World Health Organization

Critical review report:

3-Chloromethcathinone

Expert Committee on Drug Dependence

Forty-sixth Meeting

Geneva, 16–20 October 2023

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

Contents

Executive summary

3-Chloromethcathinone (3-CMC) (CAS: 1049677-59-9), 1-(3-chlorophenyl)-2-(methylamino)-1-propanone, is a synthetic stimulant of the cathinone family. 3-CMC is one isomeric form of the drug "chloromethcathinone", in which 2-chloromethcathinone (2-CMC) and 4-chloromethcathinone (4-CMC) are the other two positional isomers. 3-CMC was first reported on the drug market in Sweden in October 2014. Cases involving 3-CMC have been reported in four global regions: Europe, North and South America and Oceania. 3-CMC is not currently under international control, but its isomer 4-CMC was placed under international control in 2020.

Limited information on 3-CMC is available in the scientific literature. Drug use forum posts suggest that its primary routes of administration are oral ingestion of tablets or capsules and insufflation of powders. Anecdotal reports from people who use 3-CMC suggest high euphoric effects after ingestion of suspected 3-CMC products. The metabolism of 3-CMC has not been well characterized; however, one study showed biotransformation to *N*-desalkyl and ketone reduction metabolites, which were considered good biomarkers of its use. The bioactivity of the metabolites is unknown. The mechanism of the psychoactive effects of 3-CMC is linked to its role as a releasing agent at dopamine, serotonin and norepinephrine transporters. The potency and effects of 3-CMC, 4-CMC and 3-methylmethcathinone (3-MMC) appear to be similar.

Use of 3-CMC has been associated with eight deaths in Sweden and more than 30 investigations of drug impaired driving. In an additional investigation, the autopsy findings were pulmonary oedema, hyperaemia of internal organs, enlargement of the heart cavities, slight atherosclerosis of the coronary arteries, signs of hepatic steatosis and scars in the kidney cortex. More than 2700 kg of 3-CMC have been seized in European drug markets. Sweden reported increased drug seizures in 2021 and 2022, of 50 kg and 68 kg of the product, respectively.

3-CMC has been available for sale online by Internet retailers and can be purchased from street drug markets. Little further evidence was found on use of 3-CMC; however, international forensic data provide evidence of polydrug use, with 3-CMC combined with other drugs, including its isomer 4-CMC. People who ingest drug products containing 3-CMC may also be consuming other drugs, which complicates evaluation of the direct effects of the drug. 3-CMC has been found with other drugs in toxicological studies.

1 Substance identification

A International nonproprietary name

Not assigned

B Chemical Abstracts Service (CAS) registry number

1049677-59-9 (free base)
1607439-32-6 (hydrochloride salt)
2291021-63-9 ((2*R*)-enantiomer)
2107425-89-6 ((2*S*)-enantiomer)

C Other chemical names

1-(3-Chlorophenyl)-2-(methylamino)-1-propanone (ACI)
1-(3-Chloro-phenyl)-2-methylamino-propan-1-one
3′-Chloro-2-methylaminopropiophenone
2-(Methylamino)-1-(3´-chlorophenyl)-1-oxopropane
(2*S*)-1-(3-Chlorophenyl)-2-(methylamino)-1-propanone (ACI)
(*S*)-3-Chloromethcathinone
(2*R*)-1-(3-Chlorophenyl)-2-(methylamino)-1-propanone (ACI)
(*R*)-3-Chloromethcathinone
3-Chloromethcathinone
3-Cl-methcathinone
3-Cl-MCAT
Clophedrone
Metaclephedrone
Meta-chloro-*N*-methyl-cathinone
Meta-chloromethcathinone
PAL-434

D Trade names

The hydrochloride salt form of 3-CMC is sold as a reference analytical standard under the names "3-chloromethcathinone (hydrochloride)" and "1-(3-chlorophenyl)-2-(methylamino)propan-1-one hydrochloride" *(1)*.

E Street names

Street names for 3-CMC include its own chemical names, principally 3-CMC, 3CMC, clophedrone and metaclephedrone. In Sweden, the drug is referred to as "Kristall" on the street.

F Physical appearance

In pure form, the hydrochloride salt of 3-CMC has been described as a grey solid *(2)*, a white solid *(3)* and a white powder *(4)*.

Seized samples containing 3-CMC have been mostly in powder form and, to a lesser extent, capsule, tablet and liquid form *(5)*.

G WHO review history

3-CMC has not been reviewed previously by WHO.

2 Chemistry

A Chemical Name

IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one

Chemical Abstracts index name: 1-Propanone, 1-(3-chlorophenyl)-2-(methylamino)-(ACI)

Free base

Canonical SMILES
O=C(C=1C=CC=C(Cl)C1)C(NC)C

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

InChI Key
VOEFELLSAAJCHJ-UHFFFAOYSA-N

Hydrochloride salt

Canonical SMILES
Cl.O=C(C=1C=CC=C(Cl)C1)C(NC)C

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

InChI Key
QXEPSICDXPPHTO-UHFFFAOYSA-N

(2R)-enantiomer

Canonical SMILES
O=C(C=1C=CC=C(Cl)C1)C(NC)C

Isomeric SMILES
C([C@H](NC)C)(=O)C1=CC(Cl)=CC=C1

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

InChI Key
VOEFELLSAAJCHJ-SSDOTTSWSA-N

(2S)-enantiomer

Canonical SMILES
O=C(C=1C=CC=C(Cl)C1)C(NC)C

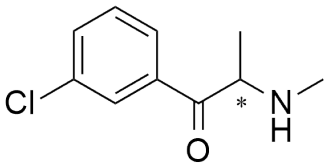
Isomeric SMILES
C([C@@H](NC)C)(=O)C1=CC(Cl)=CC=C1

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

InChI Key
VOEFELLSAAJCHJ-ZETCQYMHSA-N

B Chemical structure

Free base:

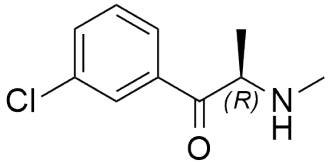


Molecular formula: $C_{10}H_{12}ClNO$

Molecular weight: 197.66 g/mol

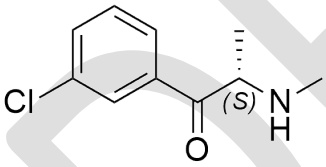
C Stereoisomers

As 3-CMC contains a chiral centre, two enantiomers may exist: (*R*)-3-CMC and (*S*)-3-CMC. No information was available on the enantiomeric composition of 3-CMC on the drug market, but it is probably available as a racemic mixture of the (*R*)- and (*S*)- enantiomers, although the appearance of individual stereoisomers cannot be excluded *(5)*.



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

CAS RN 2291021-63-9



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

CAS RN 2107425-89-6

D *Methods and ease of illicit manufacture*

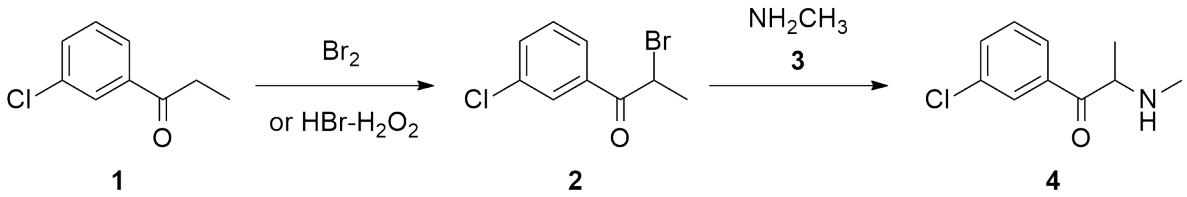
Two methods have been reported for the synthesis of 3-CMC *(2,3)*.

Shalabi et al. *(3)* used a general procedure according to **Scheme 1**, in which 3-CMC is obtained from 2-bromo-1-(3-chlorophenyl)propan-1-one (**2**) by nucleophilic substitution with methylamine (**3**) to give 3-CMC free base (**4**) *(3)*.

Blough et al. *(2)* used a slightly different method, involving an *N*-protected amine, also starting from 2-bromo-1-(3-chlorophenyl)propan-1-one *(2)*.

2-Bromo-1-(3-chlorophenyl)propan-1-one (**2**) is a commercially available chemical, which can be used to prepare different cathinones according to the amine in the nucleophilic substitution, facilitating synthesis.

The α-bromoketone **2** can be obtained by α-bromination of 1-(3-chlorophenyl)-1-propanone (**1**), a commercially available compound.

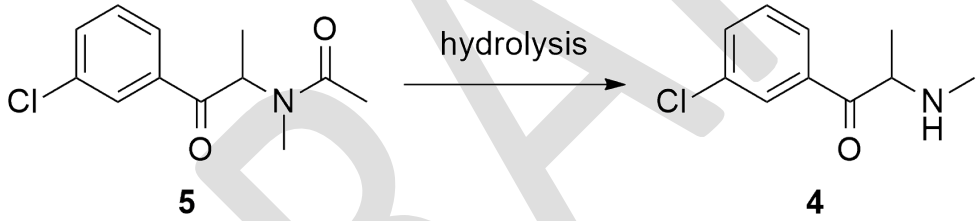


Scheme 1. Synthesis of 3-CMC

As cathinones are generally unstable as a free base, 3-CMC has been isolated as chlorohydrate in both synthetic methods.

Alternative synthetic methods have been reported, but no information was available about that used for illicit manufacture of 3-CMC, although the method shown in scheme 1 is the most probable *(5)*.

For other cathinones, such as 3-methylmethcathinone (3-MMC), so-called "masked derivatives", "masked precursors" or "designer precursors" have been seized *(6)*. In these cathinones, the amino group has been reacted with ''masking'' or ''protecting'' groups, such as acetyl groups (see **Scheme 2**), generating different chemical entities, which are easily hydrolysed to produce the controlled cathinones *(6)*. Various protecting groups can be used to this purpose.



Scheme 2. Hydrolysis of N*-acetyl-3-CMC*

While the total synthesis of 3-CMC requires qualified personnel and equipped laboratories, both preparation by amination of 2-bromo-1-(3-chlorophenyl)propan-1-one (**2**) and hydrolysis of the acetyl derivative can be achieved with only simple equipment and unskilled personnel.

E Chemical properties

Stability

Romańczuk et al. *(7)* reported that 3-CMC is unstable in biological samples (e.g. blood, urine), and its major degradation product is the dehydro-3-CMC metabolite. As this metabolite was highly stable under all storage conditions tested, it can be monitored to assess consumption of 3-CMC and avoid false negative results. Acidification of the biological matrix and/or storage at low temperature were recommended to preserve 3-CMC concentrations.

Melting-point

Hydrochloride salt

182–183 °C *(2)*

193 °C *(3)*

Boiling-point

No information was found.

Solubility

Little information was available. Analytical standards are reported to have been prepared by dissolving 3-CMC in dimethyl sulfoxide or chloroform *(1,4)*.

The hydrochloride salt of 3-CMC should be more soluble in water-soluble than the free base.

F Identification and analysis

The analytical standard 3-CMC in its hydrochloride form is commercially available for identification and quantification purposes *(1)*.

In its pure form, 3-CMC has been fully characterized by proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance, Fourier transform infrared spectroscopy, gas chromatography–mass spectrometry (GC-MS) and liquid chromatography high-resolution mass spectrometry (LC-HRMS) *(2–4)*.

3-CMC can be identified and quantified in seized samples by the general procedure described by the United Nations Office on Drugs and Crime (UNODC) for cathinones, involving presumptive colour tests followed by confirmation with, for example, GC-MS or GC-IR *(8)*.

Published methods for chiral separation of the two enantiomers of 3-CMC are based on LV–ultraviolet detection and capillary electrophoresis *(9–12)*. In view of the high cost of enantiomerically pure material, however, the products on the market are probably in the racemic form *(5)*.

Generic GC-MS methods may not allow distinction between 3-CMC and its positional isomers, 2-CMC and 4-CMC, as they have close retention times and identical MS/MS spectra *(13)*; however, the isomers can be resolved with special GC-MS methods. The isomeric forms can also be separated after derivatization and their retention time compared with that of the corresponding analytical standards *(5,7,13,14)*. Kadkhodaei et al. *(12)* showed that chiral analysis with a specific stationary phase can be used to discriminate between different cathinones, including 2-, 3- and 4-CMC *(12)*. Positional isomers of 3-CMC, including 2-CMC *(15)* and 4-CMC *(16)*, are commercially available as standards.

3-CMC can be analysed in biological matrices such as blood, urine, vitreous fluid and oral fluid by LC coupled with either low-resolution (e.g. triple quadrupole) *(17)* or high-resolution (e.g. quadrupole time-of-flight) MS *(18,19)*. 3-CMC has been characterized in whole blood and urine by direct analysis in real time coupled to tandem MS, a screening method with the advantage of fast sample preparation and low environmental impact *(20)*.

3 Ease of conversion into controlled substances

No information was available on whether 3-CMC can be converted into a controlled substance.

4 General pharmacology

A Routes of administration and dosage

No clinical studies on 3-CMC were found, and information on dosage and routes of administration from Internet discussion forums was limited. The routes of administration most commonly reported were oral ingestion and intranasal application. It was reported that an oral dose of 350 mg resulted in high euphoric effects *(21)*. Another reported that snorting six 50-mg doses over 5–6 h each resulted in onset of a euphoric effect after 10 min, with side-effects including tachycardia and craving *(22)*. Some users reported that 3-CMC was neurotoxic *(23)*, and one reported a painful ulcer in the mouth after use *(24)*. These reports are difficult to assess, not least because people who use the substance might be unable to confirm the actual substance or the amount used. Given the difficulty of collecting accurate self-reported data, these reports should be interpreted with caution.

B Pharmacokinetics

No information was available on the absorption and distribution of 3-CMC. The metabolism of 3-CMC in human biological samples (Fig. 1) has been reported to include dihydro-3-CMC, *N*-desmethyl-3-CMC and *N*-desmethyl-dihydro-3-CMC *(25)*.

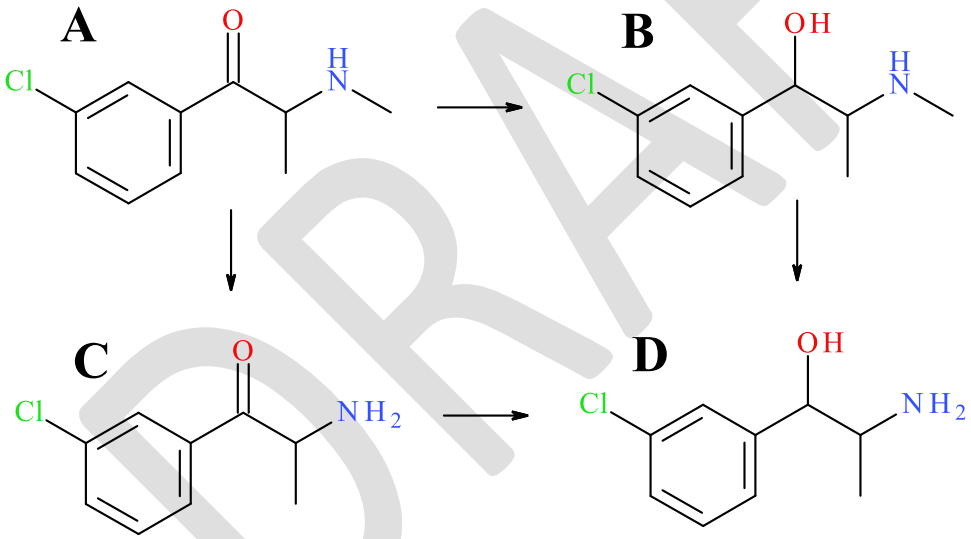


Fig. 1. Reported human metabolism of 3-CMC (A) to dihydro-3-CMC (B), *N*-desmethyl-3-CMC (C) and *N*-desmethyl-dihydro-3-CMC (D)

C Pharmacodynamics

Little information was available on the pharmacodynamics of 3-CMC. 3-CMC has psychoactive effects in both humans and animals, including dose-dependent increases in horizontal spontaneous locomotor activity in mice *(26)*. Walter et al. *(27)* showed that 3-CMC is an active stimulant and releasing agent at dopamine, serotonin and norepinephrine transporters. The effects of the isomer 4-CMC were similar to those of 4-methylmethcathione (mephedrone), with nearly identical potency *(28)*.

5 Toxicology

No information was found on the acute or chronic preclinical toxicology of 3-CMC.

6 Adverse reactions in humans

Between 2018 and 2022, eight deaths involving 3-CMC were reported in Sweden, in seven of which the drug was considered to be the cause of death and one in which the drug was listed as contributing to death *(29)*. In 38 cases of drug-impaired driving, 3-CMC was confirmed in blood and/or urine. Physiological and adverse effects reported after cases of poisoning included vomiting, headache, large pupils, hyperventilation, agitation, motor restlessness, sweating, increased pulse, high blood pressure, chest pain and seizures.

Wonderen et al. *(30)* reported two clinical cases of prolonged excited delirium after exposure to CMC; however, the isomer configuration was not determined. Both patients showed aggressive behaviour and anxiety at hospital admission. Their Glasgow Coma Scale was 4-6-1 and 3-6-5. Clinical signs were blood pressure of 129/100 and 129/60 mm Hg, heart rate of 110 and 110 beats per min, body temperature of 37.1 °C and 36.7 °C, respiration rate of 18 and 16 breaths per min, and oxygen saturation of 97% and 97% in room air. The pupils of one patient were normal in size but unresponsive to light. Both patients survived and were discharged from hospital after about 2 days.

3-CMC was reported in one medicolegal death investigation case after suspected poisoning *(25)*. Internal autopsy revealed pulmonary oedema, hyperaemia of internal organs, enlargement of the heart cavities, slight atherosclerosis of the coronary arteries, signs of hepatic steatosis and scars in the kidney cortex. 3-CMC and its metabolites were confirmed in biological samples.

A drug user reported online short-term neurological adverse effects after prolonged use of 3-CMC *(24)*.

3-CMC was reported in an acute non-fatal case in Spain in one individual *(5)*. The case report described “chemsex” practices, and additional drugs were detected during testing of biological samples. No further details were provided.

No additional studies of human exposure to 3-CMC were found, except for a case report involving 4-CMC, which is mentioned because the two isomers are expected to have similar effects. Tomczak et al. *(31)* reported 15 forensic cases involving 4-CMC, including both fatal and non-fatal drug overdoses and exposure. Autopsy of the decedents revealed acute cardiac failures, vomit in the respiratory tract and passive congestion of internal organs; however, 4-CMC might not have been the sole drug taken.

7 Dependence potential

A Studies in experimental animals

No studies on the dependence potential of 3-CMC in experimental animals were found.

B Studies in humans

No studies on the dependence potential of 3-CMC in humans were found.

8 Abuse potential

A Studies in experimental animals

No studies on the abuse potential of 3-CMC in experimental animals were found.

B Studies in humans

No studies on the avuse potential of 3-CMC in humans were found.

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

No information was found on therapeutic use.

10 Listing on the WHO Model List of Essential Medicines

3-CMC is not listed on the 23rd List of Essential Medicines List or the 9th List of Essential Medicines for Children as of July 2023.

11 Marketing authorizations (as a medicinal product)

No information was found on marketing authorization of 3-CMC as a medicinal product.

12 Industrial use

No information was found on industrial use of 3-CMC.

13 Non-medical use, abuse and dependence

3-CMC was first reported on the European drug market in 2014 by Sweden *(32)*. Since 2014, 3-CMC has been reported annually in Europe and other countries.

According to the UNODC Early Warning Advisory on New Psychoactive Substances, 3-CMC was detected in 31 countries in four regions between 2019 and 2022. Cases involving 3-CMC were reported in 21 countries in 2019, 17 in 2020, 20 in 2021 and 15 in 2022 *(33)*. A total of 161 cases involving 3-CMC were reported between 2015 and up to August 2023 (Table 1).

Table 1. Numbers of cases involving 3-CMC reported to the UNODC Early Warning Advisory on New Psychoactive Substances, by year

Year	No. of cases	Countries
2015	19	Belgium, Czechia, Estonia, Finland, France, Hungary, Kazakhstan, Netherlands (Kingdom of the), Norway, Poland, Romania, Russian Federation, Singapore, Slovakia, Slovenia, Sweden, Ukraine, USA

2016	13	Germany, Hungary, Kazakhstan, Netherlands (Kingdom of the), Norway, Poland, Slovakia, Spain, Sweden, Ukraine, USA
2017	13	Denmark, Estonia, France, Hungary, Italy, Netherlands (Kingdom of the), Norway, Poland, Slovakia, Spain, Sweden, United Kingdom, USA
2018	14	Austria, Belgium, Denmark, Finland, France, Lithuania, Luxembourg, Netherlands (Kingdom of the), Poland, Portugal, Slovenia, Spain, Switzerland, United Kingdom
2019	27	Austria, Belgium, Czechia, Denmark, Estonia, France, Germany, Greece, Hungary, Latvia, Lithuania, Netherlands (Kingdom of), Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom, USA
2020	21	Belgium, Denmark, Estonia, Finland, France, Germany, Hungary Italy, Malta, Netherlands (Kingdom of the), New Zealand, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom
2021	22	Austria, Bulgaria, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherlands (Kingdom of the), Norway, Poland, Slovakia, Spain, Sweden, Switzerland, United Kingdom, USA
2022	30	Argentina, Austria, Chile, Czechia, France, Germany, Hungary, Ireland, Italy, New Zealand, Panama, Poland, Romania, Spain, Switzerland, United Kingdom, USA
2023 (to August)	2	Austria, Switzerland

According to the UNODC, 3-CMC has been reported in the USA about once a year since 2015 *(33)*. 3-CMC has not been detected by toxicological investigations and seized drugs in the laboratory for New Psychoactive Drugs Discovery at the Center for Forensic Science Research and Education in the USA since 2018 *(34)*. According to the Drug Enforcement Administration National Forensic Laboratory Information System Drug Query System, 3-CMC was reported one to eight times a year between 2015 and 2021 by all participating crime laboratories *(35)*.

No epidemiological evidence for use of 3-CMC was found. It may be used in combination (intentionally or unintentionally) with other drugs, and people using the substance may be unaware of the exact dose or drug(s) being ingested. 3-CMC has been reported in products with 4-CMC and other drugs; however, the frequency and/or prevalence of use are not well understood *(33)*. 3-CMC is also available alone.

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

3-CMC has been offered for sale by numerous Internet retailers. As people who use drugs are likely to obtain 3-CMC from unregulated sources, its purity and dose are not assured, presenting an additional risk of adverse reactions. Currently, 3-CMC has only a small impact on public health, as its presence on the drug market is minimal. Given its pharmacological profile, however, 3-CMC appears to present a moderate risk for recreational use, physiological dependence and overdose.

15 Licit production, consumption and international trade

3-CMC is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use. Some Internet retailers have advertised it for sale as a "research chemical" or for similar use.

16 Illicit manufacture and traffic and related information

It was reported from Sweden that the amount of 3-CMC seized by customs increased in 2021 and 2022 to approximately 50 kg and 68 kg, respectively *(29)*.

The European Monitoring Centre for Drugs and Drug Addiction has received reports of seizures of 3-CMC totalling more than 2700 kg. Between 2020 and 2021, 2500 kg were seized, most seizures occurring in 2021. In the seizures reported, 3-CMC was found mainly as a powder and less frequently as tablets and capsules *(5)*.

17 Current international controls and their impact

3-CMC is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18 Current and past national controls

See Annex 1.

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

Detection of 3-CMC may be under-reported if it is not included in routine screening in all laboratories that receive samples for analysis.

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