distributed in wholesale and retail amounts in Europe either online (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 the closely related cathinone, 3-chloromethcathinone (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 1 800 kilograms per year,

and falling to 750 kilograms by 2019, during 2020 there was a significant increase, with approximately 3 300 kilograms of powders seized. At least in part, this increase has been driven by 3-MMC which accounted for almost a quarter of the quantity of powders seized during 2020 (just under 750 kilograms). In addition, 3-chloromethcathinone (3-CMC), which is also currently the subject of a risk assessment following its emergence in Europe, accounted for a similar quantity (just under 880 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 mephedrone, 3-MMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. Other routes have also been reported occasionally.

The substance appears to be used by existing stimulant users, such as those who use cocaine, amphetamines, ecstasy, and other cathinones, who either add it to their existing repertoire or use it as a replacement substance. This includes recreational use, and, in some cases high risk use, such as injecting. In the latter case, this may be part of chemsex practices including men who have sex with men. In addition, information from one Member State shows that 3-MMC may also be used by vulnerable groups such as young people, including inexperienced drug users. At least in part this is because it was reported to be easily available, not controlled, and having a relatively low cost. It appears that 3-MMC is used in private spaces (such as homes and domestic parties), as well as recreational settings (such as nightclubs, bars/pubs, music festivals), and as part of chemsex settings.

Limited information from self-reported experiences in people who use 3-MMC 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-MMC with other drugs may be intentional or unintentional. The repeated administration of 3-MMC in a single session is common because of the apparent short-lived effects of the substance. In some cases, 250 milligrams to 1.5 grams or more may be used in a single session.

As noted, 3-MMC 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-MMC 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 mephedrone, amphetamine, cocaine, and MDMA. In addition, it may also be missold as other drugs, including mephedrone and MDMA (ecstasy). There is also limited information, such as from parts of Spain, that indicate that 3-MMC may also currently be sold at street-level along with controlled stimulants.

Alongside the desired effects and the claimed high purity of 3-MMC, important factors in why the substance is used by some groups, such as young people in the Netherlands, appears to include its ease of availability (both online and from dealers), that it is not controlled, and its relatively low cost. In addition, at least some people cited boredom as a reason for using 3-MMC which may be related to restrictions on public socialising during the COVID-19 pandemic, such as stay-at-home measures.

Information on the current price of 3-MMC is limited. Information from the Netherlands from April 2021 before control measures were introduced in October 2021, noted that 1 gram of 3-MMC costs 5–25 euro, depending on the type of vendor and the amount purchased.

Reports of the mis-selling of 3-MMC as other drugs have so far been limited. Despite this, the potential for 3-MMC to be mis-sold as other drugs, particularly controlled stimulants such as mephedrone and MDMA, exists. For example, during 2020, information from the Netherlands shows, that, while 3-MMC only represented a small proportion of samples tested by the national drug checking service, approximately half of the samples that were sold as mephedrone were in fact 3-MMC; however, samples containing 3-MMC never contained mephedrone.

The further diffusion of 3-MMC 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-MMC. This includes the positional isomer 2-MMC that has been identified on the drug market in 2014, but rarely encountered since 2015. 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-MMC 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-MMC as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States due to a lack of information.

Aside from limited use as an analytical reference standard and in scientific research, there is currently no information that suggests that 3-MMC is used for other legitimate purposes.

## Other relevant information

### Restrictive measures

#### *International restrictive measures*

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

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

#### *National restrictive measures*

##### *Europe*

3-MMC is subject to restrictive measures in 22 Member States. Fifteen Member States reported that 3-MMC is controlled under drug control legislation: Croatia, Czechia, Denmark, Estonia, France, Germany, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Slovenia, Slovakia, and Sweden. Six Member States reported that 3-MMC is controlled under new psychoactive substance legislation: Austria, Belgium, Cyprus, Finland, Hungary, and Malta. Lithuania reported that 3-MMC is controlled under medicines legislation.

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

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

##### *Other countries*

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

The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution and use of 3-MMC is currently unknown. However, seizures of more than of 720 kilograms of bulk powders by customs agencies and 100 kilograms by police between 2020 and 2021 suggest that 3-MMC continues to be imported and distributed in Europe. It is possible that, in case of a reduced availability of controlled stimulants (such as mephedrone, 4-CMC, and MDMA) in Europe, criminal groups, as well as people who use drugs, may use a range of replacement substances, including 3-MMC.

## Conclusion

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

3-MMC has been available on the drug market in the European Union since at least June 2012 and has been identified in 23 Member States as well as Turkey and Norway. The available information indicates that 3-MMC has re-emerged in Europe during 2020. At least in part, it appears that 3-MMC is being manufactured, traded, imported, and used as a 'legal' replacement to mephedrone and other controlled psychostimulants.

The limited information suggests that 3-MMC is typically sold and sought after as a stimulant drug in its own right, but it may also be mis-sold as other drugs. Similar to other cathinones, such as mephedrone, 3-MMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It appears to be used by existing stimulant users, such as those who use cocaine, amphetamines, ecstasy, and other cathinones, who either add it to their existing repertoire or use it as a replacement substance. This includes recreational use, and, in some cases high risk use, such as injecting. In the latter case, this may be part of chemsex practices including men who have sex with men. In addition, information from one Member State shows that 3-MMC may also be used by vulnerable groups such as young people, including inexperienced drug users. At least in part this is because it was reported to be easily available, not controlled, and having a relatively low cost. Among other settings, 3-MMC is used in private spaces (such as homes and domestic parties), as well as recreational settings (such as nightclubs, bars/pubs, music festivals), and as part of chemsex practices.

Since 2012, approximately 2790 kilograms of 3-MMC powder has been seized in Europe, including at least 2360 kilograms by customs and 340 kilograms by police, in more than 8 000 seizures. Following a decline in seizures in Europe between 2016 and 2018, which coincides with the control of 3-MMC in China in October 2015, the substance appears to have re-emerged, particularly during 2020. During that year, approximately 740 kilograms of powder was seized, including 630 kilograms by customs and 110 kilograms by police. This represents just over a quarter of the total quantity of 3-MMC powders seized since monitoring of the substance began in Europe in 2012. During 2021, 3-MMC continues to be imported, distributed,



and used in parts of Europe; this includes a single large-scale seizure of just over 120 kilograms of powder at the external EU border, originating in India.

The available information suggests that 3-MMC is currently imported into Europe in bulk quantities mainly from India, with approximately 600 kilograms of pure powders that originated from the country seized in 2020 (95 % of the total seized by customs during the year). It is then processed, packaged, and distributed in wholesale and retail amounts in Europe either online or by street dealers. In order to avoid detection, 3-MMC may also be imported as a masked drug and then presumably converted into 3-MMC in Europe. In addition, at least three illicit sites, including some directly involved in the production of 3-MMC, have been seized in Europe, with the most recent site seized in 2020.

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

A total of 14 acute non-fatal poisonings with confirmed exposure to 3-MMC have been reported by four Member States: France, Germany, Netherlands, and Spain. In at least seven cases other substances were identified. Where reported, the cases occurred between 2014 and 2021. Four of the cases could be classified as life-threatening. Similar cases from Europe have been reported in the scientific literature. Overall, where known, the cases involved stimulant-type toxicity. In addition, information from poisonings suspected to involve 3-MMC reported in the Netherlands, suggests that the incidence of poisoning has increased significantly between 2020 and 2021 compared to previous years and that this coincides with an increased availability and use of the substance.

A total of 27 deaths with confirmed exposure to 3-MMC have been reported by five Member States: France, Netherlands, Slovenia, Spain, and Sweden. In at least 13 of the cases, other substances were identified. Where reported, the cases occurred between 2013 and 2021. In at least eight cases, 3-MMC was the cause of death or contributed to the death. Similar cases from Europe have been reported in the scientific literature.

The chronic health effects of 3-MMC, including abuse liability and dependence producing potential in humans, have not been studied. However, two cases of substance dependence with confirmed exposure to 3-MMC have been reported by one Member State. 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-MMC within Europe. However, based on information reported to the EMCDDA, there is information to suggest criminal acts, such as large-scale trafficking, illicit production, and supply offences, involving 3-MMC.

The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution and use of 3-MMC is currently unknown. However, seizures of more than of 720 kilograms of bulk powders by customs agencies and more than 100 kilograms by police between 2020 and 2021 suggest that 3-MMC continued to be imported and distributed in Europe. It is possible that, in case of a reduced availability of controlled stimulants (such as mephedrone and MDMA) in Europe, criminal groups, as well as people who use drugs, may use a range of replacement substances, including 3-MMC.

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

3-MMC is subject to restrictive measures in 22 Member States as well as Turkey and Norway. 3-MMC has been controlled in China since October 2015. It is unknown if 3-MMC is controlled in India, from where bulk quantities of pure powder have originated and recently been seized by customs agencies in Europe.

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

Since the WHO Expert Committee on Drug Dependence critical review in 2016, significant new information has been reported by the Member States to the EMCDDA that suggests that 3-MMC might pose health and social threats at Union level. This includes information on large-scale importation (including seizures of large quantities of bulk powders of pure 3-MMC during 2020 and 2021), illicit production of the substance in Europe, as well as recent reports that suggest an increase in poisonings involving the substance in parts of Europe. Taken together, this suggests that the availability of 3-MMC has increased significantly in around 2020, leading to its re-emergence in parts of Europe.

There is currently limited information on the extent or patterns of use of 3-MMC in Europe. 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-MMC causes harm to health associated with its acute toxicity and abuse liability or dependence-producing potential. This 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-MMC that are posed by the lack of data on the risks could be answered through further research. 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-MMC and other substances; the abuse liability and dependence-producing potential; and the public health and social risks associated with its use.

The Committee considers that to prevent wide diffusion of 3-MMC 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-MMC 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-MMC. 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-MMC 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 socioeconomic stigmatisation and marginalisation.

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

## ANNEX 1

## **Technical report on the new psychoactive substance 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC)**

### ***Purpose***

The purpose of this technical report is to provide an analysis of the available information on 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC), a synthetic cathinone that has emerged on the drug market in Europe in 2012, 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 (as amended).

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 (as amended) (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 (as amended).
- 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-MMC.

### ***Literature search and review***

Literature searches used both chemical structure and textual queries in online databases; searches were conducted in October 2021. The retrieved publications were then scanned for additional relevant references (snowballing technique).

SciFinder® and Reaxys were searched by exact structure-based search. PubMed was searched for '3-methylmethcathinone', '3-MMC' and the IUPAC name '2-(methylamino)-1-

(3-methylphenyl)-1-propanone'. 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; 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, 2020a).

### ***Methodology***

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

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

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

Complementary data sources have been used in the preparation of the technical report:

- For the period comprised between 1 January 2014 and 31 December 2020, annual aggregated seizure data which is systematically reported to the EMCDDA has been used.
- For the period comprised between 1 January and 30 September 2021, event-based data reported spontaneously to the EMCDDA, as well as data reported through targeted requests for information (a structured reporting form sent to the Reitox national focal points and responses to ad hoc information requests) have been used. 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-MMC (EMCDDA, 2021), additional clarifications on the information initially reported and updates have been received. These have been included in the technical report.

It is also important to note that, in some settings, the ongoing 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-MMC.

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  - Dr Leon Van Aerts, Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht;
  - Dr Piotr Adamowicz, Institute of Forensic Research, Krakow;
  - Professor Dr Simon Brandt, School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool.

## 1. Summary

Synthetic cathinones, such as 3-MMC, 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-MMC, which accounted for almost a quarter of the quantity of powders seized during 2020.

2-(Methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) is a synthetic cathinone with stimulant effects that is monitored as a new psychoactive substance by the EMCDDA in accordance with Regulation (EC) No 1920/2006. The substance is an *N*-alkylated and ring-substituted cathinone and contains a chiral centre so two enantiomers may exist: (*R*)-3-MMC and (*S*)-3-MMC. 3-MMC is closely related to and appears to share similar stimulant effects with methcathinone (ephedrone) and 4-methylmethcathinone (4-MMC; mephedrone). Cathinone, methcathinone, and 4-MMC are controlled under the 1971 United Nations Convention on Psychotropic Substances.

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

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

On the drug market, cathinones are typically found in powders and tablets. To date, seizures and collected samples containing 3-MMC 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 are branded legal-high type products), herbal material and blotters. Information on the enantiomeric composition of seized and collected samples has not been reported. 3-MMC has been identified in combination with other cathinones, including but not limited to 4-MMC and 4-chloromethcathinone (4-CMC, clephedrone) and a variety of other substances including synthetic cannabinoids and internationally controlled substances such as cocaine and MDMA.

Since 2012, 3-MMC has been identified in 23 Member States, as well as Turkey and Norway. In total, approximately 2 630 kg of 3-MMC powder has been seized, including at least 2 360 kg by customs and 184 kg by police. In addition, 154 kg of 3-MMC crystals were seized by police in 2019. Following a decline in seizures in Europe between 2016 and 2019, which coincides with the control of 3-MMC in China in October 2015, the substance appears to have re-emerged during 2020. During that year, approximately 740 kg of powder was seized, including 631 kg by customs (of which at least 605 kg originated from India) and 110 kg by police. This represents just over a quarter of the total quantity of 3-MMC powders seized since monitoring of the substance began in Europe in 2012. During 2021, 3-MMC continues to be imported, distributed, and used in parts of Europe; this includes a single large-scale seizure of 122 kg of powder at the external EU border, originating in India.

The available information suggests that 3-MMC is currently imported into Europe in bulk quantities mainly from India, with at least 605 kg of pure powders that originated from the country seized in 2020. It is then processed, packaged, and then distributed in wholesale and retail amounts in Europe either online or by street dealers. The substance may also be imported as a masked drug (where non-controlled chemicals are used) and then presumably converted into 3-MMC in Europe. In addition, at least three illicit laboratories producing 3-MMC have been seized in Europe, with the most recent laboratory seized in 2020.

In general, natural and synthetic cathinones, including 3-MMC, interact with monoamine transporters in the brain, i.e. with dopamine, serotonin and norepinephrine transporters. Limited pharmacokinetic studies have been conducted in animals. Pharmacokinetics of 3-MMC in humans have not been studied. The metabolism of 3-MMC is thought to be similar to 4-MMC with several metabolites already identified in human tissue samples.

There is limited information on the acute toxicity of 3-MMC. 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-MMC might include neurological (e.g. hallucination, seizures, agitation, anxiety, psychosis, reduced consciousness), cardiovascular (e.g. tachycardia, hypertension, chest pain, cardiac arrest)



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

A total of 14 acute poisonings with confirmed exposure to 3-MMC have been reported by France (6), the Netherlands (6), Germany (1), and Spain (1). Exposure to other substances was reported in 7 cases, including central nervous system depressants and central nervous system stimulants. At least some of the clinical features of the poisonings were consistent with exposure to synthetic cathinones. Based on the reported information, four of the cases could be classified as life-threatening (required admission to intensive care unit or involved life-threatening condition such as respiratory arrest or coma).

A total of 27 deaths with confirmed exposure to 3-MMC were reported by Sweden (9), the Netherlands (8), France (6), Spain (3), and Slovenia (1). In some of the cases, 3-MMC was reported to be the cause of death or to have contributed to the death.

Cases of acute poisonings, death investigations and suspected cases of driving under the influence with confirmed exposure to 3-MMC have been published in the scientific and medical literature. Some of the reported cases occurred in Europe: France, Norway, Poland, Sweden, and the United Kingdom. The clinical features of poisoning were similar to those reported for other synthetic cathinones under international control.

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

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

Although not formally studied, the psychological and behavioural effects of 3-MMC 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-MMC within Europe. However, based on information reported to the EMCDDA, there is evidence of criminal acts, such as trafficking, illicit production, and supply offences, involving 3-MMC.

The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution and use of 3-MMC is currently unknown. However, seizures of approximately 757 kg of bulk powders by customs agencies during the pandemic (2020 and 2021) suggest that 3-MMC continues to be imported and distributed in Europe. It is possible that, in case of a reduced availability of other controlled stimulants (such as 4-MMC and MDMA) in Europe, criminal groups, as well as people who use drugs, may use a range of replacement substances, including 3-MMC.

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

3-MMC is subject to restrictive measures in 22 Member States, Turkey, and Norway – in some cases, being covered by a generic definition of cathinones. 3-MMC has been controlled in China since October 2015. It is unknown whether 3-MMC is controlled in India, from where bulk quantities of pure powder have originated and recently been seized by customs agencies in Europe.

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

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

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

### 2.1. Background

2-(Methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC, also known as metaphedrone) is an *N*-alkylated and ring-substituted synthetic cathinone. It was first described in the scientific literature in the months prior to its first detection on the drug market in Europe in June 2012 (Power et al., 2011).

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

3-MMC is the 3-methyl derivative of methcathinone <sup>(4)</sup> and a positional isomer <sup>(5)</sup> of 4-MMC <sup>(6)</sup>, which are both internationally controlled. 3-MMC is structurally related to 3-chloromethcathinone (3-CMC, also known as clophedrone) <sup>(7)</sup>, differing on the substituent present at the 3-position of the phenyl ring. 3-Methylethcathinone (3-MEC) <sup>(8)</sup> is a higher homologue of 3-MMC, also monitored by the EMCDDA.

3-MMC has a chiral centre at the C<sub>2</sub> carbon of the propanone side chain thus two possible enantiomers exist: (*R*)-3-MMC and (*S*)-3-MMC.

### 2.2. Names and chemical structure

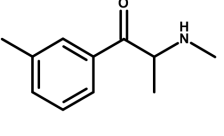
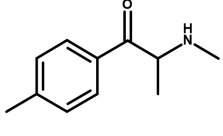
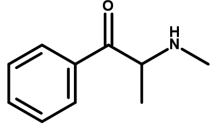
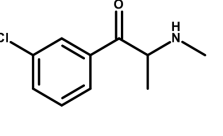
The common name 3-MMC is derived from 3-methylmethcathinone <sup>(9)</sup>.

- 
- <sup>(1)</sup> Listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances.  
<sup>(2)</sup> Diethylpropion, also known as amfepramone (2-(diethylamino)propiofenone), is listed in Schedule IV of the 1971 United Nations Single Convention on Psychotropic Substances.  
<sup>(3)</sup> 2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one.  
<sup>(4)</sup> 2-(Methylamino)-1-phenyl-propan-1-one; listed in Schedule I of the 1971 United Nations Single Convention on Psychotropic Substances.  
<sup>(5)</sup> 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.  
<sup>(6)</sup> 2-(Methylamino)-1-(4-methylphenyl)-1-propanone; formally notified by the EMCDDA in March 2008; listed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.  
<sup>(7)</sup> 1-(3-Chlorophenyl)-2-(methylamino)propan-1-one; formally notified by the EMCDDA in October 2014.  
<sup>(8)</sup> 2-(Ethylamino)-1-(3-methylphenyl)propan-1-one; formally notified by the EMCDDA in July 2014.  
<sup>(9)</sup> The origin for the abbreviated common name is indicated by underlining the relevant letters in the common name.

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

FIGURE 1

**Molecular structure, molecular formula, molecular mass and monoisotopic mass of 3-MMC**

				
	3-MMC (metaphedrone)	4-MMC (mephedrone)	Methcathinone	3-CMC (clorphedrone)
Molecular formula	C <sub>11</sub> H <sub>15</sub> NO	C <sub>11</sub> H <sub>15</sub> NO	C <sub>10</sub> H <sub>13</sub> NO	C <sub>10</sub> H <sub>12</sub> ClNO
Molecular mass	177.24	177.24	163.22	197.66
Monoisotopic mass	177.364102	177.115364	163.099714	197.060742

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

*Common name(s):*

3-MMC

3-Methylmethcathinone

*Systematic (IUPAC) name:*

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

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

*Other chemical names:*

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

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

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

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

*Other names:*

3-Methyl-methcathinone  
3-Me-methcathinone  
3-Methyl-N-methylcathinone  
3-Me-MCAT  
3-Methyl MC  
Metaphedrone  
Mepedrone  
3-Mephedrone

*Chemical Abstracts Service (CAS) registry numbers:*

1246911-86-3 (base)  
1246816-62-5 (hydrochloride salt)  
2291027-30-8 (*R*-isomer)  
2107851-15-8 (*S*-isomer)

*IUPAC International Chemical Identifier Key (InCHI Key):*

QDNXSIYWHYGMCD-UHFFFAOYSA-N (base)  
RPFQEIQTWQCQH-UHFFFAOYSA-N (hydrochloride salt)  
QDNXSIYWHYGMCD-SECBINFHSA-N (*R*-isomer)  
QDNXSIYWHYGMCD-VIFPVBQESA-N (*S*-isomer)

*IUPAC International Chemical Identifier String (Inchl string):*

1S/C11H15NO/c1-8-5-4-6-10(7-8)11(13)9(2)12-3/h4-7,9,12H,1-3H3 (base)  
1S/C11H15NO.ClH/c1-8-5-4-6-10(7-8)11(13)9(2)12-3;/h4-7,9,12H,1-3H3;1H (hydrochloride salt)  
1S/C11H15NO/c1-8-5-4-6-10(7-8)11(13)9(2)12-3/h4-7,9,12H,1-3H3/t9-/m1/s1 (*R*-isomer)  
1S/C11H15NO/c1-8-5-4-6-10(7-8)11(13)9(2)12-3/h4-7,9,12H,1-3H3/t9-/m0/s1 (*S*-isomer)

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

Cc1cccc(c1)C(=O)C(C)NC (base)  
Cl.CNC(C)C(=O)c1cccc(C)c1 (hydrochloride salt)  
CN[C@H](C)C(=O)c1cccc(C)c1 (*R*-isomer)

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

*EC / List No:*

824-776-2

*Other identifiers*

PubChem CID 71741532

NIST Number 386254

UNII-73Q9QTO1N4

73Q9QTO1N4

SCHEMBL20472228

DS-016274

FT-0701142

Q27266198

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

‘Synthacaine’/‘Synthacaine’

‘Charly Sheen’

‘Crystal’

### 2.3. Physical properties

The hydrochloride salt of 3-MMC is a white crystalline powder, reported to be soluble in DMF (1 mg/ml); DMSO (2 mg/ml); ethanol (5 mg/ml); and PBS (pH 7.2; 10 mg/ml) (Cayman Chemical, 2012a). Solubility in water is reported as  $2.0 \pm 0.1$  mg/ml (Shimsoni et al., 2015).

Physico-chemical properties for 3-MMC are reported in the literature.  $\lambda_{\max}$  (ultraviolet wavelength of maximum absorbance) of 252 and 292 nm (Cayman Chemical, 2012a) and a UV-absorption max in water of 206.2 nm is reported (Shimsoni et al., 2015).  $pK_a$  values of  $7.84 \pm 0.1$  (Shimsoni et al., 2015) and 8.68 by capillary electrophoresis are reported (Nowak et al., 2018a; Woźniakiewicz et al., 2018). Melting point ranges of 188–190 °C (Power et al., 2011),  $193.2 \pm 0.2$  °C (Shimsoni et al., 2015) and 193–195 °C (Walther et al., 2019) have been reported for the hydrochloride salt.

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

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

3-MMC has been identified in combination with other cathinones, including but not limited to: 2-MMC <sup>(10)</sup>, 4-MMC, 3-CMC, 4-CMC <sup>(11)</sup>, 3-CEC <sup>(12)</sup>, 4-CEC <sup>(13)</sup>, 4-MEC <sup>(14)</sup>,  $\alpha$ -PVT <sup>(15)</sup>, ethylone <sup>(16)</sup>, pentedrone <sup>(17)</sup> and *N*-ethylhexedrone <sup>(18)</sup>. 3-MMC has also been identified in combination with a variety of other categories of substances including synthetic cannabinoids such as 4F-MDMB-BINACA (4F-MDMB-BUTINACA) <sup>(19)</sup> and internationally controlled substances such as cocaine and MDMA.

## 2.4. Methods and chemical precursors used for the manufacture or extraction

Limited information is available about the chemical precursors or manufacturing methods used to make the 3-MMC which has been identified in Europe. Information about route-specific by-products produced during the synthesis of 3-MMC is not available.

General methods for the synthesis of cathinones, including the specific methods for the preparation of 3-MMC, are described below.

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

The interest in cathinones (and  $\alpha$ -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 <sup>(20)</sup>. The propiophenone ((I), see Scheme 1) precursor needed to afford 3-MMC and its *N*-alkyl-homologues can be synthesized from:

- 3-methylbenzonitrile, using a Grignard reaction (with ethylmagnesium bromide) as described in the original patent for bupropion (after Mehta, 1974; Carroll et al., 2009) (Scheme 1),

<sup>(10)</sup> 2-(Methylamino)-1-(2-methylphenyl)propan-1-one

<sup>(11)</sup> 1-(4-Chlorophenyl)-2-(methylamino)propan-1-one

<sup>(12)</sup> 1-(3-Chlorophenyl)-2-(ethylamino)propan-1-one

<sup>(13)</sup> 1-(4-Chlorophenyl)-2-(ethylamino)propan-1-one

<sup>(14)</sup> 2-(Ethylamino)-1-(4-methylphenyl)propan-1-one

<sup>(15)</sup> 2-(Pyrrolidin-1-yl)-1-(thiophen-2-yl)pentan-1-one

<sup>(16)</sup> 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)propan-1-one

<sup>(17)</sup> 2-(Methylamino)-1-phenylpentan-1-one

<sup>(18)</sup> 2-(Ethylamino)-1-phenylhexan-1-one

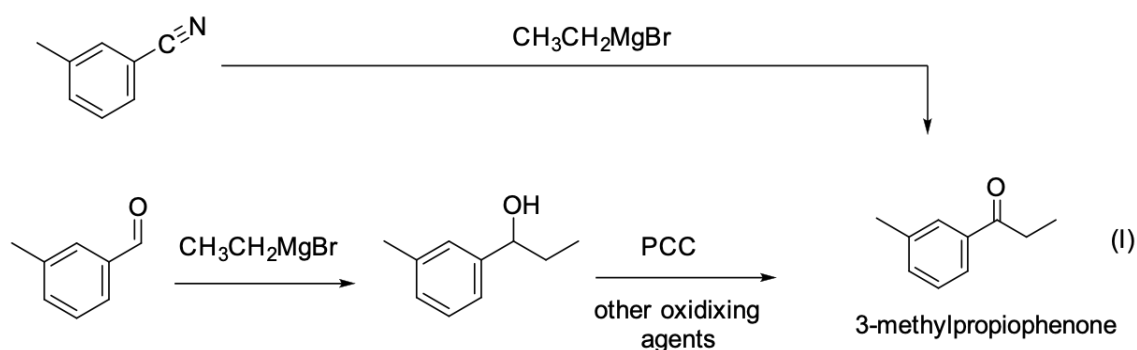
<sup>(19)</sup> Methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate

<sup>(20)</sup> In the case of mephedrone (4-MMC) and some of its analogous compounds, the starting propiophenone can be produced *via* a Friedel-Crafts acylation between toluene (or other ring-substituted benzenes) and, typically, an acyl chloride (such as propionyl chloride) or an acid anhydride (such as propionic anhydride).

- 3-methylbenzaldehyde, 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).

## SCHEME 1

**Preparation of 3-methylpropiophenone (I), a precursor of 3-MMC** (Carroll et al., 2009; Power et al., 2011)

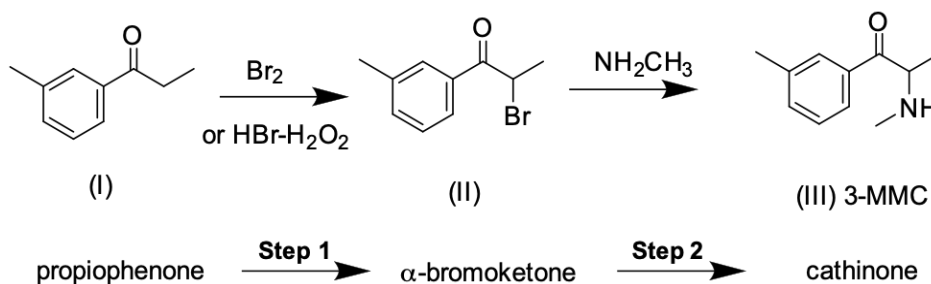


Importantly, propiophenone precursors like (I) can also be purchased from chemical suppliers and imported in bulk.

Once available, they can be transformed into ring-substituted cathinones, such as 3-CMC and 3-MMC, 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-MMC via the 'bromination-amination' pathway** (Carroll et al., 2009; Power et al., 2011)





This 2-step bromination-amination procedure, starts with the  $\alpha$ -bromination of the propiophenone (I) to produce the corresponding  $\alpha$ -bromoketone (II). The product is then reacted with an amine (<sup>21</sup>) 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) in 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  $\alpha$ -bromoketone (II) intermediate is also available from chemical suppliers. Data reported to the European Commission (DG TAXUD, unpublished) indicates that between 2017 and 2019, at least 2.1 tonnes of  $\alpha$ -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 (<sup>22</sup>), 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 of *N*-bromosuccinimide (NBS) in the presence of an acid catalyst avoids the hazardous reagent bromine, which might also be a preferred approach for an industrial-scale production of intermediate (II) (Reddy et al., 2010; see also Guha et al., 2015). Methods that avoid the use or the isolation of the lachrymatory  $\alpha$ -bromoketone (II) have also been developed (Allen et al., 2021). As shown by Walther et al. (2019), for the second step, *N*-benzyl-*N*-methylamine might also be used instead of *N*-methylamine. 1-Chloroethyl chloroformate was then used to remove the protective *N*-benzyl group.

Numerous alternative synthetic methods exist and one example is the so-called 'permanganate process' (Scheme 3), which involves the oxidation of a suitable ephedrine analogue (I) with a strong oxidant (e.g. potassium permanganate) to yield the desired cathinone (III). If (I) is obtained in a specific enantiomeric form, the synthesis is

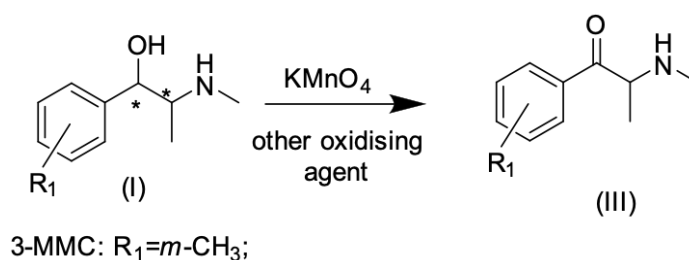
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(<sup>21</sup>) This step promotes the nucleophilic substitution of the bromine to obtain the  $\alpha$ -bromoketone. For ring substituted cathinones, the amine is typically methylamine hydrochloride and triethylamine in an acidic scavenger.

(<sup>22</sup>) Bromine can be commercially obtained as a liquid or prepared from a bromide salt (e.g. KBr), an acid (e.g. H<sub>2</sub>SO<sub>4</sub>), and an oxidizing reagent (e.g. H<sub>2</sub>O<sub>2</sub>).

stereoselective and the resulting cathinone (II) will be enantiopure. 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).

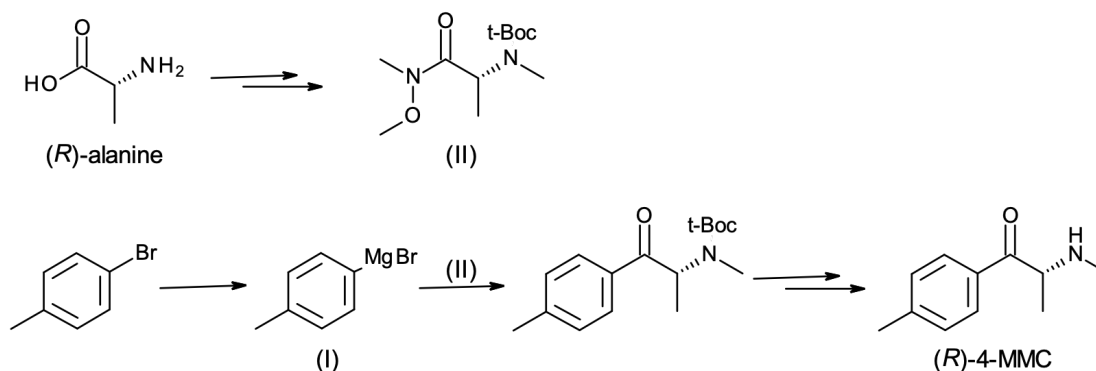
## SCHEME 3

**'Permanganate process' for the preparation of ring substituted cathinones**

Note: For 3-MMC, the process starts with 3-methylephedrine (2-(methylamino)-1-(*m*-tolyl)propan-1-ol). Asterisk (\*) indicates chiral centre.

The synthesis of enantiopure stereoisomers of 3-MMC has not been described in the literature. However, each can be readily obtained following the route described recently for the (*R*)- and (*S*)-enantiomers of 4-MMC (Scheme 4) (Gregg et al., 2015; Niello et al., 2021). It appears, however, that either 4-MMC enantiomer undergoes slow racemization under physiological conditions (Gregg et al., 2015). The same phenomenon is expected for the enantiomers of 3-MMC using 3-bromotoluene in place of 4-bromotoluene.

## SCHEME 4

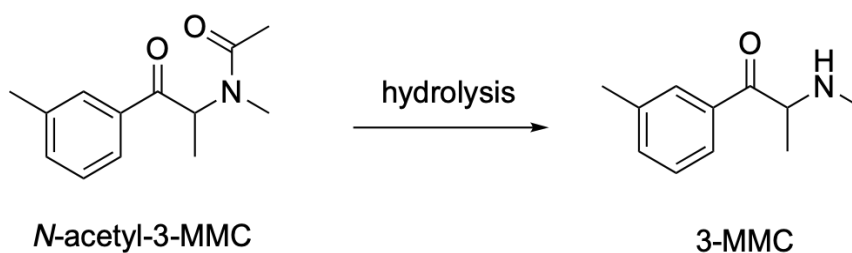
**Synthesis of (*R*)-4-MMC involving *p*-tolyl magnesium bromide (I) and a Weinreb-Nahm amide (II), obtained from (*R*)-alanine, as key step**

**'Designer' precursors**

Other than standard organic synthesis methods using known precursors, cathinones can also 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 conversions to '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 quantitative yields to produce the controlled amine of choice. In Scheme 5, an example is provided using the *N*-acetyl protected cathinone derivative of 3-MMC.

It should be noted that approximately 350 kg of *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 3-MMC.

## SCHEME 5

**Use of acetyl protecting groups to yield cathinones, such as 3-MMC**

Note: Hydrolysis may occur preferably via acid catalysed reaction.

***Illicit production of 3-MMC***

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

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

Seizures of precursors reported to the European Commission do not contain information on the specific chemicals needed for the synthesis of 3-MMC. Most of the reports consisted of precursors for 4-MMC and 4-CMC, which can nonetheless be taken as indicative of the processes also used for their positional isomers. The majority of the 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 but that they may be focused on the final stages of cathinones production ('finishing labs').

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

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

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

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

## 2.5. Methods for identification and analysis

The analysis of positional isomers of methyl methcathinones has been extensively published in the scientific literature. Table 1 contains a broad selection of references on the determination of 2-, 3-, and 4-MMC either alone or from mixtures with other NPS, from buffers or biological material (including hair, plasma, whole blood or urine samples). Enantiomer-selective determinations have also been performed and described.

The first description of analytical methodology has been provided by Power et al. in 2011, through gas chromatography–mass spectrometry (GC–MS), infrared (IR) and nuclear magnetic resonance (NMR) (Power et al., 2011). This combination of methodologies is

currently the most frequently used especially when analysing drugs available in bulk. Raman spectroscopy has been shown to further facilitate detection (Christie et al., 2013), later on by the combination with microcrystalline testing (Elie et al., 2016).

TABLE 1

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

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

Liquid chromatography-high resolution accurate mass-mass spectrometry (LC-HRAM-MS)	Frison et al., 2020
High-performance liquid chromatography coupled to flowing atmospheric pressure afterglow ion source (LC-FAPA-MS)	Labuz et al., 2019
Liquid chromatography-diode array detection (LC-DAD)	Armenta et al., 2015
High-performance liquid chromatography-ultraviolet (HPLC-UV)	Fu et al., 2020 Hägele et al., 2020 Kadkhodaei et al., 2018 Kadkhodaei et al., 2020 May et al., 2020 Taschwer et al., 2014
Ultra-high performance liquid chromatography (UHPLC)	Carnes et al., 2017
High-performance liquid chromatography with chiral ion-exchange stationary phases and diode array detection	Wolrab et al., 2016
High-performance liquid chromatography-diode array detection (HPLC-DAD) and ultra-performance liquid chromatography- mass spectrometry (UPLC-MS) followed by gas chromatography	Ameline et al., 2019
Ultra-high performance supercritical fluid chromatography (UHPSFC)	Carnes et al., 2017 Pauk et al., 2015 Rowe et al., 2017
Fourier transform infrared spectroscopy (FTIR)	Armenta et al., 2015 Christie et al., 2013 Johnson et al., 2020 Kolodziejczyk et al., 2017 Piorunska-Sedlak and Stypulkowska, 2020 Power et al., 2011 RESPONSE, 2012 SWGRDUG, 2013
Infrared ion spectroscopy (IRIS)	Kranenburg et al., 2020c
Raman spectroscopy	Christie et al., 2013 Johnson et al., 2020 Kranenburg et al., 2021
Combination of microcrystalline testing with Raman micro-spectroscopy	Elie et al., 2016

<sup>1</sup> H Nuclear magnetic resonance spectroscopy (NMR)	Bäckberg et al., 2018 Power et al., 2011 Strano Rossi et al., 2014 Stolarska et al., 2020 SWGRDUG, 2013 Walther et al., 2019
<sup>13</sup> C NMR	Bäckberg et al., 2018 Power et al., 2011 Stolarska et al., 2020
Ion mobility spectrometry (IMS)	Armenta et al., 2015
Capillary electrophoresis (CE)	Hägele et al., 2019 Nowak et al., 2018a Nowak et al., 2018b Woźniakiewicz et al., 2018
Color spot test method for the detection of synthetic cathinones (copper(II)-neocuproine as color test reagent)	Philp et al., 2016
<b>Biological samples</b>	
<b>Analytical method</b>	<b>References</b>
GC-MS	Alremeithi et al., 2016 Alremeithi et al., 2018 Institóris et al., 2015 Maas et al., 2015 Maas et al., 2017 Mercieca et al., 2018
GC-MS/MS	Woźniak et al., 2020
LC-MS	Labuz et al., 2019
LC-MS/MS	Adamowicz and Tokarczyk, 2016 Adamowicz et al., 2016 Bäckberg et al., 2018 Boumba et al., 2017 Goncalves et al., 2021 Grumann and Auwärter, 2018 Helander et al., 2020 Labuz et al., 2019 Maas et al., 2015 Maas et al., 2017 Vaiano et al., 2016
Liquid chromatography-high resolution mass spectrometry (LC-HRMS)	Bäckberg et al., 2018 Frison et al., 2016 Goncalves et al., 2021 Stephanson et al., 2017

Liquid chromatography-high resolution mass spectrometry tandem mass spectrometry (LC-HRMS/MS)	Bäckberg et al., 2018 Helander et al., 2020
Ultra-high performance liquid chromatography-mass spectrometry (UHPLC-MS)	Borovcová et al., 2018 Sorribes-Soriano et al., 2019
Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS)	Odoardi et al., 2015 Karinen et al., 2014
Ultra-high performance supercritical fluid chromatography-mass spectrometry (UHPSFC-MS)	Borovcová et al., 2018
HPLC-DAD	Romanek et al., 2017
HPLC-MS/MS	Sánchez-González et al., 2019

Quantification of 3-MMC in products can be carried out according to the general procedure described by the UNODC (2020). Quantification of 3-MMC in biological samples can be carried out according to methods described by Adamowicz et al. (2016) and others (Frison et al., 2016; Grumann and Auwärter, 2018; Mercieca et al., 2018; Woźniak et al., 2020).

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

### ***Discrimination of 3-MMC from its positional isomers***

3-MMC has two positional isomers, 2-MMC<sup>(23)</sup> and 4-MMC, differing only in the position of the methyl group on the phenyl ring. Reference standards of the hydrochloride salt of 3-MMC (Cayman Chemical, 2012a), 2-MMC (Cayman Chemical, 2012b), and 4-MMC (Cayman Chemical, 2018) are commercially available. Reference standards are also commercially available for the base form and the (S)-isomer of 3-MMC (Aurora Fine Chemicals, 2021a; Aurora Fine Chemicals, 2021b).

Positional and structural isomers have the same molecular formula and molecular mass, therefore their discrimination can pose analytical challenges, as techniques solely relying on mass will not allow for an unequivocal identification. The positional isomers of 3-MMC, 2-MMC and 4-MMC, can be discriminated in many, but this might not apply to 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 analytical methods in addition to GC-MS, such as FTIR or NMR. The discrimination of these isomers is described in further detail below.

<sup>(23)</sup> 2-(Methylamino)-1-(2-methylphenyl)propan-1-one; formally notified by the EMCDDA in May 2014.



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

Carnes et al., highlighted that chromatographic analysis of cathinones can be problematic using gas chromatography due to the potential for sample decomposition in the hot injection port, with high injector temperatures potentially resulting in the production of enamine or imine artifacts, affecting peak shape and quantification (Carnes et al., 2017). The authors noted however that split mode injection and a relatively low injection port temperature can significantly reduce this issue. The use of a combination of UHPSFC and GC for cathinone analysis and for the discrimination of positional isomers, such as 2-, 3- and 4-MMC, has been suggested (Carnes et al., 2017).

Hägele et al. demonstrated that not only positional isomers but stereoisomers can be discriminated by  $\beta$ -cyclodextrin-assisted CE, providing examples for the discrimination of 2-, 3- and 4-MMC as well as other cathinones including three different fluorinated methcathinone derivatives, 2-FMC<sup>(24)</sup>, 3-FMC<sup>(25)</sup> and 4-FMC<sup>(26)</sup>, using carboxymethyl- $\beta$ -CD as the chiral selector (Hägele et al., 2019). Kadkhodaei et al., also demonstrated that using an isocratic HPLC method with a specific chiral stationary phase (CSP) could discriminate between the positional isomers of 3-MMC (Kadkhodaei et al., 2020).

Kranenburg et al. (2019) and Skultety et al. (2017) described the discriminating potential of GC-VUV. Kranenburg et al. (2020a) also reported on the application of a derivatisation step

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<sup>(24)</sup> 1-(2-Fluorophenyl)-2-(methylamino)propan-1-one  
<sup>(25)</sup> 1-(3-Fluorophenyl)-2-(methylamino)propan-1-one  
<sup>(26)</sup> 1-(4-Fluorophenyl)-2-(methylamino)propan-1-one

for GC–MS-based NPS identification and use of IRIS (Kranenburg et al, 2020c), for the discrimination of the positional isomers of 3-MMC.

### ***Differentiation of enantiomers***

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

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

Under optimised conditions using HPLC with various types of CSP the enantiomers of 2-, 3- and 4-MMC could be separated (Fu et al., 2020; Kadkhodaei et al., 2018; Kadkhodaei et al., 2020). It is of note, however, that while the enantiomers of mephedrone (4-MMC) were separated using HPLC with two common reverse-phase columns and sulfated  $\beta$ -cyclodextrin added to the mobile phase under isocratic conditions the enantiomers of 3-MMC could not be separated (Taschwer et al., 2014).

### ***Stability***

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).

## **2.6. Dosage regimens**

### ***Pharmaceutical and posological information***

Based on the available information, it appears that 3-MMC is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe.

Racemic 3-MMC is commercially available as analytical reference material (e.g., at LGC standards <sup>(27)</sup>).

On the drug market, cathinones are typically found in powders and tablets. To date, seizures and collected samples containing 3-MMC 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 rocks' to white/off-white powders (mostly pure), and in some cases encountered in yellow and orange colour (mostly with other substances). In a limited number of cases for which this information exists, it was traded as 'synthacaine'. 3-MMC may also be sold under its own name, or as other new psychoactive substances (including '5CL-ADB-A', a synthetic cannabinoid; and mephedrone).

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

Detailed information available with regards to route-specific by-products produced during the synthesis of 3-MMC is currently not available.

With respect to purity of the samples, there is only scarce information available. Marillier et al. (2017) analysed samples collected from NPS users in France: Overall, 8 samples contained 3-MMC and the range of purity was between 51 % and 88 % as determined by HPLC-HRMS. A recent study reported an internet purchase of 3-MMC which was shown to be >99.5 % pure by GC-MS analysis (Zwartsen et al., 2020).

### ***Route of administration and dosage***

Information on the dose and dosage regimens <sup>(28)</sup> for 3-MMC is limited. Most information available is from reports posted on Internet forums and surveys.

The most common routes of 3-MMC administration are via oral ingestion, insufflation (snorting) or injection. 3-MMC is often swallowed after wrapping it in tissue paper (bombing or dabbing). Sometimes it is used in conjunction with alcohol (dissolved in a drink). Repeated administration during single sessions is common, which suggests that the

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<sup>(27)</sup> <https://www.lgcstandards.com/DE/de/3-MMC-HCl-3-Methylmethcathinone-Hydrochloride-/p/LGCFOR1387.03> accessed on October 10, 2021.

<sup>(28)</sup> 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.

psychoactive effects might be relatively short-lived. In pigs, the half-life of 3-MMC has been determined as being 0.8 h (Shimshoni et al., 2015; also see Section 4). Often, users describe the application by different routes during one single session (Adamowicz et al., 2016).

3-MMC users describe doses close to the threshold at around 10–20 mg, a low dose as 25–100 mg, a typical (regular) dose as 75–175 mg and a strong dose as 125–250 mg (Adamowicz et al., 2014). Doses vary between 50 and 150 mg depending on the individual user (Ameline et al., 2019; Sande, 2016). The onset of 3-MMC-induced effects appear to occur between 15 minutes and 1 hour, and last for 4 to 6 hours. In contrast to oral administration, nasal insufflation has been associated with painful experiences. Many users report binge administrations to prolong the euphoric experience, accounting for doses as high as 2 g consumed during a single session or within a few hours (Ameline et al., 2019; Sande, 2016).

It has been suggested by some people who use 3-MMC, that the effects are considered to be less intense/potent compared to those induced by 4-MMC (with estimates suggesting two to five times less powerful), even though the doses are relatively similar. Reports from people who are using 4-MMC report taking between 150–250 mg, including repeated application, often resulting in ingestions of 0.5–1 g during a single session, with effects establishing between 15–45 min after oral administration and lasting up to 4–5 h (Green et al., 2014; Kelly et al., 2011).

A recent patent application proposing the use of 3-MMC in drug-assisted psychotherapy provides in case study examples human oral dose data ranging from 200 to 400 mg with effects lasting maximum 4 hours (Golan et al., 2019).

### *Risk-modifying factors*

The composition of products is likely to vary over time and place, as well as based on the specific location in the drug supply chain in which the sample is obtained from (for example, from the manufacturer, wholesaler, retailer, or at street-level markets). The available information suggests that 3-MMC might be mis-sold as other drugs such as 4-MMC or ‘ecstasy’.

Another risk-modifying factor is that some countries do not control synthetic cathinones; this is insofar a note of caution since this may influence the patterns of use within the community. Easy availability of non-controlled substances and low prices are factors that might make 3-MMC more appealing to some users, including vulnerable users.

### *Uncertainty analysis*

The dosage regimens used for 3-MMC can differ within and between individuals, thus it is not possible to discern typical dosage regimens. These also depend on the tolerance of the

user, the use of other drugs, and the desired effects. Given the difficulties of collecting such data, the information presented should be used with caution. Furthermore, the purity, amount and/or composition of the substance ingested are not typically known by people who are using 3-MMC. As stated above, the actual composition of the substance may differ over time and place.

### 3. Legitimate use

#### 3.1. Summary

Based on the available information, it appears that 3-MMC is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe.

However, although highly unlikely, the use of 3-MMC as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States (EMCDDA, 2021). There is currently no information to suggest that 3-MMC is used for legitimate purposes other than scientific research or clinical/forensic investigations.

#### 3.2. Medical use

Based on information from the European Medicines Agency for the initial report (EMCDDA, 2021), it appears that 3-MMC 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-MMC is not an active substance in the following, although the information, especially in relation to use in extemporaneously prepared products, is unknown in some cases:

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

As part of the initial report process, the European Chemical Agency (ECHA) reported to the EMCDDA that there are no registrations or classification and labelling (C&L) notifications for 3-MMC in the C&L Inventory database <sup>(29)</sup>. ECHA reported a C&L notification for the hydrochloride salt of 3-MMC that has been labelled with the hazard statements H335 ('may cause respiratory irritation') and H336 ('may cause drowsiness or dizziness') (ECHA, 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-MMC and have not assessed this substance in any context.

According to the critical review of 3-MMC published by the World Health Organization in 2016 (WHO, 2016a), no evidence was found that 3-MMC was or had been used in industry, other than as an analytical reference standard.

#### ***Risk-modifying factors***

At least some part of 3-MMC 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-MMC might have legitimate uses outside the EU.

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<sup>(29)</sup> 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.

## 4. Pharmacological and toxicological properties

### 4.1. Summary

In general, natural and synthetic cathinones including 2-, 3- and 4-methylated analogues of methcathinone interact with monoamine transporters: dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) as transported substrates in the synapse. This leads to (i) a competitive inhibition of re-uptake of the physiological substrate into the presynaptic neuron 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). Such pharmacodynamic effects of 3-MMC have been confirmed by investigations carried out *in vitro* and also by observations *in vivo* such as microdialysis experiments.

Based on the DAT/SERT ratio, which is thought to predict the reinforcing or dependence producing properties associated with highly dopaminergic compounds, no clear evidence has yet emerged as to the dependence potential of 3-MMC. In addition, 3-MMC interacts with other neurotransmitter receptors, possibly explaining some of the clinically relevant effects.

Information on the pharmacokinetic properties of 3-MMC have so far only been described in administration studies involving pigs, which indicated low bioavailability via the gastrointestinal (oral) route. In pigs, fast absorption and distribution and rapid excretion with a relatively short half-life (0.8 h) was reported.

The corresponding information in humans is not yet available, though the metabolism of 3-MMC is thought to be similar to 4-MMC with several metabolites already identified in human tissue samples.

Although not formally studied, the psychological and behavioural effects of 3-MMC 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-MMC 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

Several studies examined the effect of 3-MMC *in vitro*. Where available, the relevant data on the positional isomer 4-MMC are given for comparison.

The studies below used the racemic substance and it appears that no study has investigated the pharmacological properties of the individual stereoisomers of 3-MMC. Nevertheless, it is conceivable that the biological properties of the individual (*R*)- and (*S*)-enantiomers differ, as has been shown for 4-MMC *in vitro* (Mayer et al., 2016; Simmler et al., 2013), *ex vivo* (Gregg et al., 2015) and in rodents (Philogene-Khalid et al., 2017), and also in a recent human pharmacokinetics study (Czerwinska et al., 2021). It appears, however, that either 4-MMC enantiomer undergoes slow racemization under physiological conditions (Gregg et al., 2015).

### 4.2.1. *In vitro* data

#### 4.2.1.1. Uptake inhibition studies

The results of the study on the interaction of 3-MMC with DAT, NET and SERT in comparison to 4-MMC *in vitro* in human embryonic kidney 293 (HEK293) cells stably expressing the human isoforms of the respective transporters are shown in Table 2 (Luethi et al., 2018). The IC<sub>50</sub> values obtained show that NET is inhibited with the highest potency; however, 3-MMC more potently inhibits DAT compared to SERT – which is in clear contrast to 4-MMC displaying a higher potency toward SERT over DAT. This is also reflected in the DAT/SERT ratio of 3.7 (3-MMC) compared to 0.63 in the case of 4-MMC. For 3-MMC the rank order of potency was NET > DAT > SERT, whereas for 4-MMC it was NET > SERT > DAT. Typically, stimulants with low DAT/SERT ratios (< 1) are thought to reflect an MDMA-like (e.g. entactogenic) profile, whereas substances with a high DAT/SERT ratio (> 10) are associated with distinct psychostimulant effects with a high abuse potential similar to methamphetamine (METH).

Another study using HEK293 cells expressing the recombinant hDAT, hSERT or hNET, confirmed the high DAT selectivity of 3-MMC with a similar rank order of uptake inhibitory potency of NET > DAT > SERT as discerned from data shown in Table 2 (Eshleman et al., 2019). Using [<sup>125</sup>I]RTI-55<sup>(30)</sup> as radioligand, this study also determined competitive inhibition of binding involving several stimulants, including 3-MMC. For 3-MMC, the respective K<sub>i</sub> values for DAT, NET and SERT were 6.33, 2.85, and 7.9 μM. In comparison, for METH the respective K<sub>i</sub> values for DAT, NET and SERT were 4.41, 2.51, and 150 μM,

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<sup>(30)</sup> RTI-55, that is methyl (1*R*,2*S*,3*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate, is a phenyl-tropane-derived cocaine analogue which binds to all three monoamine transporters with low nanomolar affinity.



which meant that the potency was comparable at DAT and NET whereas the potency of 3-MMC was around 19 times higher at SERT.

Interestingly, another study reported a potency rank order of DAT > NET > SERT for a pharmaceutical grade 3-MMC purchased from an established supplier while a rank order of NET > DAT > SERT for 3-MMC purchased on the internet as discerned from the data shown in Table 2 (Zwartsen et al., 2020). As reported by the authors, these differences are likely due to biological or technical variation.

Such between-lab and between-sample differences reflected by rank orders illustrate the variability in an otherwise robust experimental approach, even when the same cell line is in use (HEK293 cells) and the identical human isoform of the monoamine transporters stably expressed. It has also been pointed out that some laboratories carry out the assay at ambient temperature while some at the physiologically more relevant 37 °C which could, at least partially, account for the different experimental values reported by the different laboratories (Zwartsen et al., 2020).

Using HEK293 cells expressing hDAT, hNET and hSERT, Mayer et al. (2016) report the same overall range for 4-MMC albeit with some differences: the uptake inhibition is much stronger at DAT (by a factor of 7) while less pronounced at NET (by a factor of close to 10) and similar, yet less pronounced again at SERT (by a factor of 2). This is also reflected by a much larger DAT/SERT ratio of around 10 which allows a different interpretation in terms of abuse potential (rather high, see above). The uptake inhibition assay results presented by Eshleman et al. (Table 2; Eshleman et al., 2013) show much lower IC<sub>50</sub> values, thus higher affinity of 4-MMC compared to both other publications. However, and importantly, the rank order of potencies again deviates: NET > SERT > DAT (Luethi et al., 2018), DAT > NET > SERT (Mayer et al., 2016) and NET > DAT > SERT (Eshleman et al., 2013). Furthermore, the differences in DAT/SERT ratios for 4-MMC range from 0.6 up to 10.2 – which again reflects the apparent variability (Table 2).

TABLE 2

**IC<sub>50</sub> values of test drugs on monoamine uptake mediated by hDAT, hNET and hSERT, stably expressed in HEK293 cells**

Drug	DAT IC <sub>50</sub> [μM]	NET IC <sub>50</sub> [μM]	SERT IC <sub>50</sub> [μM]	DAT/SERT ratio
3-MMC	2.6 (2.0–3.3) <sup>a</sup>	0.27 (0.21–0.36) <sup>a</sup>	9.5 (6.9–13.2) <sup>a</sup>	3.7
	0.433 ± 0.089 <sup>b</sup>	0.084 ± 0.023 <sup>b</sup>	4.5 ± 1.3 <sup>b</sup>	10.4
	2.5 (2.1–2.9) <sup>c</sup>	5.2 (4.5–6.0) <sup>c</sup>	134 (108–165) <sup>c</sup>	53.6
	4.1 (3.5–4.8) <sup>c*</sup>	3.1 (2.2–4.5) <sup>c*</sup>	129 (110–151) <sup>c*</sup>	
4-MMC	5.7 (4.5–7.2) <sup>a</sup>	0.26 (0.19–0.35) <sup>a</sup>	3.6 (2.8–4.6) <sup>a</sup>	0.63 <sup>a</sup>
	0.77 (0.53–1.08) <sup>d</sup>	2.77 (1.92–3.97) <sup>d</sup>	7.83 (6.32–9.75) <sup>d</sup>	10.2
	0.098 ± 0.027 <sup>e</sup>	0.0536 ± 0.0087 <sup>e</sup>	0.51 ± 0.15 <sup>e</sup>	5.2
METH	0.097 ± 0.013 <sup>b</sup>	0.0258 ± 0.0030 <sup>b</sup>	9.3 ± 1.1 <sup>b</sup>	96
	0.0260 ± 0.010 <sup>e</sup>	0.0260 ± 0.0077 <sup>e</sup>	4.1 ± 1.3 <sup>e</sup>	15.8
MDMA	0.479 ± 0.070 <sup>b</sup>	0.63 ± 0.14 <sup>b</sup>	0.118 ± 0.019 <sup>b</sup>	0.25
	0.201 ± 0.047 <sup>e</sup>	0.0242 ± 0.0050 <sup>e</sup>	0.109 ± 0.017 <sup>e</sup>	0.54
Cocaine	0.425 ± 0.036 <sup>b</sup>	0.382 ± 0.037 <sup>b</sup>	0.364 ± 0.040 <sup>b</sup>	0.86
	0.370 ± 0.072 <sup>e</sup>	0.217 ± 0.025 <sup>e</sup>	0.257 ± 0.048 <sup>e</sup>	0.69

Note: IC<sub>50</sub> values are means and 95 % confidence intervals. DAT/SERT ratios were calculated as reciprocal SERT IC<sub>50</sub>/DAT IC<sub>50</sub> values. Legend: (a) Luethi et al., 2018; (b) Eshleman et al., 2019; (c) Zwartsen et al., 2020 (sample purchased from an established supplier); (c\*) Zwartsen et al., 2020 (sample purchased on the internet); (d) Mayer et al., 2016; (e) Eshleman et al., 2013.

The work published by Iversen et al. (2013) reported their 4-MMC uptake inhibition data as follows: DAT IC<sub>50</sub> = 543 nM; NET IC<sub>50</sub> = 511, and SERT IC<sub>50</sub> = 4943. The rank order of potencies conforms well with the data presented by Eshleman who also observed NET > DAT > SERT (Eshleman et al., 2013). For Iversen et al. (2013), the calculated DAT/SERT ratio is 9.1 which aligns rather closely with the ratio calculated from the data presented by Mayer et al. (2016).

#### 4.2.1.2 Transporter-mediated release

In addition to competitive inhibition experiments at monoaminergic transporters, cathinones, including both 3-MMC and 4-MMC have been shown to induce transporter-mediated neurotransmitter release from synaptosomal preparations (Blough et al., 2019; Walther et al., 2019).

In an exploratory experiment using all three human monoamine transporter isoforms expressed in HEK293 cells and a 100  $\mu\text{M}$  concentration of the test drugs, the increase of efflux elicited by 3-MMC and MDMA was found to be similar for the monoamines norepinephrine and serotonin but the release of dopamine caused by 3-MMC was about 10 % higher relative to MDMA (Luethi et al., 2018). Interestingly, the induced release was largest in this assay in SERT-expressing cell lines while being lower, but comparable, for DAT- and NET mediated efflux at this single, high concentration. In comparison, 4-MMC was confirmed as an amphetamine-type stimulant and releaser using a similar approach in HEK293 cells stably expressing the human isoforms of monoamine transporters (Mayer et al., 2016). Eshleman et al. (2013) described the concentration-dependent effect of 4-MMC in HEK293 cells stably expressing the human DAT, NET and SERT with  $\text{EC}_{50}$  values of 1.19  $\mu\text{M}$ , 0.41  $\mu\text{M}$  and 11.9  $\mu\text{M}$ , respectively.

Mayer and colleagues have recently documented a supporting role for organic cation transporter 3 (OCT3) in the effects of 4-MMC by inducing substrate efflux via OCT3 in the presence of another synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV; Mayer et al., 2019a). This is the first observation of a cathinone-mediated influence on transport activity of the SLC22 transporter family, characterized as ‘low affinity, high capacity’ transporters for monoamines, in contrast to the ‘high affinity, low capacity’ transporters for monoamines, DAT, NET, SERT, which are members of the SLC6 family of sodium-chloride dependent transporters (Sitte and Freissmuth, 2015). It remains to be determined how and to what extent these previously ‘uptake-2’ termed transporters contribute to the overall effects of 4-MMC and related substances such as 3-MMC.

In an *in vitro* release assay using rat brain synaptosomes (Walther et al., 2019), 3-MMC as well as 4-MMC triggered efflux in a concentration-dependent manner at NET ( $\text{EC}_{50}$  for 3-MMC and 4-MMC, respectively: 27 nM and 63 nM) and DAT ( $\text{EC}_{50}$  for 3-MMC and 4-MMC, respectively: 27 nM and 49 nM), with slightly lower potency at SERT ( $\text{EC}_{50}$  for 3-MMC and 4-MMC, respectively: 268 nM and 118 nM). From these data, the DAT/SERT ratios calculated for 3-MMC and 4-MMC were 9.9 and 2.4, which meant that 3-MMC was more potent at DAT and less potent at SERT compared to 4-MMC.

#### 4.2.1.3 Interactions with neurotransmitter receptors

Receptor binding and functional activation studies carried out with recombinant receptor preparations indicate that the pharmacological profile of 3-MMC *in vitro* differs somewhat from that of 4-MMC. 3-MMC bound to the 5-HT<sub>2A</sub> receptor (Luethi et al., 2018) as previously shown for 4-MMC and MDMA (Eshleman et al., 2013; Simmler et al., 2013) and typically for serotonergic hallucinogens (Eshleman et al., 2014; Nichols, 2016). Interestingly, 3-MMC has a lower affinity in binding to the alpha1-adrenergic receptor while the affinity of 4-MMC is 8 times higher. Conversely, 3-MMC showed a 10-fold higher affinity at the alpha2-adrenergic receptor. Similar to 4-MMC, 3-MMC also binds to the trace amine-associated receptor 1 (TAAR1) (Luethi et al., 2018). For TAAR1, certain species-related differences

may be noted. The activation potency, as expressed by EC<sub>50</sub> values, of 3-MMC was found to be comparable to 4-MMC in one study (Luethi et al., 2018) but different in another (Simmler et al., 2016); the latter study reported negligible activation in human TAAR1 preparations for both 3- and 4-MMC. None of the drugs were cytotoxic at the investigated concentrations. Table 3 summarizes the transporter and receptor binding affinities and activation energies.

TABLE 3  
Monoamine transporter and receptor binding

		3-MMC	4-MMC
NET	K <sub>i</sub>	5.6 ± 1.5	>26
DAT	K <sub>i</sub>	3.2 ± 0.6	2.9 ± 0.2
SERT	K <sub>i</sub>	>22	>22
D <sub>2</sub>	K <sub>i</sub>	>12	>11
α <sub>1A</sub>	K <sub>i</sub>	7.9 ± 0.2	1.1 ± 0.1
α <sub>1A</sub>	K <sub>i</sub>	1.1 ± 0.1	11 ± 1
5-HT <sub>1A</sub>	K <sub>i</sub>	4.8 ± 0.5	>17
5-HT <sub>2A</sub>	K <sub>i</sub> EC <sub>50</sub>	3.4 ± 0.8 >20	1.6 ± 0.2 0.36 ± 0.19
5-HT <sub>2B</sub>	EC <sub>50</sub>	>20	>10
5-HT <sub>2C</sub>	K <sub>i</sub>	3.6 ± 1.0	8.1 ± 5.4
TAAR1 <sub>human</sub>	EC <sub>50</sub>	>10 <sup>a</sup>	>30 <sup>a</sup>
TAAR1 <sub>rat</sub>	K <sub>i</sub> EC <sub>50</sub>	5.7 ± 1.4 <sup>a</sup> >10 <sup>a</sup>	5.0 ± 0.1
TAAR1 <sub>mouse</sub>	K <sub>i</sub> EC <sub>50</sub>	11.1 ± 1 <sup>a</sup> 3.8 ± 0.04 <sup>a</sup>	12.1 ± 1

Note: affinities K<sub>i</sub> values are given as μM (mean±standard deviation); activation efficacy is expressed relative to 5-HT (100 %) (Luethi et al., 2018). Legend: (<sup>a</sup>) Simmler et al., 2016

### *Effects on neuronal activity*

One recent approach to consider alternative pharmacotoxicology screening procedures involved the *in vitro* assessment of neuronal activity, which reflects the effects of a drug on multiple targets, in contrast to single targets such as monoamine transporters or receptors. The changes in activity upon drug exposure have been studied by Zwartsen et al. (2020). The effects after acute (30 min) and prolonged (4.5 h) exposure to a range of synthetic cathinones, including 3-MMC and 4-MMC, on spontaneous neuronal activity using rat primary cortical cultures grown on microelectrode arrays (MEAs) has been explored as an integrated endpoint for what was interpreted as neurotoxicity (Zwartsen et al., 2020). In the study, all cathinones transiently inhibited mean spike rate, mean burst rate, and mean network burst rate after acute exposure. For 3-MMC, the respective IC<sub>50</sub> values were 65, 79, and 67 µM. For 4-MMC, the respective IC<sub>50</sub> values were 101, 118, and 120 µM. The extent these observations can be correlated with neurotoxicity in the human brain remains warrants further study.

#### **4.2.2. *In vivo* data**

Information on the *in vivo* effects of 3-MMC is limited. In a pharmacokinetic study with pigs, intravenous or oral administrations of 3-MMC induced a 50 % decrease in plasma triglyceride levels which remained at the same reduced levels for at least 48 h after a single intravenous dose (9 mg per animal) or 24 after the end of a multiple oral drug regimen lasting for five days (5 x 90 mg per animal); other biochemical markers remained within the respective reference values (Shimshoni et al., 2015). In this study, a statistically significant reduced feed intake and lower body weight of the treated animals on the eight day were also noted (1 kg weight gain for the treated versus 3 kg weight gain for untreated animals).

A number of studies investigated *in vivo* effects of 4-MMC. A brief summary is provided below, however, considering different pharmacological profiles of 3-MMC and 4-MMC revealed in *in vitro* studies (see Section 4.2.1 above) caution should be exercised when extrapolating these observations to 3-MMC.

Kehr and colleagues collected extracellular dopamine and serotonin by *in vivo* microdialysis in the conscious rat. They injected 4-MMC (3 mg/kg) subcutaneously, which increased the release of dopamine by 496 % and of serotonin by 911 %, while release induced by (+)-amphetamine enhanced release of dopamine by 412 % and of serotonin by 165 % and by MDMA to only 235 % in the case of dopamine and to 911 % for serotonin (Kehr et al., 2011); these experiments supported thereby the notion that 4-MMC does not only stimulate transporter-mediated release of substrates under *in vitro* conditions but also confirmed that 4-MMC displayed amphetamine-like stimulant activity in an *in vivo* setting. Locomotor activity was increased most by amphetamine, whereas both 4-MMC and MDMA showed about three times lower and shorter-lasting effects (Kehr et al., 2011).

With respect to locomotor activity, similar results were found by Lisek and colleagues who report that 4-MMC induces locomotor activity in rats in a dose-dependent manner (Lisek et al., 2012). Baumann and colleagues reported the results from an *in vivo* microdialysis study in the rat nucleus accumbens (Baumann et al., 2012) where it was shown that i.v. administrations of 0.3 and 1.0 mg/kg 4-MMC produced dose-related increases in extracellular dopamine and serotonin, with greater effects on serotonin. 4-MMC acted as a weak motor stimulant when compared with methamphetamine. Repeated administration of 4-MMC (3.0 and 10.0 mg/kg, s.c., 3 doses) caused hyperthermia but no long-term change in cortical or striatal amines, whereas similar treatment with MDMA (2.5 and 7.5 mg/kg, s.c., 3 doses) evoked robust hyperthermia and persistent depletion of cortical and striatal serotonin (Baumann et al., 2012). However, this is in contrast to the results reported by Wright et al. who report on the thermoregulatory and locomotor effects of 4-MMC; they monitored male Wistar and Sprague-Dawley rats after subcutaneous administration of 4-MMC (1–10 mg/kg) using an implantable radiotelemetry system under conditions of low (23 °C) and high (27 °C) ambient temperature and report a distinct reduction in body temperature at all starting conditions (Wright et al., 2012). The same group also observed a significant decrease in body temperature, again in two different rat strains using a 4-MMC self-administration paradigm (Aarde et al., 2013).

Conflicting evidence related the lack of monoamine depletion was presented by Hadlock and colleagues: here, the results revealed that 4-MMC (i) caused a substantial depletion of dopamine and serotonin from rodent brain, thus pointing to a potential neurotoxic effect of 4-MMC, (ii) was self-administered by rodents, pointing to a potential abuse liability (Hadlock et al., 2011). The last part was lent support by the previously mentioned study conducted by Aarde and colleagues (Aarde et al., 2013) who also ascribed self-administration properties to 4-MMC larger than MDMA and less pronounced than MDPV.

### 4.3. Psychological and behavioural effects

To date, no published formal studies assessing the psychological and/or behavioural effects of 3-MMC in humans are available. Some studies examined the behavioural effects of 3-MMC in animals though only a few systematically examined 3-MMC. There is some information on the psychological and/or behavioural effects of 3-MMC in conjunction with the clinical reports of acute 3-MMC toxicity. Some reports including subjective dose–response information have been disseminated by people who report the use of 3-MMC in ‘trip reports’ on Internet forums dedicated to information-exchange on psychoactive drugs (e.g. Bluelight or Erowid; Bäckberg et al., 2015).

In general, many ring-substituted synthetic cathinones have been reported to exert similar effects compared to other amphetamine-type stimulant drugs (Karinen et al., 2014). Since 3-MMC is a positional isomer of 4-MMC, it may be assumed that the psychostimulant properties in humans associated with a typical dose might include alertness, euphoria, excitement, increased physical energy, feelings of empathy, stimulation and enhanced

awareness (Adamowicz et al., 2014, 2016; Dias Da Silva et al., 2019; Sande et al., 2016). It appears that the effects of 3-MMC are less pronounced than those of 4-MMC (considered two to five times less powerful according to user reports). Ameline et al. (2019) claimed the effects to be comparable to MDMA and amphetamine but with less intensity. The authors also considered the effects of cocaine, ethylphenidate and methylenedioxypyrovalerone (MDPV) to include so-called roller coaster like sensations whereas the effects induced by 3-MMC were considered rather 'constant' and 'clean' according to user reports (Ameline et al., 2019). 3-MMC has been reported to be stimulating on a physical and psychological level, euphoric, and in some reports empathogenic-like with enhancement of sexual arousal and libido.

Users describe the onset of the first effects after oral administration of 3-MMC between 20 and 30 min and peak effects after 50 min, lasting up to 3–4 h (Ameline et al., 2019). With respect to the declining phase of the compound effect (the 'comedown'), users describe the effects of 3-MMC as softer than those of 4-MMC and, therefore, preferable (Adamowicz et al., 2016). The effects of 3-MMC have been described to be similar to MDMA and the effects are subjectively not felt to be as strong as with 4-MMC, which may, however, lead to increased and/or repeated doses to achieve the desired effects (Adamowicz et al., 2014).

For example, one of the persons reporting the use of 3-MMC on Internet forum [bluelight.org](http://www.bluelight.org) compares the effects of 3-MMC and 4-MMC as follows (user 'adder' on [bluelight.org](http://www.bluelight.org)):

'It's very easy to tell apart 3-MMC and 4-MMC, 3-MMC lacks the powerful buzz of 4-MMC when it comes up, and when it peaks, the overall feeling of well-being is somewhat 'blurred' and much less intense. What I like about 4-MMC is that surge of warmth and fullness in my head when it hits, with 3-MMC there is none. With 4-MMC I would start feeling cold in like 3 hours after a single dose, with 3-MMC it's almost instant. Re-dosing 3-MMC doesn't give any more empathogenic effects, actually 3-MMC is hardly empathogenic at all for me, often it would just produce some stimulation less pronounced but much dirtier than plain amphetamine with no willingness to talk, definitely not resembling methcathinone though (methcathinone is really a stimulant all the way – hard to fall asleep when it wears off, a lot like methamphetamine but less powerful and shorter living, more euphoric and more 'chaotic' compared to amphetamine for me). Also, after binging with 3-MMC I wouldn't see trees as people etc., well, at least, it wasn't as psychotic. Also, I noticed that re-dosing 3-MMC made me nauseous at 'satisfying' doses unlike 4-MMC. It's not really worth the load it puts on the heart, and it somehow pushes me away contrary to 4-MMC, so a lot less moreish too. I can't see it growing on me as mephedrone did, no way.'<sup>(31)</sup>

The user self-reports need to be taken with caution as they reflect subjective impressions of individuals and cannot substitute a formally conducted, standardized study on the

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<sup>(31)</sup> [http://www.bluelight.org/vb/threads/608696-3-MMC-\(3-Methylmethcathinone\)-Megathread-\(v1\)/](http://www.bluelight.org/vb/threads/608696-3-MMC-(3-Methylmethcathinone)-Megathread-(v1)/) (accessed October 2021).

psychological and behavioural effects of the compound. In addition, the compound 3-MMC is rarely used as the only drug which means that considerable multi-drug use might have to be considered (e.g. amphetamine, MDMA, cocaine or cannabis). Also, users might be unaware of the identity and/or composition and the dose of the substance they are consuming.

Finally, as mentioned above in a recent patent application describing four human case studies carried out in psychotherapeutic settings the effect of oral doses ranging from 200 to 400 mg lasted up to 4 hours (Golan et al., 2019).

#### **4.4. Safety pharmacology**

In a panel of genotoxicity tests (Al-Serori et al., 2016), no evidence for the induction of gene mutations in a Salmonella/microsome assay was found, but 3-MMC caused positive results in a single cell gel electrophoresis assay that can detect single and double strand breaks of DNA in a human derived buccal cell line (TR146). Negative results obtained in the single cell gel electrophoresis assay experiments with lesion specific enzymes (FPG and Endo III) show that 3-MMC does not cause any oxidative damage of DNA. In experiments with exogenous liver enzyme homogenate (S9) containing enzymes involved in phase I metabolism, no evidence was found of increased DNA damage in the used concentration range of 0.01 to 1.00 mM of 3-MMC; however, a moderate reduction of comet formation was observed which is likely to be due to protein binding effects.

Since the liver is one of the main sites of cathinone metabolism (Valente et al., 2014) it constitutes a prime target for their harmful effects especially upon oral ingestion. The hepatotoxicity of 3-MMC has been examined (Dias da Silva et al., 2019). In these experiments hepatocytes were isolated from Wistar rats and were exposed for 24 h to 3-MMC at concentrations ranging from 31 nM to 10 mM. 3-MMC induced toxicity was perceived at the lysosome at lower concentrations (no observed effect concentration (NOEC): 312.5 µM), compared to mitochondria (NOEC: 379.5 µM) and cytoplasmic membrane (NOEC: 1.04 mM). Higher 3-MMC concentrations increased the amount of intracellular reactive species. Both intrinsic and extrinsic apoptosis pathways were significantly elevated at 3-MMC concentration of 10 µM. Necrosis and autophagy prevail at 3-MMC concentrations higher than 10 µM, based on nuclear morphology and formation of cytoplasmic acidic vacuoles. The authors discuss a role of 3-MMC metabolism for the hepatotoxicity of this compound, which seems to be induced both by autophagic and apoptotic/necrotic mechanisms.

It was also noted that inhibition of CYP2D6 and CYP2E1 diminished 3-MMC cytotoxicity suggesting the involvement of these enzymes in the toxicological effects of 3-MMC and raising the possibility of harmful drug-drug interactions in multidrug users.



A number of cases were observed with liver injury or abnormal liver function as clinical adverse effects associated with 4-MMC use (Schifano et al., 2012). Similarly, 4-MMC was shown to induce liver damage in animal models as well (Tarkowski et al., 2018), thus, supporting some of the observations on 3-MMC reported by Dias Da Silva et al. (2019) *in vitro*.

In addition, there have been observations on 3-MMC as well as 4-MMC-related adverse effect affecting specific organ systems. For example, amphetamine-like stimulants in general have been implicated in causing neurotoxicity, hyperthermia and significant effects on the cardiovascular system (Davidson et al., 2001; Docherty et al., 2021, Levi et al., 2012).

The detrimental effects on the cardiovascular system can be the result of a plethora of different activities in both the central nervous system and the peripheral nervous and organ system. Amphetamine-type stimulants increase the heart activity by stimulation in the brain which directly stimulates the heart, but these effects will, in parallel, be also compounded by hyperthermia, peripheral vasoconstriction and thereby increasing blood pressure (Docherty et al., 2021). A sudden death resulting from such manifold of cardiovascular issues may follow to the use of these compounds.

In the case of 4-MMC, a clinical study has been conducted (Papaseit et al., 2016) starting with a clinical pharmacological study of 4-MMC's effect in comparison to MDMA with outcome variables which included physiological, subjective, and psychomotor effects, and pharmacokinetic parameters (Papaseit et al., 2016). 4-MMC increased systolic and diastolic blood pressure significantly, as well as the heart rate and the pupillary diameter. 4-MMC elicited stimulant-like effects, euphoria, and induced well-being and changes in perception similarly to MDMA administration; however, 4-MMC's effects peaked earlier and were shorter in duration compared to MDMA in accordance with maximal plasma concentration values for 4-MMC and MDMA (1.25 h and 2.00 h, respectively; Papaseit 2016).

These authors also report that 4-MMC exhibits high abuse liability and suggest that the earlier onset and shorter duration of effects of 4-MMC, probably related to its short elimination half-life, might explain a more compulsive pattern of use as described by the users (Papaseit et al., 2016; Valente et al., 2014). In a follow-up observational study, mephedrone self-administrations (intranasal and oral) in people experienced in substance use led to enhanced ratings of euphoria and well-being effects and increased cardiovascular effects (Papaseit et al., 2021).

#### **4.5. Pharmacokinetics**

The pharmacokinetics of 3-MMC have so far only been investigated in pigs (Shimshoni et al., 2015). Detailed data on the metabolic transformation of 3-MMC in humans are not

available; however, several clinical studies involving 4-MMC have been conducted that included the determination of pharmacokinetic parameters.

The maximal plasma concentration values for 4-MMC and MDMA peaked at 1.25 h and 2.00 h, respectively (Papaseit et al., 2016). The elimination half-life for 4-MMC was considerably shorter than for MDMA (2.15 h and 7.89 h, respectively; Papaseit et al., 2016) and comparable to the half-life of 3-MMC determined in the pig study (Shimshoni et al., 2015).

Self-administration of intranasal mephedrone have been followed by measurements of oral fluid concentrations which were observed to increase rapidly, reaching a peak after 1 h followed by a rapid decreased after 4 h.  $C_{max}$  values of 4950 ng/mL were determined at  $T_{max} = 1$  h. At the 4 h time point, the mephedrone concentration was 9 times lower compared to  $C_{max}$ . The  $AUC_{0-4 h}$  was 7917 ng·h/mL and oral fluid mephedrone concentrations varied considerably among oral and intranasal doses and subjects (Papaseit et al., 2021).

#### **4.5.1. Pharmacokinetic parameters of 3-MMC in comparison to 4-MMC**

##### **4.5.1.1. Absorption**

Shimshoni and colleagues administered the hydrochloride salt form of 3-MMC orally or via intravenous injection to three male pigs (Landrace, no further specification of the breed). A single oral dose of 3 mg/kg of the drug resulted in a peak plasma concentration of 3-MMC ( $C_{max} = 27$  mg/L) at 5–10 min (Shimshoni et al., 2015). The oral bioavailability of the drug was only 7 % and occurred during the initial 12 min (>80 % of the overall absorbed drug). In case of 4-MMC, the oral pharmacokinetic parameters determined in rats revealed that the  $C_{max}$  values were achieved rapidly and showed a  $T_{max}$  within 0.43–0.93 h. The plasma concentrations decayed to undetectable levels at around 9 h (Martínez-Clemente et al., 2013).

Similar to 3-MMC, also 4-MMC has been shown to display a low absolute oral bioavailability of 7.3 % and 10 % (for 30 and 60 mg/kg 4-MMC, respectively; Martínez-Clemente et al., 2013), though species differences should be taken into account.

It has been suggested that the poor oral bioavailability results from a possible interaction with efflux transporters in the intestinal epithelia (Ferreira et al., 2019). The low oral bioavailability may explain the use of 3-MMC via alternative administration routes such as insufflation (Shimshoni et al., 2015).

In the pig pharmacokinetic study, a single intravenous dose of 0.3 mg/kg of 3-MMC resulted in a rapid decay of the plasma levels. After 4 h 3-MMC was almost undetectable (detection limit of the method was 0.1 mg/L) (Shimshoni et al., 2015).

Similarly, the observed plasma concentrations after intravenous administration of 4-MMC (10 mg/kg) to rats reveal that the drug was almost undetectable at around 4 h after administration (Martínez-Clemente et al., 2013). In the case of 4-MMC, other authors have reasoned that the pharmacokinetic characteristics of the drug including the relatively rapid loss from plasma and concomitant decay of psychoactive effects would underpin the need for binging and mixing different application routes to achieve both rapid and long-lasting effects (Valente et al., 2014).

#### 4.5.1.2. Distribution

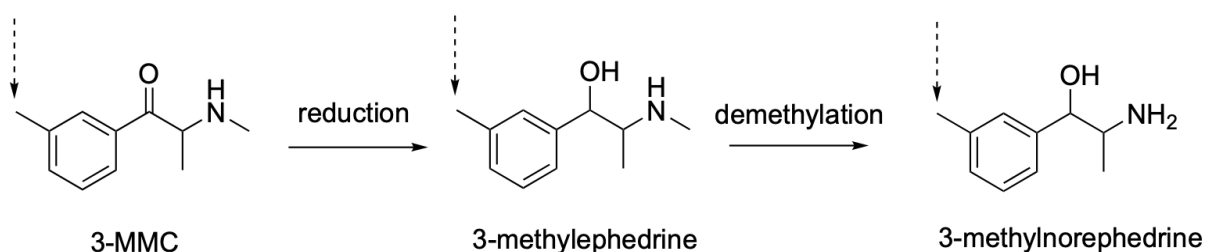
In the male pig, 3-MMC had a total clearance of 199 L/h and a volume of distribution of 240 L (Shimshoni et al., 2015). Analysis of brain and liver tissues indicated 3-MMC concentrations below detectable level (0.5 µg/kg by LC-MS/MS method) 24 hours after last dosage. The study does not contain protein binding results for 3-MMC, however, the percentage of 4-MMC protein binding has been determined in the male rat to amount to 22 % (Martínez-Clemente et al., 2013). In the rat, brain levels of 4-MMC have been assessed to yield 104 ng per gram wet tissue, resulting in a ratio of brain levels to free plasma concentration determined as 1.85 (Martínez-Clemente et al., 2013).

#### 4.5.1.3. Metabolism

There is only scarce information on the metabolism of 3-MMC to date; however, based on information obtained from the combined analysis by liquid chromatography and high-resolution mass spectrometry of pubic hair, it is known that 3-methylephedrine and 3-methylnorephedrine are metabolites of 3-MMC (Frison et al., 2016). A hypothetical metabolic human pathway was proposed and presented in Scheme 6.

#### SCHEME 6

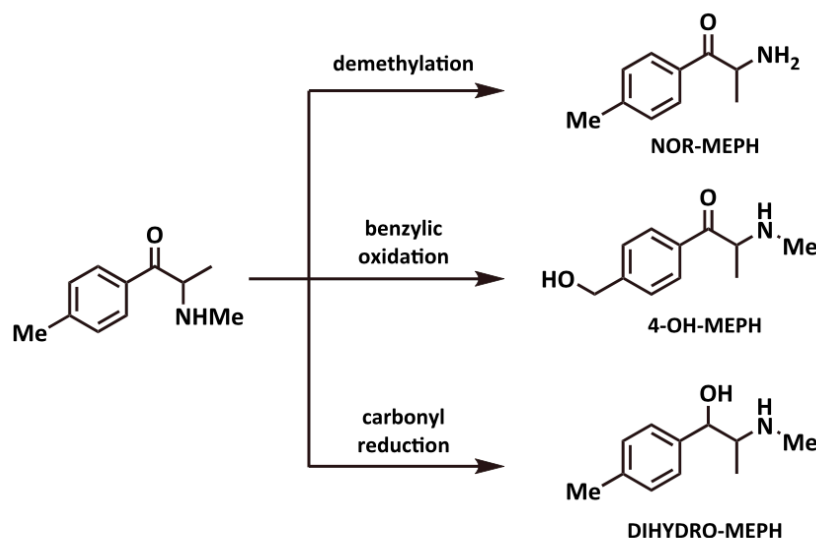
##### Hypothetical metabolism of 3-MMC into 3-methylnorephedrine through $\beta$ -keto-reduction



Note: (Coppola et al., 2012) followed by *N*-demethylation (Valente et al., 2014) into 3-methylnorephedrine (Frison et al., 2016). Broken line arrows indicate a potential hydroxylation site at the methyl group substituent on the benzene ring.

The relevance of the metabolism for the pharmacological and toxicological profile of 3-MMC is yet to be revealed. In case of 4-MMC, Meyer et al. (2010) first reported on the hepatic metabolism of 4-MMC and detailed three main metabolic pathways (Scheme 7): (i) *N*-demethylation to form 4-methylcathinone or nor-mephedrone; (ii) hydroxylation of the 4-methyl ring-substitution to form 4-hydroxytolylmephedrone (4-OH-mephedrone); and (iii) reduction of the  $\beta$ -keto-oxygen group, which forms dihydromephedrone (Meyer et al., 2010). Pedersen and co-workers (Pedersen et al., 2013) identified cytochrome P450 2D6 (CYP2D6) as the main enzyme responsible for the phase 1 metabolism of 4-MMC in humans and detected nor-mephedrone, 4-OH-mephedrone and dihydromephedrone in human urine specimens (Pedersen et al., 2013).

## SCHEME 7

**Proposed pathways for the metabolism of mephedrone to its phase I metabolites**

Note: (i) demethylation forms 4-methylcathinone (NOR-MEPH); (ii) benzylic oxidation forms 4-hydroxytolylmephedrone (4-OH-MEPH); (iii) carbonyl reduction forms dihydromephedrone (DIHYDRO-MEPH; scheme reproduced from Mayer et al., 2016).

Mayer and colleagues have examined the bioactivity of metabolites of 4-MMC in HEK293 cells expressing monoamine transporters and rat brain synaptosomes: 4-MMC and its metabolites interacted with monoamine transporters (by inhibiting the re-uptake of substrates), nor-mephedrone and 4-OH-mephedrone served as transportable substrates and led to the induction of transporter-mediated release (Mayer et al., 2016). When administered to rats, 4-MMC and nor-mephedrone produced elevations in extracellular dopamine and 5-HT, whereas 4-OH-mephedrone did not. Similarly, 4-MMC and nor-mephedrone, but not 4-OH-mephedrone, induced locomotor activity. A subsequent study compared the effects of the enantiomers of the phase 1 metabolites nor-mephedrone, 4-

hydroxytolyl-mephedrone (4-OH-mephedrone) and dihydro-mephedrone on (i) DAT, NET and SERT mediated substrate fluxes and (ii) determined their binding affinities towards a battery of monoamine receptors (Mayer et al., 2019b). No marked differences were detected at DAT and NET. However, at SERT, the (*S*)-enantiomers of nor-mephedrone and 4-OH-mephedrone were several times more potent than the corresponding (*R*) enantiomers. Moreover, the (*R*)-enantiomers were markedly less effective as releasers at SERT. (*S*)-Normephedrone displayed moderate affinities towards human alpha1A, human 5-HT2A and rat and mouse TAAR 1. These results demonstrate that stereochemistry dictates the pharmacodynamics of the phase-1 metabolites of mephedrone at SERT, but not at DAT and NET, which manifests in marked differences in their relative potencies, i.e. DAT/SERT ratios (Mayer et al., 2019b). These findings have also been supported by findings of less abundant metabolites of 4-MMC, expand the previous studies highlighting the importance of the stereochemistry in the pharmacodynamics of phase-1 metabolites of 4-MMC (Niello et al., 2021). Importantly, 3-MMC also contains a chiral centre, however, the functional effects and possible pharmacological differences of the (*R*)- and (*S*)-enantiomers of 3-MMC have not been assessed so far. They might also follow the example of the positional isomer 4-MMC and display differences in eliciting transporter-mediated efflux *in vitro* and stimulant behaviour *in vivo*; however, this warrants further investigation.

#### 4.5.1.4. Excretion

The pharmacokinetics of 3-MMC appears to follow a one-compartment model in the pig (Shimshoni et al., 2015). In the rat, Martínez-Clemente et al. (2013) have fitted their data on 4-MMC to a two-compartment model. The total clearance in the study in pigs represented more than the sum of liver and kidney blood flow (88 L/h; body weight 30–40 kg; Shimshoni et al., 2015). This may suggest that additional elimination sites or mechanisms besides hepatic and renal metabolism could exist; it may be an alternative pathway possible via other transporter such as ABC transporters or OCTs as alluded to above. The elimination half-life of 3-MMC was 0.83 h which supports the ascertained values for the total clearance and volume of distribution. Most of the dose was readily excreted after 4 h of administration and the excretion was independent of the administration route, either via injection or orally (Shimshoni et al., 2015).

Table 4 summarises the pharmacokinetic parameters of 3-MMC following consecutive single intravenous and oral administration to three male pigs (three months old, weighing 28–34 kg) with a washout period of three days between both administration mode in comparison to the parameters of 4-MMC determined in male Sprague-Dawley rats (Martínez-Clemente et al., 2013).

TABLE 4

**Pharmacokinetic parameters of 3-MMC in the pig (Shimshoni et al., 2015) in comparison to 4-MMC in the rat (Martínez-Clemente et al., 2013)** (Table reproduced from Shimshoni et al., 2015)

Mode of administration	Pharmacokinetic parameter	3-MMC Mean±standard deviation	Mephedrone <sup>a</sup> Mean
Intravenous (i.v.) administration	Dose (D)	0.3 mg/kg	9 mg/kg
	Clearance (CL)	199±55 L/h	1.7 L/h
	Apparent volume of distribution (V)	240±84 L	0.5 L (at steady-state)
	Half-life $t_{1/2}$	0.83±0.1 h	0.4 h ( $t_{1/2\beta}$ )
	$k^b$	0.84±0.1 h <sup>-1</sup>	–
Oral administration (p.o.)	Area under the curve (AUC)	48±15 µg×h/L	1332 µg×h/L
	Dose (D)	3 mg/kg	30 mg/kg
	AUC	31±11 µg×h/L	294 µg×h/L
	Bioavailability (F)	7.0±2	7.3
	$T_{max}^c$	0.08 h	0.9 h
	$C_{max}^c$	27±5 µg/L	331 µg/L
	$k_a^c$	40.9 h <sup>-1</sup>	0.3 h <sup>-1</sup>

<sup>a</sup> The pharmacokinetic profile was determined in Sprague-Dawley rats and fits a two-compartment model (Martínez-Clemente et al., 2013).

<sup>b</sup> Elimination rate constant.

<sup>c</sup> Time at maximal concentration ( $T_{max}$ ), the maximal concentration ( $C_{max}$ ) and absorption rate constant ( $k_a$ ) were obtained from the predicted concentration vs time curve calculated using the Gauss-Newton method utilizing the WinNonline nonlinear estimation program version 4.1.

## 4.6. Toxicology

The acute and prolonged effects of 3-MMC and 4-MMC on neuronal activity at physiological and hyperthermic conditions were determined. Neuronal activity of rat cortical cultures grown on microelectrode arrays led to a decrease in neuronal activity, especially upon acute exposure to compound, all drugs concentration- and temperature-dependently inhibited neuronal activity (Zwartsen et al., 2020). The extent to which these observations relate to neurotoxicity in the human brain remains to be investigated.

Dias Da Silva et al. (2019) investigated the potential hepatotoxicity of 3-MMC using Wistar rat hepatocytes and evaluated the modulatory effects of cytochrome P450 (CYP) inhibitors on 3-MMC hepatotoxicity. These authors point to a role of drug metabolism in the hepatotoxic effects of 3-MMC, which seems to be triggered both by autophagic and apoptotic/necrotic mechanisms. The authors also stated that 3-MMC was considered ‘generally less damaging to mitochondria than most cathinones and other substituted amphetamines’.

In a study by Zhou et al. (2019), all investigated synthetic cathinones, including 3-MMC, have been shown to (i) deplete ATP, (ii) disturb the cellular membrane and its integrity, and (iii) increase superoxide levels in C2C12 myoblasts in a concentration-dependent manner (Zhou et al., 2019). Therefore, in addition to sympathetic nervous system effects and

strenuous muscle exercise, direct effects of some cathinones on skeletal muscle mitochondria may contribute to myotoxicity in susceptible cathinone users (Zhou et al., 2019).

A recent study in mice of both sexes compared the lethal doses of 4-MMC in comparison to methamphetamine and MDMA (Muskiewicz et al., 2020). The determined LD<sub>50</sub> values for methamphetamine and MDMA were 85 and 101 mg/kg respectively, similar to previous observations. The LD<sub>50</sub> for 4-MMC was 119 mg/kg. For all drugs, death was associated with seizure. Contrary to initial expectations, 4-MMC did not have a LD<sub>50</sub> values lower than methamphetamine or MDMA, hence, it was considered less potent than methamphetamine and MDMA (Muskiewicz et al., 2020).

### ***Risk-modifying factors***

A major risk-modifying factor in terms of toxic effects on various different organ systems is represented by drug-drug interactions, where for instance ethanol may enhance the detrimental effects of 3-MMC; however, this has only been examined for 4-MMC (Papaseit et al., 2020). Other concomitantly used 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 – these are widespread and discussed further below.

### ***Uncertainty analysis***

The instability of 3-MMC, especially in free base form, may pose problems, particularly if the material is stored under improper conditions (Adamowicz et al., 2016; also see Shimshoni et al., 2015). Studies show that the storage of frozen (– 20 °C) blood does not cause degradation of 4-MMC, while temperature of 4 °C and room temperatures significantly propel the degradation of the compound (Adamowicz et al., 2019; Johnson et al., 2013). Recent reports suggest that such degradation processes are also to be observed for 3-MMC (Jamey et al., 2016). Therefore, in the present state of knowledge correlating the blood concentrations of 3-MMC with symptoms and degree of impairment may not be feasible.

## **4.7. Abuse liability and dependence producing potential**

Many synthetic cathinones have been associated with abuse liability (Baumann et al., 2018) and whilst few data are available on 3-MMC, there is a wealth of data on 4-MMC which has been outlined above (section on ‘Pharmacological and toxicological properties’).

#### **4.7.1. *In vitro* data**

The *in vitro* data on 3-MMC obtained in cultured cell lines expressing the monoamine transporters 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-MMC acts as a stimulant in terms of inducing release of the neurotransmitters dopamine, norepinephrine and serotonin via DAT, NET and SERT in a way similar to 4-MMC (Eshleman et al., 2019; Luethi et al., 2018). However, when considering the DAT/SERT ratio as a preliminary or proxy indicator of reinforcing effects or abuse (dependence), DAT/SERT ratios estimated in various studies are consistently several-fold higher for 3-MMC as for 4-MMC. In addition, experiments performed in rat brain synaptosomes came to the same conclusion in an *ex vivo* paradigm, thus substantiating the findings over different species (Blough et al., 2019; Walther et al., 2019).

This has been interpreted to underlie abuse liability because the data resemble most of the amphetamine-type stimulants in this respect.

#### **4.7.2. *Animal data***

With respect to 3-MMC, there is no animal study available that examined the abuse potential. However, several studies on 4-MMC examined the potential of the drug to induce locomotion: the acute exposure to 4-MMC increased the ambulatory activity of rats in a concentration-dependent manner (Baumann et al., 2012; Hadlock et al., 2011; Kehr et al., 2011; Lisek et al., 2012; Martinez-Clemente et al., 2014; Motbey et al., 2012).

4-MMC has been shown to be self-administered in the rat (intravenously; Hadlock et al., 2011; Aarde et al., 2013; Motbey et al., 2012), similar as methcathinone was examined as a stimulant and laid the foundation that cathinones may substitute for amphetamine in drug-discrimination assays in rats (Glennon et al., 1987).

In experiments employing intracranial self-stimulation, Robinson and colleagues examined the influence of 4-MMC on brain stimulation reward. They implanted unipolar stimulating electrodes into the lateral hypothalamus of mice and compared the effects of various doses of 4-MMC and cocaine. According to their results, 4-MMC potentiates the brain stimulation reward similar to cocaine, which is indicative for its abuse potential according to the authors (Robinson et al., 2012). In addition to these *in vivo* experiments, Lisek and colleagues (2012) examined the effects of 4-MMC in a condition place preference paradigm; their results point to a preference shift detected following 4-MMC conditioning which suggests a possibility for rewarding properties, again consistent with a risk of abuse liability. However, it needs to be noted that the preference shift between the chambers occurred only at high dosage of 4-MMC (Green et al., 2014).



In addition, Lisek and coworkers show that repeated administration of 4-MMC lead to sensitization of ambulatory activity after repeated exposure (Lisek et al., 2012) which is typically discussed as a common preclinical feature of addictive substances (Robinson et al., 2008).

#### **4.7.3. Human data**

To date, there are no relevant studies examining the abuse potential of 3-MMC in humans. However, repetitive 3-MMC exposures have been claimed to result in 'significant psychological dependence' (Ameline et al., 2019) with doses used being 'quickly increased' and a decline of the effect is usually avoided by repetitive application over short time as the 'comedown' has been described to be unpleasant. However, these effects were felt to be milder compared to 4-MMC. The authors state that 'the risks are the same as MDMA or cocaine' in the short term though further explanations were not provided.

One clinical study involving the comparison between 4-MMC and MDMA has been conducted (Papaseit et al., 2017). The authors reasoned that 4-MMC exhibits high abuse liability and suggest that the earlier onset and shorter duration of effects induced by 4-MMC probably related to its short elimination half-life potentially resulting in a more compulsive pattern of use as described by people using this substance (Papaseit et al., 2017; Valente et al., 2014).

#### *Risk-modifying factors*

It has been suggested that a greater blood–brain barrier permeability of 4-MMC over methamphetamine and MDMA may produce a relatively greater reinforcing effect of the drug (Simmler et al., 2013). This effect is likely to extend to 3-MMC. Furthermore, due to other pharmacokinetic factors, there could be differences in the overall (psycho)pharmacological effects of orally, nasally, or for that matter intravenously, administered cathinones. Users noted that the 'high' obtained with the intranasal use of mephedrone was similar to or better than the high produced by cocaine (Winstock et al., 2011). In an observational study involving oral and intranasal administrations of 4-MMC by experienced substance users, it was found that mephedrone effect profiles can vary considerably depending on the route of administration due to the dose administered and the interindividual differences in pharmacodynamic and pharmacokinetic effects (Papaseit et al., 2021).

Furthermore, 3-MMC has been described to be frequently combined with other drugs as this is being used to enhance the recreational experience (Ameline et al., 2019).

Among the circumstances under which drug consumption takes place, and actually related to the risk mentioned above, new patterns and settings of use of drugs need be considered

carefully. ‘Chemsex’<sup>(32)</sup> and ‘slamsex’<sup>(33)</sup> represent a public health concern not only from poisoning from overdosing via the intravenous route, but also co-administration with other drugs to enhance the user experience can significantly increase the associated risks (Drevin et al., 2021). In addition, the risk of the occurrence of sexually transmitted diseases poses a health risk as the users may engage in riskier sexual behaviours with regard to human immunodeficiency virus and hepatitis C virus transmission (Drevin et al, 2021).

Socioeconomic conditions, for example poor living circumstances or unemployment, may increase the likelihood of abuse liability for 3-MMC. 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-MMC 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-MMC. Boredom, anxiety, reduced availability of other controlled stimulants could increase the possibility of 3-MMC use.

### *Uncertainty analysis*

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

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<sup>(32)</sup> Chemsex is a term used to describe intentional sex under the influence of psychoactive drugs, mostly among men who have sex with men.

<sup>(33)</sup> Slam is a form of chemsex in which psychostimulant drugs are administered by injection.

## 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-MMC 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.

3-MMC has been present on the European drugs market since at least June 2012. As of October 2021, the substance has been detected in 23 Member States, Turkey and Norway. These detections relate to 9 038 seizures (amounting 2.82 tonnes of seized material in all physical forms), 672 collected samples and 730 biological samples. Most of the first identifications of 3-MMC in a reporting country occurred around the date of its first identification in Europe, between 2012 and 2014 (n=17; 68 %).

The appearance of 3-MMC on the drug market in 2012 followed the introduction of increasing control measures of 4-MMC across Europe as well as in China, which at the time was identified as a main producer of 4-MMC <sup>(34)</sup> <sup>(35)</sup>. At least in part, it appears that 3-MMC is being used as a 'legal' replacement to 4-MMC. Since it first emerged in the drug market, approximately 2.63 tonnes of 3-MMC powders have been seized, including at least 2.36 tonnes by customs and 184 kg by police.

Following a decline in seizures in Europe between 2016 and 2018, coinciding with the control of 3-MMC in China in October 2015, the substance appears to have re-emerged during 2020 (Figure 2). During that year, approximately 747 kg of powders were seized, including 631 kg by customs (96 % of which originated from India) and 110 kg by police. This represents just over a quarter of the total quantity of 3-MMC powders seized since monitoring of the substance began in Europe in 2012.

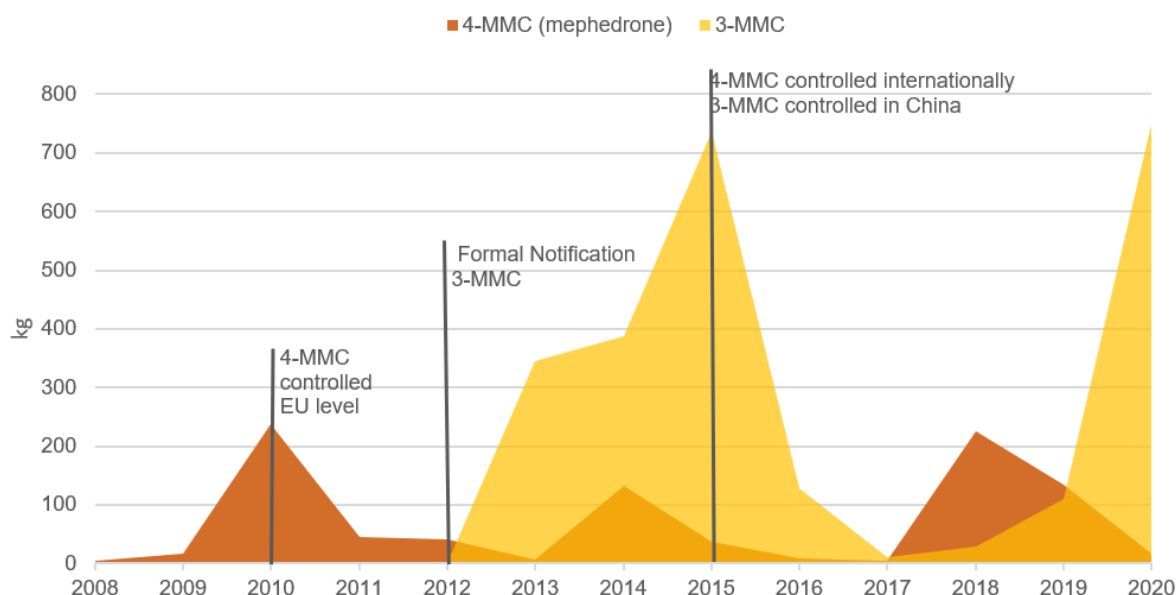
During 2021, 3-MMC continues to be imported, distributed, and used in parts of Europe; this includes a single large-scale seizure of 122 kg of powder at the external EU border, originating from India.

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<sup>(34)</sup> Council Decision of 2 December 2010 on submitting 4-methylmethcathinone (mephedrone) to control measures (2010/759/EU).

<sup>(35)</sup> Mephedrone was internationally controlled in 2015. Decision 58/1; Inclusion of mephedrone (4-methylmethcathinone) in Schedule II of the Convention on Psychotropic Substances of 1971.

FIGURE 2

**Quantity of powders containing 4-MMC (mephedrone) and 3-MMC seized in Europe 2008–2020**

Seizures of 3-MMC, alongside seizures of 3-CMC (also currently the subject of an EMCDDA risk assessment) and *N*-ethylhexedrone (internationally controlled <sup>(36)</sup>) have, in part, driven a sharp increase in the quantity of cathinone powders seized in Europe in 2020. Following a peak in 2015 and 2016, when around 1.80 tonnes of cathinone powders were seized per year, reports steadily decreased, reaching 750 kg by 2019. In 2020, seizures of approximately 3.30 tonnes of powders were reported in Europe, almost quarter of which contained 3-MMC. While information reported to the EMCDDA through the EU 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-MMC and 3-CMC. Additionally, as shown in Section 2.4, a part of the cathinone powders available in Europe are produced within the European Union.

The limited information reported to the EMCDDA and available in the literature suggests that 3-MMC is typically sold and sought after as a stimulant drug in its own right, but it may also be mis-sold as other drugs, including 4-MMC.

<sup>(36)</sup> *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.

Similar to other cathinones, such as 4-MMC, 3-MMC is typically administered by insufflation (snorting), orally, and in some cases by intravenous injection. It appears to be used by existing stimulant users, such as those who use cocaine, amphetamines, ecstasy, and other cathinones, who either add it to their existing repertoire or use it as a replacement substance. This includes recreational use, and, in some cases high risk use, such as injecting. In addition, in at least the Netherlands, it may also be used by vulnerable groups such as young people, partly because it is easily available, not controlled, and affordable.

It appears that 3-MMC is used in private spaces (such as homes and domestic parties), as well as recreational settings (such as nightclubs, bars/pubs, music festivals), and as part of chemsex settings (CAM, 2021; de Jonge et al., 2021; Drevin et al., 2021; Nijkamp et al., 2021).

Several publications report on gender and sex differences among users, the majority of cases of 3-MMC users were men (>90 %) while women accounted for less than 10 % (Adamowicz et al., 2016, Bäckberg et al., 2015). The age ranged from 17 to 50 (Adamowicz et al., 2016; Bäckberg et al., 2015).

The effect of the ongoing COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020b; WHO, 2020) on the manufacture, trafficking, distribution and use of 3-MMC is currently unknown. However, seizures of more than of 720 kg of bulk powders by customs agencies during the pandemic suggest that 3-MMC continues to be imported and distributed in Europe. It is possible that, in case of a reduced availability of controlled stimulants (such as 4-MMC and MDMA) in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including 3-MMC.

## 5.2. Information from seizures

Between 1 January 2012 and 8 October 2021, a total of 9 038 seizures, amounting to 2.82 tonnes of material (in all physical forms) were reported by 25 countries. Of these, 1.93 tonnes were reported in the period of 2012 to 2019, and 747 kg were reported in 2020 (27 % of all material seized). The remaining 138 kg were reported in 2021.

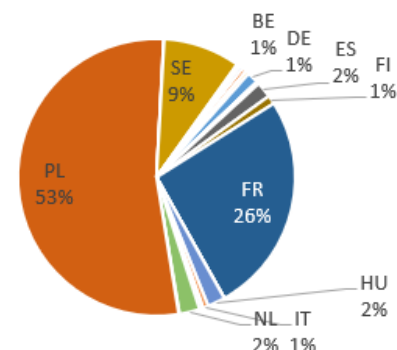
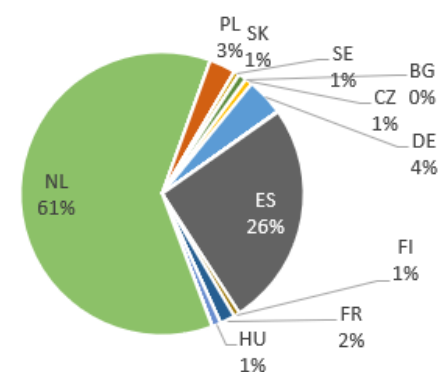
The majority of the cases reported (n = 8 343; 92 %) were seizures of powders, amounting to 2.63 tonnes. To a much lesser extent, seizures of other forms were also reported: tablets and capsules (560 cases), other or unknown physical forms (79), liquids (33), herbal material (16), and blotters (7). For this reason, the analysis in this report 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 5. These values include the period of 1 January 2012 to 8 October 2021. Approximately half of the seizures of powders (4 454 cases; 53 %) were

TABLE 5

**Number of seizures of powders containing 3-MMC and quantity seized, by country**

Country	Number of seizures (powders)	Quantity powders (kg)
Poland	4454	78.1
France	2153	45.2
Sweden	748	16.4
Netherlands	197	1613.2
Hungary	171	25.9
Spain	154	675.0
Germany	111	112.5
Finland	85	18.1
Italy	53	1.1
Belgium	43	0.7
Austria	31	0.4
Czechia	31	21.6
Latvia	27	0.1
Slovakia	19	22.6
Estonia	17	0.0
Slovenia	16	0.3
Norway	8	0.0
Lithuania	6	0.0
Portugal	5	0.5
Denmark	4	0.1
Greece	4	2.0
Luxembourg	3	0.0
Bulgaria	2	0.2
Croatia	1	0.0
<b>Total</b>	<b>8343</b>	<b>2634.2</b>

Seizures of 3-MMC powders (n)  
2012 - 2021\*Quantity of 3-MMC powders seized (kg)  
2012 - 2021\*

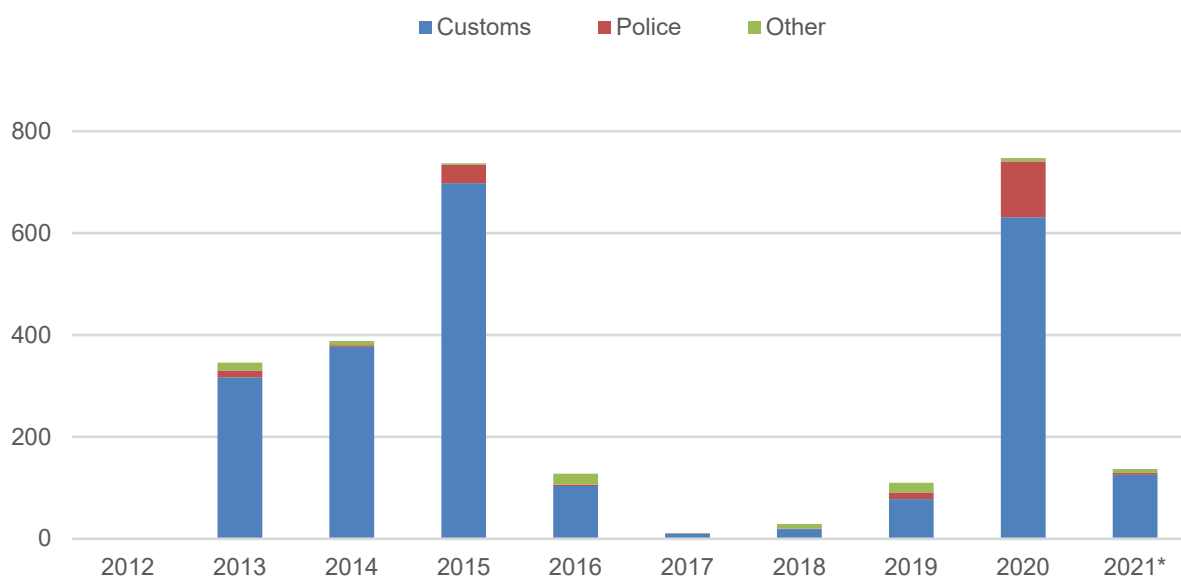
Note: The values include all seizures reported to the EMCDDA between 1 January 2012 and 8 October 2021. Quantities are expressed in kilograms and, in some cases, for quantities below 100 grams, they appear as '0' due to rounding conventions. Pie charts. Seizures and quantities of powders seized by country in Europe, 2012–2021.

(\*) 2021 data are not comparable to data from previous years.

reported by Poland. The country reporting the largest quantities of seized powders was the Netherlands (1.6 tonnes; 61 %).

A total of 8 343 seizures of 3-MMC powders were reported by police (3 365 cases; 40 %), customs (3 058; 37 %) and other authorities (1 920; 23 %) (Figure 3). A summary of the information reported is provided.

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



Note: The values include all seizures reported to the EMCDDA between 1 January 2012 and 8 October 2021.

(\*) 2021 data are not comparable to other years (see methodology).

### 5.2.1. Customs seizures

Since 2012, customs authorities have reported 3 058 seizures of 3-MMC amounting to 2.36 tonnes of powders. Of these, 1 014 seizures (757 kg; 32 % of all powders seized by customs) occurred over the course of 2020 and 2021. While most seizures were reported by French customs (2 119 cases; 69 %), the largest quantities of powders were seized in the Netherlands (1.58 tonnes; 67 % of customs seizures).

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 pure 3-MMC powders to Europe.

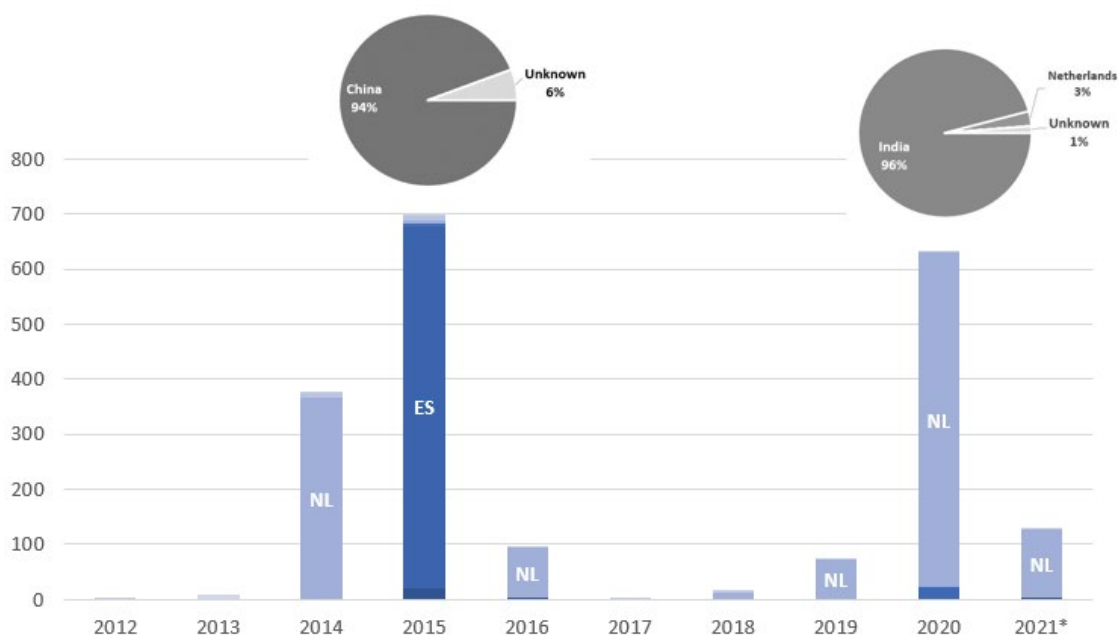
For the majority of customs seizures, the origin of the consignment was not reported (3 018 cases; 1.07 tonnes) (Figure 4). For the 40 cases where the origin of the consignment is known, the powders originated in China (5 seizures, 658 kg; all of which made by Spanish customs in 2015), India (6 seizures, 605 kg; all of which made by Dutch customs in 2020), the Netherlands (24 seizures; 18 kg), Poland (1 seizure; 5 kg), Spain (3 seizures; 0.8 kg), and Slovakia (1 seizure; less than 1 g). Additional information submitted after the data collection period indicated that 1 seizure of 122 kg by Dutch Customs in 2021 also originated in India.

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

Whenever European countries were mentioned as the country of origin (n=29), the Netherlands was the most frequently mentioned country. At least 24 seizures totalling 18 kg of powders containing 3-MMC were shipped from the Netherlands to a number of European countries (Estonia, Finland, France, Germany and Italy). Custom seizures originating in the Netherlands varied between 18 kg to 0.1 g. In one of these cases, reported by Finland, a Customs inspection in 2020 found close to 18 kg of powders containing 3-MMC which had been shipped from the Netherlands, via Germany to Finland and destined for Russia.



FIGURE 4

**Quantity of 3-MMC powders seized (kg), by customs**

Note: The values include all seizures reported to the EMCDDA between 1 January 2012 and 8 October 2021.

(\*) 2021 data is not comparable to other years – please see methodology. The country reporting the seizure is indicated in the bars; the origin of the consignment by % weight (pie charts).

In some customs seizures, 3-MMC was found as ‘crystals’ or ‘rocks’ (Figure 5). Information on the purity of the powders was typically not provided. In some cases, the powders were described as ‘pure’, especially in relation to some of the large-scale seizures being imported into the European Union. When quantitative information was available, purity was reported to be between 83–89 %. For the cases where other substances were reported, the powders typically contained other stimulants such as other cathinones (including 3-CMC, alpha-PVP<sup>(37)</sup>, ethylcathinone<sup>(38)</sup>, eutylone<sup>(39)</sup>, dibutylone<sup>(40)</sup>, pentedrone<sup>(41)</sup>, and MDPBP<sup>(42)</sup>) and, to a lesser extent, other substances such as ketamine. Adulterants and diluents reported included caffeine and benzocaine. In one case, 0.6 grams (total amount unknown) of a white powder seized in 2021 by French Customs in Postal freight was found

<sup>(37)</sup> 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one; formally notified by the EMCDDA in April 2011.

<sup>(38)</sup> 2-(ethylamino)-1-phenylpropan-1-one; formally notified by the EMCDDA in March 2008.

<sup>(39)</sup> 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one; formally notified by the EMCDDA in March 2014.

<sup>(40)</sup> 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)butan-1-one; formally notified by the EMCDDA in November 2010.

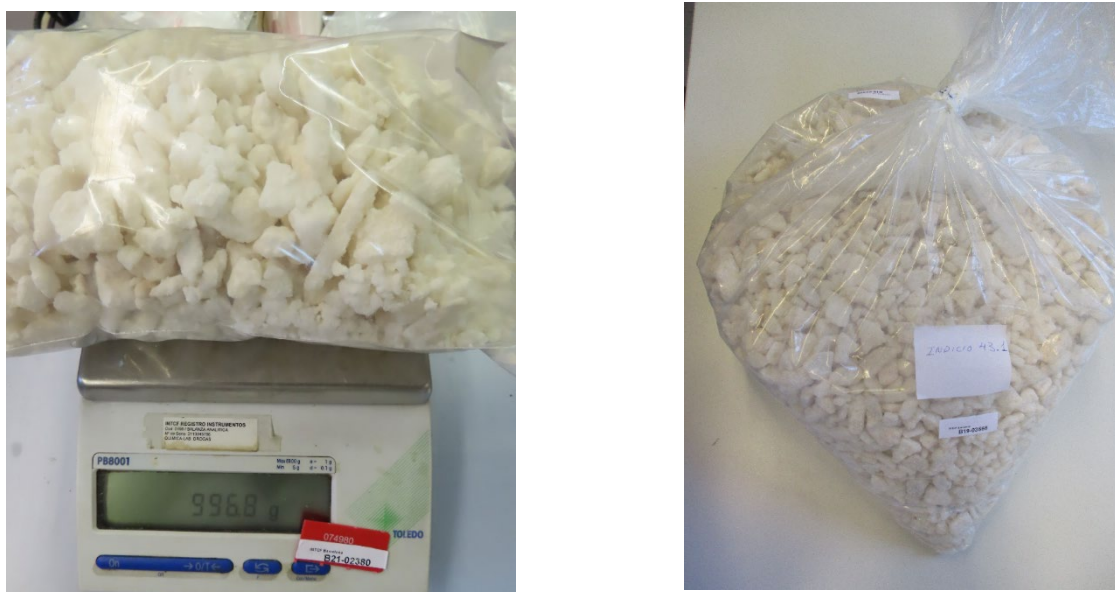
<sup>(41)</sup> 2-(methylamino)-1-phenylpentan-1-one; formally notified by the EMCDDA in September 2010.

<sup>(42)</sup> 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)butan-1-one; formally notified by the EMCDDA in November 2010.

to contain 3-MMC, MDMB-4en-PINACA <sup>(43)</sup>, 5F-EDMB-PICA <sup>(44)</sup> and benzocaine (in a mixture called 'synthacaine lite'). The consignment originated in the Netherlands.

FIGURE 5

**Seizure made by customs at International Mail Centre in Barcelona (Spain), in March 2021 (left). Origin not reported. 3-MMC was identified in 996.8 g of white powder rock. Text and markings on the packaging/container: '074980'; Seizure of 8 kg of 3-MMC powders within a larger seizure of 11 NPS (total weight 24 kg) (right), by the Spanish National Police in March 2019 in Barcelona (Spain).**



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

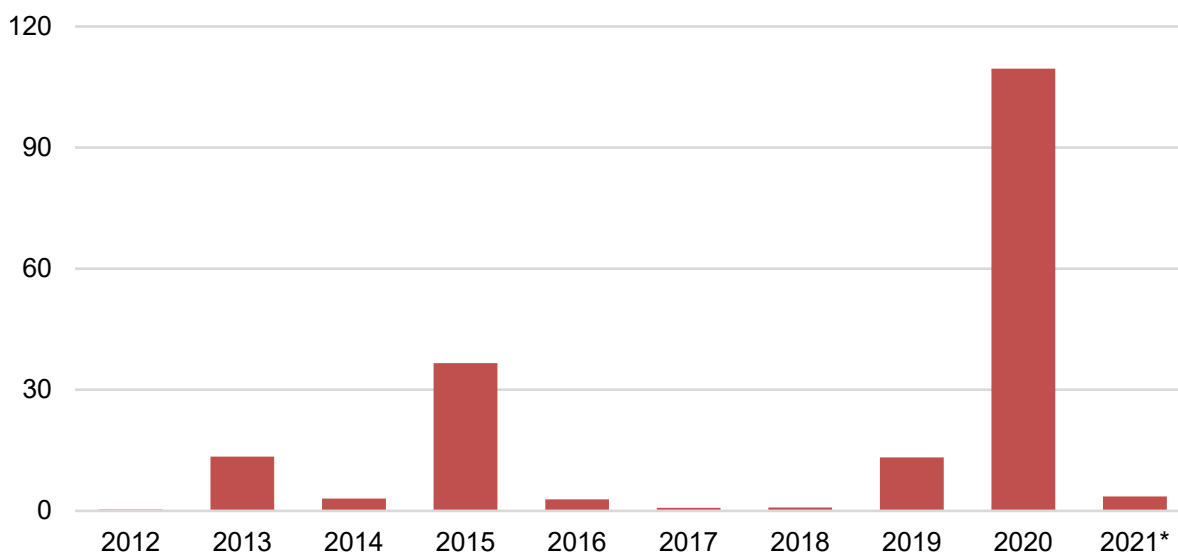
### 5.2.2. Police seizures

Since 2012, police authorities have reported 3 365 seizures of powders containing 3-MMC, amounting to 184 kg (Figure 6). Poland reported 93 % of all Police seizures (3 116 cases) and just over a quarter of the quantity of powders seized by police (48 kg). German Police reported the majority of the quantity of 3-MMC powders seized (106 kg).

<sup>(43)</sup> methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate; formally notified by the EMCDDA in August 2018.

<sup>(44)</sup> ethyl 2-(1-(5-fluoropentyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate; formally notified by the EMCDDA in September 2020.

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



Note: The values include all seizures reported to the EMCDDA between 1 January 2012 and 8 October 2021.

(\*) 2021 data is not comparable to other years (see methodology).

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

Slovakian Police reported a seizure of at least 5 kg of 3-MMC at a production site in in April 2013 <sup>(45)</sup>. In that same year, several police controls of cars resulted in 11 seizures of 3-MMC, totalling 8.4 kg.

In Spain, a large-scale police seizure occurred in 2019, where 8 kg of 3-MMC was found alongside powders containing other new psychoactive substances in different physical forms and packaging (total weight 24.4 kg) (see Figure 5, right). The other substances obtained in the same seizure included other cathinones and synthetic cannabinoids.

Information on the purity of the powders was typically not provided by police. When quantitative information was available, purity was reported between 45.7 % and 'pure'.

<sup>(45)</sup> Information provided to ERISSP regarding this operational production site suggests that an additional 10 kg of 3-MMC 'crystals' may have also been seized in the event.

Seizures of '3-MMC base' and '3-MMC HCl' were reported, albeit in a small number of cases.

In at least 31 kg of seized powders by police, 3-MMC was found mixed with other substances. These included other cathinones (including 3-CMC, 4-CMC, ethylcathinone, brephedrone <sup>(46)</sup>, and 4-MMC) and, to a lesser extent, controlled substances (namely cocaine, metamphetamine, MDMA) as well as ketamine. Adulterants and diluents reported included caffeine, benzocaine and lidocaine.

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

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

### **5.2.3. Other seizures**

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

#### *Seizure of note*

In one case reported by the Netherlands Forensic Institute in 2019, 154 kg of 3-MMC crystals were seized from a dealer/producer (CAM, 2021). The seizure of 3-MMC was distributed in a number of bags and barrels, ranging from 0.5 kg to 14 kg. Information on the physical form of this seizure was received during the preparation of this report.

Related to the same seizure, approximately 350 kg of *N*-acetyl-3-MMC, a 'masked drug' which can be conveniently converted to 3-MMC, were also found in jerrycans and barrels of 50 kg. The 3-MMC and the *N*-acetyl-3-MMC seized were imported from a chemical company in India, as well as other 'research chemicals' found in the location. There is limited information available regarding what was occurring within the seized premises. Although there was laboratory glass wear, several pieces of laboratory equipment, a fume hood and some precursor chemicals seized that could be used for the production of known NPS at the site, there were no indications that other NPS were being synthesised at the

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<sup>(46)</sup> 1-(4-bromophenyl)-2-(methylamino)propan-1-one; formally notified by the EMCDDA in September 2011.

time of the seizure of the laboratory. The location also was used as a packaging/distribution centre for NPS.

### 5.3. Information from collected samples

Between 1 January 2012 and 28 September 2021, a total of 672 collected samples were reported to the EMCDDA by 9 Member States: the Netherlands (443), France (99), Slovenia (52), Poland (40), Austria (20), Portugal (8), Czechia (4), Belgium (3), and Spain (3).

Of these 672 samples, 14 were collected in 2012, 35 in 2014, 28 in 2015, 25 in 2016, 72 in 2017, 101 in 2018, 133 in 2019, 166 in 2020 and 98 in 2021 (up until October). Collected samples of 3-MMC were mostly in powder form (577), but tablets (36), capsules (28), and samples in liquid form (16) were also reported. Samples were mostly collected by drug-checking services (590 cases), but also by the Polish National Medicinal Institute (29) and by the Slovenian National Laboratory of Health, Environment and Food (23).

3-MMC was the only substance detected in 628 cases (94 %). 3-MMC was detected in combination with other substances an average of 6 times per year since 2015 – except in 2016, where 3-MMC was found in combination with other substances in 16 collected samples, almost all of which contained ‘methylethcathinone’<sup>(47)</sup>.

Of the 35 cases in which 3-MMC was found in combination with other cathinones, these were: methylethcathinone (13 cases), 4-CMC (5), ethcathinone (3), MPHP (2), chloromethcathinone (2), alpha-PVP (2), alpha-PVP and *N*-ethylhexedrone (1), alpha-PVP and ethcathinone (1), 3-CMC (1), 3-MEC (1), 4-EMC (1), 4-methylbuphedrone (1), alpha-PHP (1), and 4-CI-PVP (1).

Of the 10 cases in which 3-MMC was found in combination with other substances, these were: 4-FMA, 5-APB and 5-MAPB (2 cases), DOC (2), 2C-B and tramadol (1), methoxyphenidine (1), diphenidine (1), methoxetamine (1), 4,4'-DMAR (1) and methamphetamine (1).

3-MMC was detected in 8 cases in combination with adulterants and diluents: caffeine (2 cases), benzocaine (2), caffeine and lidocaine (2), caffeine and benzocaine (1), and lidocaine (1).

From the 102 samples that were quantitatively tested, 1 sample was collected in 2014 (purity of 95 %), 7 samples in 2017 (mean purity 61 %), 15 samples in 2018 (mean purity 64 %), 31 samples in 2019 (mean purity 64 %), 28 samples in 2020 (mean purity 84 %), and 20 samples in 2021 (mean purity 81 %).

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<sup>(47)</sup> Isomer not specified.

Overall, purities ranged from 11 % to 100 %, with a mean purity of 76.3 %. Adulterants and diluents were reported in 18 of these cases: ‘methylethcathinone’<sup>(47)</sup> (13 cases, 85.4 % average 3-MMC content), 3-CMC (1 case, 37.8 % 3-CMC), alpha-PHP (1 case, 87, 20 % 3-MMC), caffeine (1 case, 82 % 3-MMC), caffeine and benzocaine (1 case, 15 % caffeine and 28 % benzocaine), and benzocaine (1 case, 28 % benzocaine). In these last two cases, the sample was sold as the branded product ‘Synthacaine’. Two other instances of branded products containing 3-MMC were reported: ‘Pink Panther’, containing 3-MMC, tramadol and 2C-B, and ‘Bloom’, with only 3-MMC. These instances of branded products were mostly detected in 2021.

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

When reported, prices ranged from 8€ to 37.5€ per gram (mean price 20€ from 9 samples, most of them collected during 2021). Price for tablets was reported in one case (5€ per tablet). Information on sources was only present in 16 samples, indicating that most samples were bought online (13 cases, two of them on the Darknet), though some were bought by a local dealer (3).

In addition to information from collected samples reported by the Member States, the following information was identified from open source information from Austria, the Netherlands, Switzerland, and the United Kingdom. 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 seven samples containing 3-MMC between February 2017 and September 2021. In five cases 3-MMC was sold as other substances: mephedrone (in 4 cases) and ketamine (1). Six samples contained other substances such as 4-CMC, 4-CEC, 4-CMC, lidocaine, methoxyphenidine, or other unspecified compounds (CheckIt, 2021).

### ***Netherlands***

From all the samples submitted to the Dutch drug checking project DIMS<sup>(48)</sup> in 2020, which consisted of a total of 8078 samples, around half of them contained ecstasy, while 2 % contained either 3- or 4-MMC (DIMS, 2021). This study reports that 49 % of the samples sold in the Netherlands as ‘4-MMC’ contained 3-MMC. Samples sold as ‘3-MMC’ were reported to never contain 4-MMC (CAM, 2021; DIMS, 2021).

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<sup>(48)</sup> Drugs Information and Monitoring System.

### **Switzerland**

In Switzerland, the drug checking service SaferParty reported ten samples containing 3-MMC between November 2019 and September 2021. In all but two of the cases <sup>(49)</sup>, 3-MMC was sold as other substance: mephedrone (in 4 cases), methylone (2), 3-MDMC (1), and 4-MDMC (1). Two samples contained other substances such as MDMA, 3-CMC, 4-MEC, *N*-ethylhexedrone, 4-MMC, ketamine, and caffeine (SaferParty, 2021).

### **United Kingdom**

In the United Kingdom, 29 samples containing 3-MMC were submitted to WEDINOS <sup>(50)</sup> between December 2014 and September 2021. In the majority of cases, 3-MMC was sold as other substance: mephedrone (in 9 cases), ecstasy/MDMA (6), 2C-B (2), cocaine (2), ketamine (1), 3-fluorophenmetrazine (1), and 4-fluoroamphetamine (1). The self-reported effects from users were consistent with synthetic cathinones, and included euphoria, increased energy, agitation, irregular heartbeat, visual hallucinations, chest pains, confusion, and paranoia (WEDINOS, 2020).

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

## **5.4. Information from biological samples**

Between 1 January 2012 and 8 October 2021, a total of 730 detections where 3-MMC was analytically confirmed in biological samples were reported by 11 Member States and Norway, as follows: Belgium (15), Denmark (1), France (50), Germany (1), Hungary (214), Lithuania (1), the Netherlands (14), Norway (16), Poland (37), Slovenia (12), Spain (4), and Sweden (365).

Serious adverse events with confirmed exposure to 3-MMC from biological samples are discussed in Sections 6.2.1.1 and 6.2.2.1. These include: 14 acute poisonings reported by France (6), the Netherlands (6), Germany (1), and Spain (1), and 27 deaths reported by Sweden (9), the Netherlands (8), France (6), Spain (3), and Slovenia (1).

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<sup>(49)</sup> In one of these cases, the sample was sold as '5-MMC', which would be equivalent to 3-MMC.  
<sup>(50)</sup> WEDINOS is a drug testing service in the United Kingdom operated by Public Health Wales ([http://www.wedinos.org/about\\_us.html](http://www.wedinos.org/about_us.html)).

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

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

Detections included (EMCDDA, 2021):

- 18 samples associated with deaths, reported by Hungary (5), France (4), Slovenia (4), Sweden (4), and Norway (1) <sup>(51)</sup>;
- 18 samples associated with non-fatal poisonings, reported by France (7), Hungary (6), and Slovenia (5) <sup>(52)</sup>;
- 170 samples associated with drug consumption, all reported by Hungary;
- 45 cases of persons suspected of driving under the influence of drugs (including 4 traffic accidents), reported by Hungary (20), France (15), Norway (5), Sweden (4), and Denmark (1);
- 24 samples analysed for other purposes, including drug treatment purposes, petty drug offences, emergency room visit, possession of drugs, car accident, working under influence of drugs, reported by Norway (9), Sweden (5), Belgium (3), France (3), Poland (2), Hungary (1), and Lithuania (1);
- 11 samples analysed for criminal justice purposes, reported by Hungary (8) and France (3);
- 7 samples associated with violence, sexual abuse, homicide, or criminal act, reported by France (5) and Slovenia (2);
- 396 samples reported as aggregated data associated with forensic case work (details not specified), reported by Sweden (343), Poland (35), Belgium (12), Hungary (4), France (1), and Norway (1).

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<sup>(51)</sup> 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.

<sup>(52)</sup> 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-MMC. 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-MMC might include neurological (e.g. hallucination, seizures, agitation, anxiety, psychosis, reduced consciousness), cardiovascular (e.g. tachycardia, hypertension, chest pain, cardiac arrest) and respiratory clinical features. Similar to other synthetic cathinones, the use of 3-MMC with other central nervous system stimulants, including cocaine, amphetamine, methamphetamine or MDMA, is likely to produce synergistic effects which can increase the risk of acute toxicity including a sympathomimetic toxidrome.

A total of 14 acute poisonings with confirmed exposure to 3-MMC have been reported by France (6), the Netherlands (6), Germany (1), and Spain (1). Exposure to other substances was reported in 7 cases, including central nervous system depressants and central nervous system stimulants. At least some of the clinical features of the poisonings were consistent with exposure to synthetic cathinones. Based on the reported information, four of the cases could be classified as life-threatening (required admission to intensive care unit or involved life-threatening condition such as respiratory arrest or coma).

A total of 27 deaths with confirmed exposure to 3-MMC were reported by Sweden (9), the Netherlands (8), France (6), Spain (3), and Slovenia (1). In some of the cases, 3-MMC was reported to be the cause of death or to have contributed to the death.

Cases of acute poisonings, death investigations and suspected cases of driving under the influence with confirmed exposure to 3-MMC have been published in the scientific and medical literature. Some of the reported cases occurred in Europe: France, Norway, Poland, Sweden, and the United Kingdom. The clinical features of poisoning were similar to those reported for other synthetic cathinones.

There is no information on the chronic health effects of 3-MMC, including abuse liability and dependence production potential. The chronic health risks might share some similarities to those seen with other synthetic cathinones. This may include dependence.

### 6.2. Acute health effects

#### 6.2.1. Animal data

No clinical studies were identified that have examined the acute health effects of 3-MMC and/or its metabolites in animals.

### 6.2.2. Human data

No clinical studies were identified that have examined the acute health effects of 3-MMC and/or its metabolites in humans. To date, most information about the effects of 3-MMC relates to user experiences, epidemiological data, clinical cases, and toxicological findings. There is one published study conducted to explore the users' perspectives regarding the effects and toxicity of cathinones, including 3-MMC (Assi et al., 2017). The study identified three main themes in relation to 3-MMC use, its effects and drug-related toxicity: theme 1) modalities of intake of 3-MMC, route of administration (e.g., eyeballing, insufflation, smoking, intravenous, oral, rectal, and sublingual), polydrug use, and purity of the cathinone derivative; theme 2) how users describe the main effects of 3-MMC, such as increased energy, euphoria, and empathogenic effects; theme 3) toxic effects distinguished different organ systems: nervous system (anxiety, hallucinations, nervousness, and paranoia), cardiovascular system (angina, myocardial infarction, and tachycardia), skin (discolouration, itching, and allergy), and the renal system (difficulty in urination).

In 2015, a report from the Swedish STRIDA project summarised case series of analytically confirmed intoxications involving 3-MMC presented to emergency departments in Sweden (Bäckberg et al., 2015). During the 20-month study period, 3-MMC was detected in 50 (6.4 %) of the 786 cases included in the STRIDA project. The most frequent clinical features of 3-MMC overdose were tachycardia (48 % of cases) and agitation (42 % of cases). Other symptoms included a reduced level of consciousness (32 %), dilated pupils (24 %), hallucinations (20 %), diaphoresis (12 %), seizures (8 %), and hyperthermia (6 %) (Bäckberg et al., 2015). Apart from these clinical features, other reported adverse effects following administration of 3-MMC included insomnia, difficulty to concentrate and tingling in the arms and legs (Sande et al., 2016). User self-reports on the Internet suggest that high doses of 3-MMC may cause reduced vision, numbness and an irregular pulse (Adamowicz et al., 2014). The main risks involving 3-MMC use were, however, the mixing of 3-MMC with various drugs, inappropriate dosing, lack of information prior to use, binge use spanning several days, and the concomitant or individual use of unknown substances (Sande et al., 2018). Importantly, Bäckberg and colleagues provided analytically confirmed 3-MMC exposure which aided in the association between clinical features and detection of the substance. Mainly, the typical symptoms were sympathomimetic with features similar to those associated with 4-MMC intoxication. However, the high incidence of co-exposure to other drugs renders the clinical interpretation difficult (Adamowicz et al., Bäckberg et al., 2015; 2016; Jamey et al., 2016). Also, 3-MMC was associated with a high admittance rate to intensive care: 30 %, assessed during the STRIDA project (Bäckberg et al., 2015).

On the Internet discussion forum 'drugs-forum', the following additional adverse events associated with 3-MMC intake have been named (without further specification and

reference): chest pain, diaphoresis (excessive sweating), insomnia, aggression, paranoia, depression, anxiety<sup>(53)</sup>.

In comparison, the clinical features reported for 4-MMC intoxication have been described as an acute sympathomimetic toxidrome and typically include agitation, aggression, tachycardia, confusion or psychosis, chest pain, nausea, palpitations, peripheral vasoconstriction, seizures and headache (James et al., 2011; Wood et al., 2010). Additional unwanted effects have been collected in two large surveys: i) the MixMag survey of over 2000 clubbers from the United Kingdom in 2009 included sweating (67 % of those who had used 4-MMC), headaches (51 %), palpitations (43 %), nausea (27 %), cold or blue fingers (15 %) (Dick and Torrance, 2010) and ii) a Scottish survey of students reported that 56 % out of those using 4-MMC experienced at least one adverse effect associated with its use, namely: bruxism (28.3 %), paranoia (24.9 %), sore nasal passages (24.4 %), hot flushes (23.4 %), sore mouth/throat (22.9 %), nose bleeds (22.4 %), suppressed appetite (21.5 %), blurred vision (21.0 %), palpitations (20.5 %), insomnia (19.5 %), hallucinations (18.0 %), addiction/dependence (17.6 %), nausea/vomiting (17.1 %), burns (17.1 %), blue/cold extremities (15 %) (Dargan et al., 2010).

### **6.2.3. Interactions with other drugs**

Drug-drug interactions were also reported including multiple drug use between cathinones, stimulants, depressants, and hallucinogens (Assi et al., 2017). According to the literature, 3-MMC is rarely consumed on its own and often combined with other psychoactive substances. New consumption patterns have emerged in the global drug user scene, often in combination with sexual practices (e.g., men who have sex with men). Known as 'chemsex' or 'slamsex', this poses a specific risk in terms of drug-drug interactions but also to sexually-related risks (such as sexually transmitted disease; Ameline et al., 2019; Drevin et al., 2021). Also, the co-ingestion patterns vary from region to region, and may reflect local availability and/or legal status of these drugs in those countries where the drugs are shipped from (Romanek et al., 2017). For example, Romanek et al. (2017) have described in their study that THC was not the most commonly co-ingested drug in their patient sample in the south of Germany, while in the United States of America, 85 % of 'bath salt' users self-report THC use (Johnson et al., 2014).

As discussed in Section 4.4, a study indicated potential drug-drug interactions but this issue has not been followed up in pharmacokinetic experiments *in vivo* (Dias da Silva et al., 2019).

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<sup>(53)</sup> <https://drugs-forum.com/> (accessed on October 18, 2021).

## 6.2.4. Acute poisonings

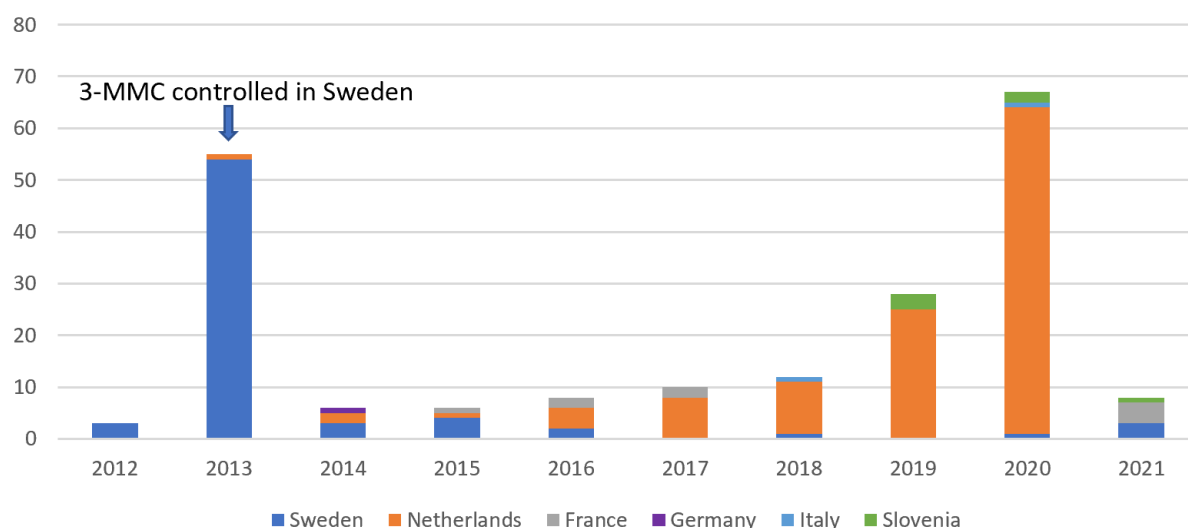
### 6.2.4.1. Acute poisonings reported by the Member States

#### Confirmed exposure

A total of 14 acute poisonings with confirmed exposure to 3-MMC were reported by France (6), the Netherlands (6), Germany (1), and Spain (1). Where reported, the cases occurred between 2014 and 2021: 2014 (1 case), 2016 (2), 2017 (2), 2021 (2). Where known, 6 of the individuals were male and 1 was female. The males were aged between 22 and 51 (mean 38; median 37). Based on the reported information, the majority of reported acute poisonings are believed to be non-fatal.

FIGURE 7

#### Timeline of acute poisoning cases (both with or without analytical confirmation) reported to the EMCDDA



#### Clinical features

Further information on the clinical features of poisoning is available for 7 cases. The following symptoms have been reported: loss of consciousness (3 cases), coma (1 case), respiratory arrest (1 case), respiratory insufficiency (1 case), epileptic seizure (1 case), sopor (1 case), uncontrolled movements of the hands, mouth, eyelids and nystagmus (1 case), and 'bad trip' (1 case). Three patients were hospitalised, two of them in intensive care unit. Based on the reported information, four of the cases could be classified as life-threatening (required admission to intensive care unit or involved life-threatening condition such as respiratory arrest or coma). In all but one of these 7 cases other substances were also identified in the biological samples taken from the patients, which may account, at least

in part, for the observed effects. No information related to management of the patients was reported.

In 7 cases other substances were identified, including:

- central nervous system stimulants: cocaine and/or benzoylecgonine (4), methamphetamine (3), amphetamine (1), 3-CMC (1), 3-fluoroamphetamine (1), 3F-phenmetrazine, and *N*-ethylhexedrone;
- central nervous system depressants: GHB/GBL (1), AB-CHMINACA (1), diazepam (1);
- other drugs: 2-FDCK <sup>(54)</sup> (1), cannabis (1), sildenafil (1), pipamperone (1).

In 4 cases users reported co-administration of other drugs and/or alcohol in addition to 3-MMC, however, the investigation in these cases is ongoing and the presence of other substances has not yet been confirmed from biological samples.

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

### *Suspected exposure*

Five Member States reported 192 cases of acute poisoning with suspected exposure to 3-MMC: the Netherlands (110), Sweden (71), Slovenia (6), France (3), and Italy (2). The cases reported by Sweden, Slovenia, France, and Italy occurred between 2012 and 2021: 2012 (3 cases), 2013 (54), 2014 (3), 2015 (5), 2016 (2), 2018 (2), 2019 (3), 2020 (4), and 2021 (6).

Further details are available for the cases reported by Slovenia, France, and Italy: 10 individuals were male and 1 was female. The males were aged between 29 and 57 (mean 40.5; median 38.5). Two of the cases were reported as related to sexual practice.

The following symptoms have been reported: coma (2 cases), cardiogenic shock (1 case), respiratory depression (1 case), confusion (3 cases), aggression (2 cases), agitation (2 cases), hyperthermia (2 cases), septic superficial venous thrombosis of limb (1 case), delirium (1 case), hallucinations (1 case), abdominal pain (1 case), psychosis (1 case), nausea (1 case), vomiting (1 case), syncope (1 case), tachycardia (1 case), bradycardia (1 case), hypertension (1 case), hypotension (1 case), chest pain (1 case), miosis (1 case), paraesthesia (1 case), dissociation (1 case), and pulmonary edema (1 case).

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<sup>(54)</sup> 2-(2-fluorophenyl)-2-methylamino-cyclohexanone, also called 2-fluorodeschloroketamine. Formally notified by the EMCDDA in October 2016.

Based on the reported information, three of the cases could be classified as life-threatening (involved life-threatening condition such as coma, respiratory depression or cardiogenic shock). Since the presence of 3-MMC was not analytically confirmed in these cases, the reported symptoms should be taken with caution.

In the Netherlands, a total of 115 poisonings were reported to the Dutch Poisons Information Centre between 2013 and 2020 (2013 (1), 2014 (2), 2015 (1), 2016 (4), 2017 (8), 2018 (10), 2019 (25), 2020 (64)), with the majority reported in 2019 and 2020 (77 %). This includes 4 cases of acute poisoning with confirmed exposure (included in the section above on acute poisonings with confirmed exposure), 110 cases of acute poisonings with suspected exposure, and one case of death with suspected exposure (included in the section below on death cases with suspected exposure).

Most patients with 3-MMC poisoning were young adults (median: 24 years, range: 15–70 years). Approximately 10 % of the patients were younger than 18 years. Approximately three quarters of the patients were male. In just over half of the 3-MMC poisonings, use was combined with other drugs and/or alcohol. The most frequent route of exposure in 3-MMC poisonings was oral ingestion, followed by snorting and injection.

About half of the poisonings were moderate to severe, requiring referral to a hospital. Eight patients required hospitalisation, including 3 that required treatment in an intensive care unit. The reported clinical features of poisoning were consistent with poisoning with stimulant and included mainly cardiovascular complaints, such as tachycardia (~30 %), palpitations (~25 %), chest pain (~20 %), increased blood pressure (hypertension, ~15 %). Agitation was also commonly reported (~30 %). After injection, moderate to severe local complaints developed in 50 % of the cases, around the injection site.

Of all 3-MMC poisonings, about one third were reported by an ambulance service and about one quarter by the emergency room or another hospital department. This suggests that more than half of the reports required immediate medical intervention.

#### *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 these substances and possible different routes of administration render it difficult to estimate the typical, toxic and lethal blood concentrations.

To date, 291 case reports of non-fatal acute poisonings involving 3-MMC have been reported in the following European countries: Sweden (50; Bäckberg et al., 2015), Poland (213; Adamowicz et al., 2016; Adamowicz and Tokarczyk, 2016; Pieprzyca et al., 2021), France (6; Turcant et al., 2017), Germany (14; Maas et al., 2015; Romanek et al., 2017), Italy (1; Frison et al., 2016), Slovenia (7; Sande et al., 2018).

From 267 of the above-mentioned cases, the determined concentrations have exemplarily been summarised to give a comprehensive overview of non-fatal and analytically confirmed intoxications involving 3-MMC (Table 5; Ferreira et al., 2019). In terms of demographic data, the age of the individuals ranges from 16 to 50 years of age, with a predominance in the twenties to thirties, 236 were of male sex, 31 were of female sex (Ferreira et al., 2019). Apart from 3-MMC, the following drugs have been confirmed in the samples: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, 5-(2-methylaminopropyl)benzofuran; GHB; 4-methylethcathinone; methoxetamine; MDMA; 3,4-methylenedioxyamphetamine (Ferreira et al., 2019).

Importantly, when looking at the acute health effects and harms posed by 3-MMC, Romanek and colleagues (2017) describe that in their study sample, most frequently hypertension and tachycardia were reported (in 36 % and 29 %, respectively). They also found an elevation of creatine phosphokinase which may have resulted from increased muscular activity or from low-grade rhabdomyolysis with or without kidney failure (Romanek et al., 2017).

### **6.2.5. Medico-legal death investigations**

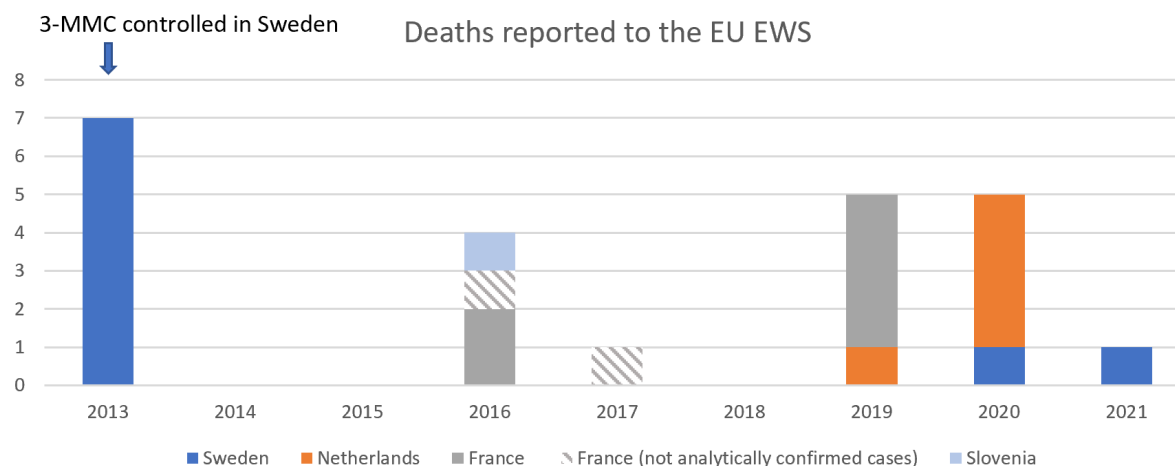
#### *6.2.5.1. Deaths reported by the Member States*

##### *Confirmed exposure*

A total of 27 deaths with confirmed exposure to 3-MMC were reported by Sweden (9), the Netherlands (8), France (6), Spain (3), and Slovenia (1). Where known, the cases occurred between 2013 and 2021: 2013 (7 cases), 2016 (3), 2019 (5), 2020 (5), 2021 (1).

Where reported, 12 were male and 1 was female. Age was reported for 7 of the males. The males were aged between 22 and 46 (mean: 29; median 27).

FIGURE 8

**Timeline of death cases (both with or without analytical confirmation) reported to the EMCDDA**

Note: Information on year of the event was available in 23 out of 31 cases.

Eighteen of the cases were reported as either reported mixed poisonings or other substances were identified in biological samples. In 7 cases, it was reported that other substances were identified in biological samples; in those cases the following substances were identified in the biological samples:

- central nervous system depressants: opioids (buprenorphine in 1 case, heroin in 1 case, tramadol in 1 case), benzodiazepines (oxazepam in 2 cases, diazepam in 2 cases, nordiazepam in 2 cases, alprazolam in 1 case, clonazepam in 1 case, norflurazepam in 1 case, lormetazepam in 1 case, lorazepam in 1 case), ethanol (1), zopiclone (1), doxylamine (1 case)
- central nervous system stimulants: 4-methylethcathinone (1), 4-fluoromethylphenidate (1), methylphenidate (1 case), cocaine (1), amphetamine (1),
- other drugs: pregabalin (2), 3-MeO-PCP (1), THC (1), metoprolol (1), mirtazapine (1 case), olanzapine (1), clozapine (1), sertraline (1), fluoxetine (1), metoclopramide (1), venlafaxine (1), sildenafil (1).

In 6 cases it was reported that other substances were involved (3 cases involving buprenorphine, 1 case involving AH-7921, 1 case involving cocaine, and 1 case involving 4F-Ritalin, 2-fluorodeschloroketamine, dimethocaine), however, no information on the analytical confirmation of these substances is available. Five remaining cases were reported as mixed intoxications without information on specific substances involved.

In 3 of the cases, the individuals were found dead. Additional information on the type of poisonings (mixed- or mono) or cause of death was reported in 18 cases:



- in the cases reported by Sweden, seven of the cases were reported as mixed intoxications (three with buprenorphine, one with AH-7921, one case reported as hanging, in one case stick injuries were reported). In the two remaining cases, the reported causes of death were intoxication with buprenorphine, clonazepam, 3-MeO-PCP and 3-MMC (1 case) and intoxication with several substances (pregabalin, tramadol) (1 case);
- in the cases reported by the Netherlands, the reported causes of deaths were: monointoxication with 3-MMC (2 cases), 1 mixed-intoxication in which 3-MMC contributed to the death (1 case), 1 mixed-intoxication in which 3-MMC did not contribute to the death (1 case), mixed intoxication with 3-MMC and other NPS (4F-Ritalin, 2-fluorodeschloroketamine, dimethocaine; analytical confirmation of other NPS not available) (1 case); intentional intoxication with 3-MMC, cocaine and caffeine in a person with no history of problematic drug use (1 case); intoxication with carbon monoxide following the use of 3-MMC (1 case);
- in one of the cases reported by France, the case was reported as accidental toxic death exclusively involving 3-MMC;
- in the case reported by Slovenia, the reported cause of death was sudden cardiac death after ingestion of 3-MMC, THC and ethanol.

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

#### *Suspected exposure*

A total of 4 deaths with suspected exposure to 3-MMC were reported by France (2) and the Netherlands (2). In two of the cases (one reported by France and one by the Netherlands), it was reported that 3-MMC was taken together with poppers and sildenafil. One of these cases was related to chemsex use.

#### *6.2.5.2. Deaths identified from other sources*

A scan of the literature for cases with fatal poisoning has revealed that 3-MMC fatal poisoning rarely occurs with the compound alone; rather frequently, 3-MMC is used in combination with other drugs (Ferreira et al., 2019; Jamey et al., 2016).

In several reports on fatal intoxications, the determined concentrations have been summarized for a comprehensive overview of fatal intoxications involving 3-MMC (see Table 5; Ferreira et al., 2019). Most of the cases were analytically confirmed, only 2 cases (from Sweden and Germany) were not analytically confirmed.

To date, 18 case reports of fatal intoxications involving 3-MMC have been reported in the following European countries: Sweden (2; Bäckberg et al., 2015), Poland (10; Adamowicz et al., 2016; Adamowicz et al., 2014; Margasinska-Olejak et al., 2019; Pieprzyca et al.,

2021), Norway (1; Karinen et al., 2014), France (4; Bottinelli et al., 2016; Bottinelli et al., 2017; Jamey et al., 2016), Germany (1; Romanek et al., 2017). There have been additional cases reported in the scientific literature from France (Aknouche et al., 2020).

The demographic data were not as well documented as in the non-fatal intoxication cases; the age of the individuals ranges from 20 to 69 years of age, with a predominance in the twenties and thirties; out of 18 well documented cases, only three were of female sex (Ferreira et al., 2019; Margasinska-Olejak et al., 2019; Pieprzyca et al., 2021).

Apart from 3-MMC, the following drugs have been confirmed in the samples: amphetamine, caffeine, codeine, diazepam (nordazepam), ethanol, MDMA, gamma-hydroxybutyric acid, 5-(2-aminopropyl)benzofuran, 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe), 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921), codeine-6-glucuronide; 2-fluoromethamphetamine (2-FMA); 4-methylethcathinone (4-MEC) (Ferreira et al., 2019; Pieprzyca et al., 2021).

Importantly, only in three cases, 3-MMC was the only analytically confirmed compound (Ferreira et al., 2019).

Goncalves et al. (2021) have recently reported the death of a 55-year old male who was found dead at home with 32 stab wounds on his body after a chemsex party. Toxicological analyses revealed the detections of MXP (2-methoxydiphenidine) concentrations in femoral blood (606 µg/L), cardiac blood (254 µg/L) and hair (13 ng/mg). 3-MMC was also detected in femoral blood (traces) and urine (238 µg/L). Two syringes were also found to contain MXP and 3-MMC though the latter was not detected in blood which suggested that its half-life might have been shorter than that of MXP.

#### **6.2.6. Driving and operating machinery under influence**

Cases of driving under influence of drugs (DUID) have been published in the scientific literature (Adamowicz et al., 2016; Maas et al., 2015). As for all psychoactive stimulants the increase of risky behavior is inherently attached to the behavioral and psychological effects described above. However, there seems to be a difficulty to clearly correlate the blood concentrations determined in drivers with the psycho-motor performance because, as outlined above, 3-MMC is rarely the only drug used (Adamowicz et al., 2016).

Nonetheless, the group with 3-MMC as the only detected substance was subdivided into drivers with and without detectable symptoms. The group of drivers without detectable symptoms consisted of 13 people with blood concentrations ranging from 0.003 to 0.171 mg/L (Adamowicz et al., 2016). The group of drivers without detectable symptoms consisted of 6 users with reported effects such as gaiety, verbosity, stuttering, fatigue, agitation, aggression, uncoordinated movements and tachycardia; these cases presented with differently wide pupils, narrow to wide, and a normal or rather sluggish reaction to light.

Interestingly, lower 3-MMC blood concentrations were determined in these cases (between 0.011 and 0.030 mg/L; median 0.024 mg/L; Adamowicz et al., 2016). The cases in the third group consisted of drivers which had concomitantly applied other drugs, mainly amphetamines or cannabinoids, the observed effects presented as anxiety, depression, disorientation, verbosity, slurred speech, strange behavior, unsteady gait, staggering and tachycardia; some drivers also presented with a reddened face and pupils wide or narrow, sluggishly reacting to light (Adamowicz et al., 2016).

Apart from the drug-drug interactions, which may pose a specific problem, another problem relies in the presumable short half-life of the compound 3-MMC which may render a correct determination difficult (Shimshoni et al., 2015). Also, symptomatic individuals seem to be rather first-time users compared to frequent or long-term users who are already adapted to the effects exerted by the drug and thereby tolerant to the effects (Ferreira et al., 2019).

Other pharmacodynamic effects after repeated use such as sensitisation may also play a role. Finally, the suggested metabolic pathway of 3-MMC relies mainly on hepatic enzymes of the cytochrome P450 monooxygenase family which is subject to not only drug-drug interactions but also to pharmacogenomics, determining the influence of the genetics on the availability of the drug in the organism.

With respect to the sample preparation, there might also occur handling problems: the protocols in use are typically prepared for testing of persons who may be under the influence of alcohol (DUI cases), not DUID cases. There are, in fact, reports demonstrating a lack of practical importance of preliminary medical examination based on the blood sampling protocol to assess whether the tested person is under the influence of drugs. In addition, in some instances, the screening of blood samples during routine lab testing revealed negative results using ELISA, thereby demonstrating that 3-MMC is not easily detectable using standard amphetamine-type stimulants immunoassay kits (Ameline et al., 2019).

#### **6.2.7. Other serious adverse events reported to the EMCDDA**

##### *Substance dependence*

Two cases of substance dependence with confirmed exposure to 3-MMC were reported by France. Both cases occurred in 2021. In one of the cases, the patient reported injecting 3-MMC (slamming) and was hospitalised for withdrawal from 3-MMC and 4-fluoromethylphenidate. In the second case, 2-fluorodeschloroketamine and 3-MeO-PCP were also detected in biological sample and the patient reported experimenting with a range of different new psychoactive substances often bought on the Internet.

In addition, France reported three cases of substance dependence with suspected exposure to 3-MMC. One of the cases involved an individual hospitalised for withdrawal

from 3-MMC. The patient reported switching from cocaine to 3-MMC due to the lower price of 3-MMC. Two remaining cases involved patients using 3-MMC in chemsex/slam practices; in one of these cases the patient was hospitalised for withdrawal symptoms related to GBL use.

#### Other types of serious adverse events

France reported one case of sexual assault with confirmed exposure to 3-MMC. The patient was unaware of taking any drugs. It was reported that the victim experienced amnesia. Other substances were identified in biological sample, including GHB, codeine, tramadol, and unspecified benzodiazepines.

In addition, France reported one case of allergic reaction with suspected exposure to 3-MMC. The patient reported a regular use of 3-MMC and poppers by inhalation. After taking 3-MMC by intravenous route for the first time, the patient experienced generalised urticaria.

### 6.3. Chronic health effects

No studies were identified that investigated the chronic health effects of 3-MMC and/or its metabolites in animals. No clinical studies were identified that have examined the chronic health effects of 3-MMC 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.

The purity of the compound is might also be subject to considerable variation. In recent study carried out in Italy during the COVID-19 pandemic, 3-MMC was the most prevalent compound seized (18.6 %) involving postal deliveries (Vincenti et al., 2021).

The use frequency is likely to impact on the potential for abuse liability similar to its positional isomer 4-MM since both induce transporter-mediated release of neurotransmitters, and in case of 4-MMC, it has been shown that rats trained to self-administer amphetamine will also do so when substituting with 4-MMC. Thus, the potential for abuse may be given, with all caution that is necessary when transferring data from animal experiments (and especially rodents) to humans.

Inter-individual differences between users may impact the outcome of 3-MMC use. Such differences include genetic differences, development of tolerance, overall state of health,

underlying medical conditions, medication, age, and gender. The available data suggest that 3-MMC is metabolised by the highly polymorphic cytochrome CYP2D6. As a result, pharmacokinetic and pharmacodynamic properties might vary between different individuals. In addition, the use of 3-MMC with inhibitors of CYP2D6, such as fluoxetine, paroxetine, and bupropion, may result in increased plasma concentration of 3-MMC and increase the risk of poisoning. Tolerance to some of the effects of 3-MMC 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.

Rather rarely, 3-MMC appears to be used on its own (knowingly or unknowingly), typically, various compounds are co-ingested, depending on the region and the user community. The variability of the occurrence of drug-drug interactions is therefore high and it may also lead to rather complicated intoxication patterns and clinical features that may not always directly link to 3-MMC ingestion alone. Therefore, the risk associated with drug-drug interactions leading to adverse events is moderate to severe, especially since the purity of either drug to be combined may also not be known.

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-MMC.

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

Similar to other stimulants, concurrent use of 3-MMC 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 wear off.

A range of factors associated with patterns of use and dosage regimens might further impact health risks associated with 3-MMC use. Dose-effect and dose-time relationships affect the likelihood of harmful effects occurring. Based on the available information, the effects of 3-MMC seem to be less intense and short-lived compared to 4-MMC and thus repeated administration of 3-MMC in a single session is commonly reported by users. This may increase the risk of accidental overdose.

The reported routes of administration of 3-MMC include 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 such as wound botulism. Infectious complications may arise from intravenous injection, but also local infections, septic emboli and the possibility of inadvertent intra-arterial injection (Romanek et al., 2017). This risk might be decreased if needle exchange programmes are available for users. Also, the nasal insufflation route has been described as unpleasant in user reports; nevertheless, since 3-MMC has a relatively low bioavailability via the oral route (at least in the pig; Shimshoni et al., 2015), this is the preferred route of application. Snorting of drugs with shared equipment might lead to the transmission of blood borne viruses as shared banknotes, cards or straws may be contaminated.

Health risks might be also affected by the context and the settings in which 3-MMC is used. For example, users involved in chemsex practices while being under the influence of drugs might not use protection (e.g. condoms) which can put them at risk of contracting 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-MMC may further increase the risk of accidental overdose and cause poisoning.

The harmful effects of any drug is influenced by environmental conditions and the physiological status of the individual ingesting the substance, and this applies to 3-MMC as well. One possible risk-modifying factor would be a potential elevation of body temperature – which has not been reported in rigorous scientific studies on 3-MMC. In some studies, 4-MMC was found to induce elevated body temperature in rodents (Baumann et al., 2012), and in other studies, a lowering of body temperatures were described after administration of 4-MMC (Wright et al., 2012; Aarde et al., 2013). Nevertheless, users also subjectively described a cold sensation pointing to a reduction of body temperature when reporting the effects associated with 4-MMC (Winstock et al., 2011).

### ***Uncertainty analysis***

In some of the cases of serious adverse events reported to the EMCDDA as well as information from user websites, exposure to 3-MMC was not analytically confirmed from biological samples from patients. In most of these cases the information on exposure to 3-MMC 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-MMC. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the reported effects. Information on monointoxications with confirmed exposure to 3-MMC 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 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-MMC. 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. For example, in some cases of hyperthermia it is possible that subjective feeling of hotness was caused to some extent by hot temperature in club.

The information on the prevalence of use of 3-MMC is limited, thus it is difficult to predict how probable is experiencing adverse effects after the use of 3-MMC. 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 information for 3-MMC, it is possible that the social risks share some similarities with those associated with other synthetic cathinones, such as 4-MMC, 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 on their family structure and employment or schooling performance, as well as increased vulnerability (Brookman et al., 2016; de Jonge et al., 2021; Nijkamp et al., 2021).

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

### 7.1. Individual social risks

While there is limited information on the individual social risks related to 3-MMC, it is possible that they might include impacts on education or career, family or other personal and social relationships. Some people reported to have used 3-MMC described psychosocial problems arising from long-term use of 3-MMC including, among others,

conflicts with friends or family, losing contact with friends or family, non-compliance with obligations, and being withdrawn (de Jonge et al., 2021; Nijkamp et al., 2021).

## 7.2. Possible effects on direct social environment

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

A limited but concerning number of cases of sexual assaults/sexual abuse in which 3-MMC has been identified in biological samples taken from victims has been reported to the EMCDDA. While the available information on these cases is limited, it cannot be excluded that 3-MMC was deliberately used by perpetrators to commit drug facilitated sexual assaults <sup>(55)</sup>.

In addition, the detection of 3-MMC 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-MMC.

The illicit manufacture of cathinones such as 3-MMC 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 the individuals operating the cathinone laboratories, and law enforcement and chemical rescue units' personnel involved in seizures of the premises. These substances include, but are not limited to, bromine, flammable liquids including solvents, concentrated acids and bases. Bromine in particular may be toxic by inhalation, accelerates the burning of

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<sup>(55)</sup> Drug facilitated sexual assaults are incidents of sexual assault in which the victim is incapacitated and/or unable to provide consent to the sexual act, as a result of drug or alcohol consumption.



combustible material, is very corrosive to tissue and metals and dangerous for the environment.

The explosion of one illicit laboratory producing 3-MMC was reported in Europe, connected to 'incompetent handling' and resulting 'environmental damage'. Generally speaking, the materials used for the synthesis of the drugs include hazardous waste, raw materials, toxic chemicals, carcinogens and phytotoxins which may be discarded at on- and off-site locations, including household drains, large containers, backyards, soil, roads and creeks may pose 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-MMC. As 3-MMC is a synthetic cathinone, any such costs may have some similarities with those associated with the use of other synthetic cathinones and other psychostimulants. 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.

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

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

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

#### **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-MMC 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. This includes recreational users and users involved in chemsex and/or slamming practices (CAM, 2021; de Jonge et al., 2021; Drevin et al., 2021; Nijkamp et al., 2021).

Based on the available information, it appears that 3-MMC is currently being used by some vulnerable groups including young people in the Netherlands and Slovenia (CAM, 2021; de Jonge et al., 2021; Nijkamp et al. 2021). In the Netherlands, 3-MMC may be used partly

because it is easily available and has a relatively low cost. The use of 3-MMC among high-risk drug users has also been reported by France and Slovenia.

Similar to other new psychoactive substances, it also appears that there is interest in 3-MMC 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-MMC within Europe. However, based on information reported to the EMCDDA, there is evidence of criminal acts, such as trafficking, illicit production, and supply offences, involving 3-MMC.

At least three illicit laboratories producing 3-MMC have been seized in Europe, with the most recent laboratory seized in 2020. Some of these may be facilities involved in packaging and in the storage of chemicals and/or equipment. In addition, Slovakia reported the discovery of several abandoned clandestine laboratories in 2018, where 3-MMC was known to have been produced in high volumes. Slovakia also reported information from the police which suggested a significant decrease in the activities of foreign criminal groups, dealing with the production of 3-MMC and 3-CMC. This decrease is considered to be as a result of Covid-19 restrictions.

No other information was received on the involvement of criminal groups in the manufacture or distribution of 3-MMC. European Investigation Orders have been issued to the Netherlands based on requests by other countries, connected to dark web sellers of 3-MMC (alongside drugs such as 4-FA, alpha-PVP and cocaine) (CAM, 2021).

The effect of the ongoing COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020b; WHO, 2020) on the manufacture, trafficking, distribution, and use of 3-MMC is currently unknown. However, seizures of more than of 720 kg of bulk powders by customs agencies during the pandemic suggest that 3-MMC continues to be imported and distributed in Europe. It is possible that, in case of a reduced availability of controlled stimulants (such as 4-MMC and MDMA) in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including 3-MMC.

## 8. Other relevant information

### 8.1. Information on restrictive measures

#### 8.1.1. International restrictive measures

At international level, 3-MMC 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).

3-MMC was assessed at the 38<sup>th</sup> meeting of the WHO Expert Committee on Drug Dependence (ECDD) that was held on 14–18 November 2016 (WHO, 2016a; 2016b; 2016c). The Committee did not make recommendations for scheduling to CND or recommended 3-MMC for surveillance. The Committee was unable to reach consensus, and instead it deferred an opinion, and requested the Secretariat to arrange another critical review of 3-MMC at a subsequent meeting of the Expert Committee (WHO, 2016d). A further ECDD review of 3-MMC has not taken place yet.

#### 8.1.2. National restrictive measures

Five Member States (Bulgaria, Greece, Luxembourg, Romania, and Spain) reported that 3-MMC is not subject to restrictive measures at national level. The remaining countries reported that 3-MMC is subjected to restrictive measures, as follows (Table 6) (EMCDDA, 2021):

- Fifteen Member States (Croatia, Czechia, Denmark, Estonia, France, Germany, Ireland, Italy, Latvia, the Netherlands, Poland, Portugal, Slovenia, Slovakia, and Sweden), Turkey and Norway reported that 3-MMC is controlled under drug control legislation.
- Six Member States (Austria, Belgium, Cyprus, Finland, Hungary, Malta) reported that 3-MMC is controlled under new psychoactive substance legislation.
- Lithuania reported that 3-MMC is controlled under medicines legislation (included in the group of cathinone derivatives) since 2015.

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

3-MMC is controlled in China since October 2015.

TABLE 6

**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	2014
Cyprus	Controlled	NPS		24/06/2011
Czechia	Controlled	Drug		01/10/2015
Denmark	Controlled	Drug	Generic	2012
Estonia	Controlled	Drug		08/06/2015
Finland	Controlled	NPS		20/12/2014
France	Controlled	Drug		02/08/2012
Germany	Controlled	Drug		13/12/2014
Greece	Not controlled			
Hungary	Controlled	NPS	Generic	03/04/2012
Ireland	Controlled	Drug	Generic	11/2011

<b>Country</b>	<b>Control status</b>	<b>Type of control</b>	<b>Generic</b>	<b>Entry into force</b>
Italy	Controlled	Drug		29/12/2020
Latvia	Controlled	Drug	Generic	n/r
Lithuania	Controlled	Medicines	Generic	10/03/2015
Luxembourg	Not controlled			
Malta	Controlled	NPS	Generic	n/r
Netherlands	Controlled	Drug		28/10/2021
Norway	Controlled	Drug		n/r
Poland	Controlled	Drug		01/07/2015
Portugal	Controlled	Drug		26/03/2012
Romania	Not controlled			
Slovakia	Controlled	Drug		15/03/2014
Slovenia	Controlled	Drug		05/07/2011
Spain	Not controlled			
Sweden	Controlled	Drug		01/12/2013
Turkey	Controlled	Drug		25/01/2014
n/r: not reported				

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ANNEX 2

## Participants of the risk assessment meeting, 18 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-MMC, 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](#)

These and all other EMCDDA publications are available from [emcdda.europa.eu/publications](https://emcdda.europa.eu/publications)

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

| [EMCDDA Risk assessment of NPS](#)

| [EMCDDA New psychoactive substances webpage](#)

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