EUDA
EUROPEAN UNION DRUGS AGENCY

Date issued: 18.12.2024

PRECURSOR ASSESSMENT REPORT of 2-bromo-3′-chloropropiophenone

This EUDA Precursor Assessment Report examines the evidence on 2-bromo-3′-chloropropiophenone, evaluating its licit use in the EU and the extent of its use in illicit production. This document was prepared at the request of the European Commission, pursuant to the Regulation (EU) 2023/1322 of the European Parliament and of the Council of 27 June 2023 on the European Union Drugs Agency (EUDA) and repealing Regulation (EC) No 1920/2006 ([1]), particularly the Article 14 (2).

The document available here is a redacted version of the original precursor assessment report. Sections that contain detailed methodology or technical information that could be misused to enable illicit synthesis have been withheld in the interest of public safety. Access to the unredacted report is restricted and will only be provided to verified law-enforcement or regulatory authorities upon request to: precursors@euda.europa.eu

Summary

Evidence

2-bromo-3′-chloropropiophenone is a chemical precursor used for the production of 3-CMC (3-cloromethcathinone or clophedrone) – a synthetic cathinone stimulant drug that has been present in the drug market in the European Union (EU) since at least 2014. The availability of 3-CMC in the EU appears to have increased significantly in 2022 and 2023, with more than 19 tonnes seized each year. This increasing availability seems to be driven mostly by large imports originating in India, but production within the EU has also been reported. 3-CMC has been under international control since December 2024.

Production of 3-CMC in the EU seems to be focused around Poland and to a much lesser extent in the Netherlands and Slovakia. At least 12 production or processing sites 3-CMC were dismantled in the EU between 2017 and 2024, of which nine were found in Poland, two in the Netherlands and one in Slovakia. Ten of these were reported to the EUDA whereas two were identified in open-source information.

2-bromo-3′-chloropropiophenone is converted into 3-CMC in a single-step chemical reaction. This reaction is straightforward and scalable, needing only basic equipment and minimal technical proficiency to be executed.

Reports of seizures of 2-bromo-3′-chloropropiophenone in the EU have been limited, likely related to its status as a non-scheduled substance, but (unquantified amounts of) the substance were seized in at least three illicit production sites in Poland. Two detections of 2-bromo-3′-chloropropiophenone were reported by two Member States (Belgium and Germany). In the Belgium case, 5 kg of the substance

([1]) https://eur-lex.europa.eu/eli/reg/2023/1322/oj

was detected in transit from China to Czechia, and in the German case an unquantified amount was found at a dumpsite.

2-Bromo-3'-chloropropiophenone is described in literature as a genotoxic impurity found in bupropion, an atypical antidepressant medication used for treatment of major depressive disorder and an aid to smoking cessation. It is present in bupropion products as an impurity and intermediate in the synthesis process, but its concentrations in medicinal preparations are strictly controlled. It is unknown to which extent the residues of 2-bromo-3'-chloropropiophenone are present in the illicitly produced 3-CMC.

2-bromo-3′-chloropropiophenone is commercially available as a reference standard for use in analytical laboratories. No other legitimate uses are known for this substance, and there is no information available about the traded volumes in the EU.

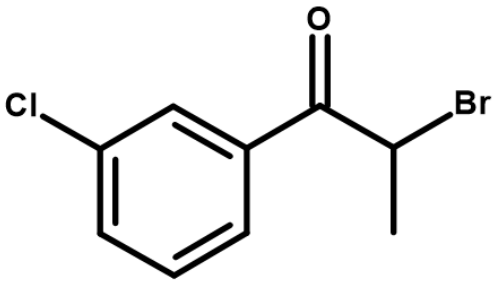
Scheduling considerations

Scheduling 2-bromo-3′-chloropropiophenone may reduce the availability of 3-CMC in the EU. However, as a result, alternative strategies can be adopted by illicit drug producers. These could possibly include the clandestine manufacture of 3-CMC starting from 3′-chloropropiophenone which requires the use of bromine and carries serious public health risks for the individuals operating the clandestine labs, on innocent people in the vicinity of the premises and any others who are exposed to the chemicals – including the law enforcement teams involved in dismantling these facilities. Given its environmental toxicity, environmental damage is likely to increase with an increasing use of bromine in this scenario. Suffice to say, if a decision is taken to schedule 2-bromo-3′-chloropropiophenone then the scheduling of 3′-chloropropiophenone should also be considered. Alternative synthetic strategies may also include the use of ‘permanganate’ oxidation of a suitable ephedrine analogue which can result in serious poisoning in people who use drugs, or the use of other designer precursors such as ‘masked cathinones'.

In addition, control may lead to a shift towards close chemical analogues of 3-CMC (such as 2-CMC or 4-CMC) or pyrrolidine-containing cathinones (alpha-PVP, alpha-PHP and alpha-PHiP) which could pose similar, or even more harms to people who use drugs. Scheduling the precursors necessary to produce these substances may mitigate these risks.

These factors should be weighed against the risks of not scheduling of the substance. If 2-bromo-3′-chloropropiophenone remains freely available illicit drug producers may be enabled to continue producing 3-CMC in EU territory. This has the potential to increase potential health risks associated with synthetic cathinone use (the extent of which is still not sufficiently understood) and the risk of generating large profits for organised crime groups.

1. Substance description

PAR_ID	RAP-2024-0002
Substance name	2-bromo-3′-chloropropiophenone
Abbreviation	2B3CPP
Chemical structure	
IUPAC name	2-Bromo-1-(3-chlorophenyl)-1-propanone
InChI code	InChI=1S/C9H8BrClO/c1-6(10)9(12)7-3-2-4-8(11)5-7/h2-6H,1H3
InChI Key	OFNMQTRHMBQQEA-UHFFFAOYSA-N
SMILES	C(C(Br)C)(=O)C1=CC(Cl)=CC=C1
Other names	2-Bromo-3′-chloropropiophenone; 2-bromo-1-(3-chlorophenyl)propan-1-one; Bupropion 2-Bromo Impurity; 2B3CP; BCP; 3'-Chlorphenyl-1-bromoethyl-ketone
Molecular formula	C9H8BrClO
Molecular weight (g/mol)	247.52
EUDA Classification	Propiophenones
CAS RN	34911-51-8
CAS page link	https://commonchemistry.cas.org/detail?cas_rn=34911-51-8&search=34911-51-8
HS/CN code	N/A
TARIC link	N/A
CUS number (ECICS)	N/A
ECICS link	N/A
EC number	252-282-1
REACH link	https://echa.europa.eu/substance-information/-/substanceinfo/100.047.514
Physical form (RT)	Liquid/Oil
Colour	Colourless to pale; yellow

Physical features	N/A
Associated with the production of	Clophedrone (synonyms: 3-chloromethcathinone, 3-CMC)
GHS Hazard Statements	H319 - Causes serious eye irritation H317 - May cause allergic skin reaction H315 - Causes skin irritation

2. Evidence of use in the illicit production

2.1 Background

2-bromo-3′-chloropropiophenone is an α-bromoketone, i.e., an aromatic ketone which is substituted in the aryl moiety – in this case with a chlorine in the *meta* position – and 'brominated' in the alkyl chain. According to published scientific literature (Blough et al., 2014; Shalabi et al., 2017) and law enforcement information, **2-bromo-3′-chloropropiophenone** is associated with the production of **3-chloromethcathinone (3-CMC)**, a synthetic cathinone stimulant drug.

Synthetic cathinones are a group of stimulant substances related to cathinone, which in itself is chemically similar to amphetamine, and is internationally controlled. Synthetic cathinones are new psychoactive substances marketed as 'legal' replacements to controlled stimulants, such as amphetamine, MDMA, and cocaine, but are also used and sought after as substances in their own right (EMCDDA, 2015).

3-CMC has been available on the European drug market at least since September 2014 (EMCDDA, 2022). It has been subject of a risk assessment by the EUDA in 2021 (EMCDDA, 2022) and, subsequently, controlled in the EU in 2022 ([2]). Following the CND Decision 67/2 ([3]) its international control in Schedule II of the 1971 Convention on Psychotropic Substances of 1971 entered into force on 3 December 2024 ([4]).

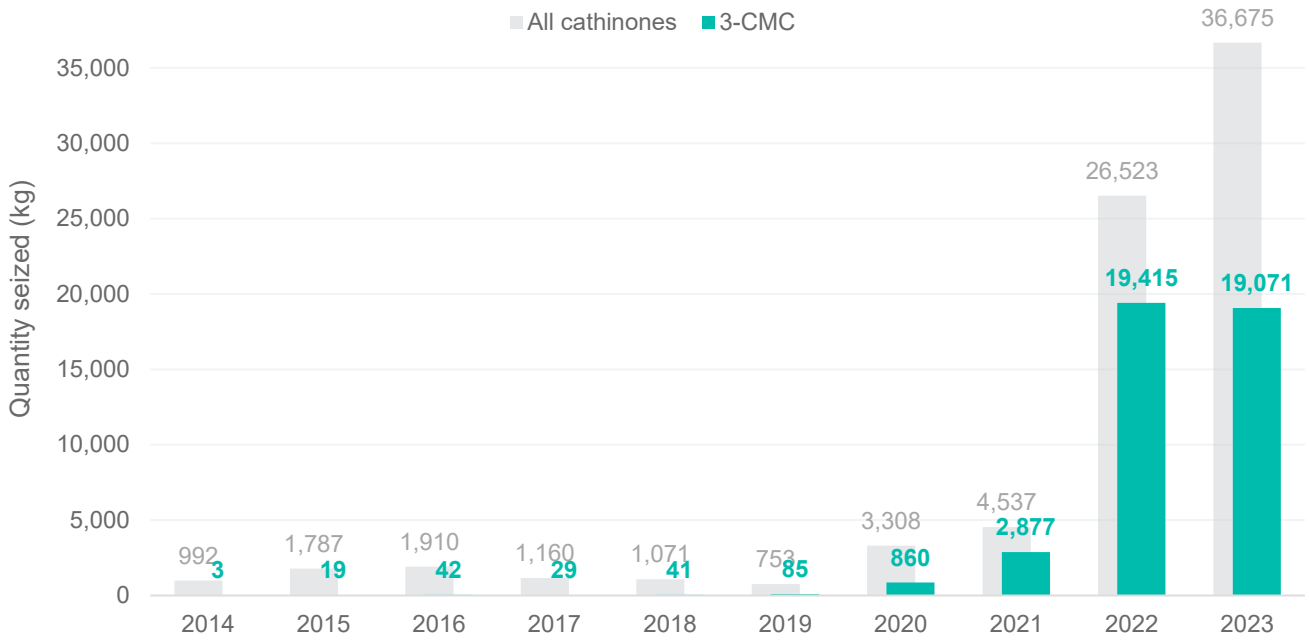
According to seizure data reported to the EU Early Warning System (EU EWS, 2024), 3-CMC is one of the most seized synthetic cathinones in Europe in 2022 and 2023 (Figure 1). From the information available, approximately 19 tonnes of 3-CMC powders were seized in the European Union in 2022 and a similar amount was seized in 2023 (Figure 1). The large majority of these seizures were shipments originating from India (18.9 and 17.5 tonnes, respectively), suggesting that imports from outside the EU are a major source for the substance in the Union (EMCDDA, 2024). Nonetheless, there is evidence that the production of 3-CMC also takes place on a large scale in Europe. For example, Poland has reported that over 600 kg of 3-CMC and 430 L of 3-CMC and precursors were seized, suggesting that large amounts of 3-CMC were produced on-site (EU EWS, 2024).

([2]) Commission Delegated Directive (EU) 2022/1326 of 18 March 2022 amending the Annex to Council Framework Decision 2004/757/JHA as regards the inclusion of new psychoactive substances in the definition of 'drug'; http://data.europa.eu/eli/dir_del/2022/1326/oj

([3]) Commission on Narcotic Drugs, Report on the sixty-seventh session (8 December 2023 and 14–22 March 2024) E/2024/28 E/CN.7/2024/15; https://documents.un.org/doc/undoc/gen/v24/021/70/pdf/v2402170.pdf

([4]) https://documents.un.org/doc/undoc/gen/v24/035/96/pdf/v2403596.pdf

Figure 1. Quantity of all synthetic cathinones and 3-CMC alone seized in the EU (2014-2013)



Source: EU Early Warning System on New Psychoactive Substances (EU EWS, EUDA) 2024.

Based on the data reported to the EUDA and Europol ([5]), between 2017 and 2022 ten sites related to the production or processing of 3-CMC have been dismantled in Europe. Of these, eight were found in Poland, one was found in Slovakia and one was found in the Netherlands. According to open-source information at least two additional production sites were dismantled: one in 2023, also in Poland ([6]) and one in the Netherlands in 2024 (PICS, see section *3. Evidence of trafficking*). From open-source information published by the Polish Police (PCBI), some of these sites appear to be large production facilities.

Data on the quantity and the identity of precursors seized at these sites is not routinely captured by any of the data sources available. From the limited information available, 2-bromo-3'-chloropropiophenone was seized in at least three of the production sites in Poland.

2.2 General methods for the synthesis of cathinones and 3-CMC

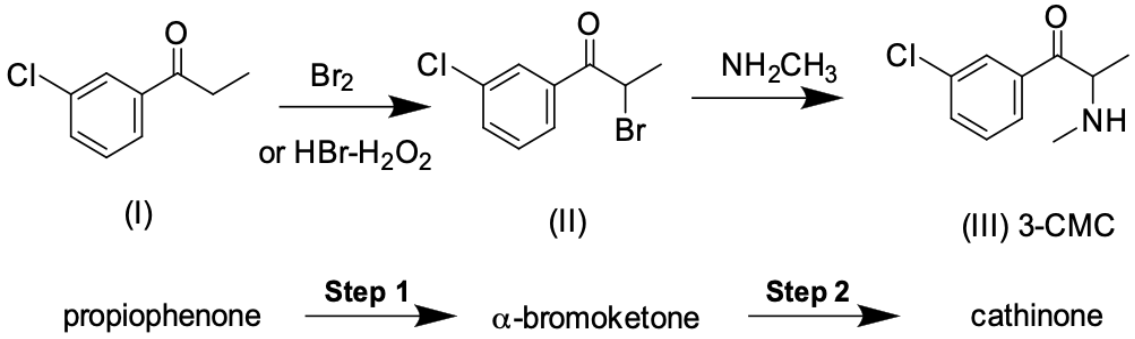
Several methods exist for the synthesis of cathinones (EMCDDA, 2022), and for the synthesis of 3-CMC in particular (Blough et al., 2014; Shalabi et al., 2017). For ring-substituted cathinones such as 3-CMC, the simplest approach involves a two-step 'bromination-amination' procedure which is a relatively straightforward process, using relatively simple equipment and no specific knowledge.

([5]) Information reported to the European Reporting Instrument on Sites Related to Synthetic Production (ERISSP).
([6]) https://cbsp.policja.pl/cbs/aktualnosci/249227,Blisko-tona-narkotykow-wartych-43-mln-PLN-zabezpieczona-przez-CBSP.html

The two-step ‘bromination-amination’ procedure starts with the bromination of a propiophenone in the ‘α’ (alpha) position to produce the corresponding α-bromoketone. The product is then reacted with an amine ([7]) to afford a free cathinone base (EMCDDA, 2011; Wrzesień, 2018). Unless steps are taken to resolve the reaction products, this synthesis produces racemic mixtures. Due to the instability of the free base, the product is converted into suitable salts (hydrochlorides or hydrobromides), which are then recrystallised (EMCDDA, 2011; Wrzesień, 2018).

Step 1 uses 3′-chloropropiophenone (I) as the starting material, obtained from direct synthesis or from commercial sources ([8]). This is by far the most hazardous step of the two-step process because it requires the use of bromine - a fuming liquid which is toxic by inhalation, may accelerate the burning of combustible materials, and is very corrosive to metals, to human tissue and dangerous for the environment. The reaction affords 2-bromo-3′-chloropropiophenone (II), an oily, colourless to pale yellow liquid soluble in acetonitrile, chloroform, dichloromethane and ethyl acetate.

Scheme 1. Preparation of 3-CMC via the ‘bromination-amination’ pathway (Shalabi et al., 2017; Blough et al., 2014).



The subject of this assessment, 2-bromo-3′-chloropropiophenone (II), is also available from chemical suppliers, meaning that the use of this precursor avoids the use of bromine and reduces the number of steps needed to obtain the final product (3-CMC). Seizures of precursors for other synthetic cathinones (4-CMC, 4-MMC) tend to reflect this preference, with larger quantities of α-bromoketone intermediates (II) being seized than propiophenones (I) (EMCDDA and Europol, 2024).

Importantly, this substance is a lacrimatory agent and causes serious eye irritation as well as skin irritation and allergic skin reactions. Methods that avoid its use have been developed (Allen et al., 2021).

Conversion of 2-bromo-3′-chloropropiophenone (II) into the final product 3-CMC (III) (step 2 in Scheme 1), can occur under mixing and heating but does not require it and can be easily scaled-up, making it a relatively simple procedure to execute in clandestine facilities (EMCDDA and Europol, 2024). The resulting base products are converted into salts (typically hydrochloride salts) and then recrystallised to remove impurities in large plastic trays that are characteristic findings in cathinone production facilities (EMCDDA and Europol, 2024).

([7]) This step promotes the nucleophilic substitution of the bromine to obtain the α-bromoketone. For ring substituted cathinones, the amine is typically methylamine hydrochloride and triethylamine in an acidic scavenger.
([8]) see Report on the Precursor Assessment of 3’-chloropropiophenone (EUDA, 2024).

It is unknown to what extent 2-bromo-3'-chloropropiophenone impurities remain in the illicitly produced 3-CMC, but considering the fact that the illicit production is often performed in poorly equipped laboratories and often with minimal purification, it might be assumed that the residues may remain in the final product and might cause concern with prolonged exposure. The substance has been found to have mutagenic, clastogenic, and aneugenic properties ([9]) mediated by reactive oxygen species generation (Meng et al., 2013), which is why its concentration in pharmacological products (e.g. bupropion) is strictly controlled.

The 2-step 'bromination-amination procedure' presents advantages for organised crime groups involved in the production of synthetic cathinones. This is because a number of different *N*-substituted synthetic cathinones can be produced in series, simply by obtaining the intermediate (II) in a large scale, and then subdividing it into lots and reacting each lot with a different amine to produce a different cathinone (Collins, 2016). For example, adding *tert*-butylamine instead of methylamine in step 2 of scheme I produces bupropion instead of 3-CMC.

3. Evidence of trafficking in the EU

2-bromo-3′-chloropropiophenone is not a scheduled precursor and thus the reporting of its seizures and stopped shipments to the European Drug Precursors Database (EDPD) is voluntary which may result in its de-prioritization in law enforcement activity and therefore data may not be recorded or reported (Singleton et al, 2018).

There are two reports of detections of 2-bromo-3′-chloropropiophenone in two EU Member States, Belgium and Germany, between 2016 and 2024. One was reported to the EDPD, and another was reported to the INCB.

4. Legitimate uses in the EU

2-bromo-3′-chloropropiophenone is available as a reference standard used in analytical laboratories ([10]). Among other things, it is used to detect impurities in the synthesis of the medicine bupropion, an atypical antidepressant used for treatment of major depressive disorder and an aid to smoking cessation. The presence of 2-bromo-3′-chloropropiophenone in bupropion is strictly controlled because the compound has been shown to have mutagenic, clastogenic, and aneugenic properties mediated by reactive oxygen species generation (Meng et al., 2013).

It is also used in research, however, the full extent of its applications in pharmaceutical research would be difficult to evaluate. No information about its legal trade in the EU has been found.

5. Legal controls

Based on the available information, 2-bromo-3′-chloropropiophenone is not a controlled substance in any searched jurisdictions ([11]), except for Taiwan. In Taiwan, it is controlled under the Schedule 4

([9]) i.e. it induces genetic mutations, damage to chromosomes and affects cell division
([10]) https://www.lgcstandards.com/BR/pt/2-Bromo-1-3-chlorophenyl-propan-1-one-2-Bromo-3-chloropropiophenone-/p/MM0745.15
([11]) Searched jurisdictions and treaties: Argentina, Austria, Belgium, Brazil, Canada, Chemical Weapons Convention, Australia Group, China, Denmark, European Union, Finland, France, Germany, India, Indonesia, Ireland, Italy, Japan, Mexico, Montreal Ozone Protocol, Netherlands, Norway, Poland, Rotterdam Convention, Saudi Arabia, Singapore, Slovakia, Spain, Sweden,

Controlled Drug Materials, Controlled Drugs Act (Item 39). In that legislation, all positional isomers of 2-bromo-chloropropiophenone (2-bromo-**2′-chloro**propiophenone, 2-bromo-3′-chloropropiophenone and 2-bromo-**4′-chloro**propiophenone) are controlled. No cathinone precursor with similar structure is scheduled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

6. Use, trafficking and distribution outside of EU

There is currently no available information about the use of 2-bromo-3′-chloropropiophenone outside of the EU. Nevertheless, in one reported case of seizure in Europe, China was indicated as the origin country of the chemical. It is possible that 2-bromo-3′-chloropropiophenone is available as a reference standard used in analytical laboratories outside of the EU. The extent of its use in chemical and pharmaceutical industry or research is unknown.

7. Conclusions and possible consequences of scheduling

The data available suggests that 2-bromo-3′-chloropropiophenone is used in the European Union as a precursor in the synthesis of 3-CMC as it has been detected in at least three illicit production sites in the EU. The use of α-bromoketones (such as 2-bromo-3′-chloropropiophenone) for the production of cathinones (such as 3-CMC) tends to be preferred in illicit drug production facilities than using 3′-chloropropiophenone (I) (see Scheme 1) as a starting material because starting the production from the second production step not only simplifies the synthesis procedure but also to avoids the handling of the toxic chemical bromine.

2-Bromo-3'-chloropropiophenone is described in literature as a genotoxic impurity found in bupropion, exhibiting mutagenic, clastogenic, and aneugenic properties mediated by reactive oxygen species generation (Meng et al., 2013). It is present in bupropion products as an impurity and intermediate in the synthesis process, but its concentrations in medicinal preparations are strictly controlled. It is unknown to which extent the residues of 2-bromo-3'-chloropropiophenone are present in the illicitly produced 3-CMC, but considering the fact that the illicit production is often performed in poorly equipped laboratories and often without employing any purification steps, it might be assumed that the residues may remain in the final product and might cause concern with prolonged exposure.

Scheduling of 2-bromo-3′-chloropropiophenone may lead to unpredictable outcomes. Some of the potential scenarios are listed below:

- ***Scheduling of 2-bromo-3'-chloropropiophenone may reduce the availability of 3-CMC in the EU.*** Inclusion of the chemical under the EU controls might make its trade and use for illicit production of 3-CMC more difficult and, thus, reduce the availability of 3-CMC in the EU. Because the extent of use of 2-bromo-3′-chloropropiophenone in illicit production of 3-CMC appears to be limited, the scale of this impact would be difficult to assess. Nevertheless, following the ban, the illicit production might shift to other starting materials, different synthetic routes or other end-products altogether.

Switzerland, Taiwan, UN (INCB), United Kingdom, United States of America, Wassenaar Arrangement, World Anti-Doping Agency.

- ***Scheduling of 2-bromo-3'-chloropropiophenone may result in different chemical routes being adapted by illicit drug producers.*** Numerous alternative synthetic methods for 3-CMC exist which avoid of 2-bromo-3′-chloropropiophenone and could potentially be used for production in case of its scheduling (Mehta, 1971; Blough et al., 2014). [This section was redacted in the interest of public safety]

- ***Scheduling of 2-bromo-3'-chloropropiophenone may result in its production by illicit drug producers.*** Rather than obtaining it commercially, 2-bromo-3′-chloropropiophenone may be produced in clandestine facilities using 3′-chloropropiophenone as the starting material. i.e., start production in step 1 of the 'bromination-amination' procedure (see Scheme 1). This would imply that the first ('bromination') step, often avoided given its associated harms could be used more often which could result in serious public health related risks for the individuals operating the clandestine labs, on innocent people in the vicinity of the premises and any others who are exposed to these chemicals including the law enforcement teams involved in dismantling these facilities. Given its chemical properties, environmental damage is likely to increase with an increasing use of bromine. Suffice to say, if a decision is taken to schedule 2-bromo-3′-chloropropiophenone, then 3′-chloropropiophenone should also be scheduled at the same time to avoid such a result.

- ***Scheduling of 2-bromo-3'-chloropropiophenone may result in the emergence of 'designer' cathinone precursors.*** The scheduling of 3′-chloropropiophenone may motivate illicit drug producers to seek alternatives to the precursor, and import 'masked' alternatives of the final product 3-CMC. [This section was redacted in the interest of public safety]

- ***Scheduling of 2-bromo-3'-chloropropiophenone may shift illicit drug production to different end-products.*** Lack of access to the precursor necessary to produce 3-CMC could result in the shift of illicit production to other types of synthetic cathinones for which the precursors are not controlled. [This section was redacted in the interest of public safety]

- ***Scheduling of 2-bromo-3'-chloropropiophenone is unlikely to impact legitimate industries*****,** as the substance appears to have no known legitimate use in the sources consulted.

The information above appears to indicate that there are some risks to be considered concerning the scheduling of 2-bromo-3′-chloropropiophenone. These should be weighed against the risks of not scheduling the substance.

Not scheduling 2-bromo-3'-chloropropiophenone may enable illicit drug producers to continue producing 3-CMC in EU territory**.** Synthetic cathinones such as 3-CMC appear to be increasingly available in the EU. The more widespread use of synthetic cathinones is a relatively new development in the European market and the potential health risks associated with this phenomenon or what might constitute appropriate interventions are still not sufficiently understood (EMCDDA, 2024). In addition, the production and trafficking of synthetic cathinones may generate large profits for organised crime groups. For example, 4-MMC powder costs EUR 21 000 per kilogram at wholesale level (equivalent to EUR 2.1 per gram) but can be sold at 22.5 EUR to the consumer (mark-up of approximately 20 EUR per gram). (EMCDDA, 2024) Although synthetic cathinones' price data is limited, it is likely that prices for 3-CMC are within this range.

8. References

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