EUDA
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# PRECURSOR ASSESSMENT REPORT of 2-bromo-4′-chloropropiophenone

This EUDA Precursor Assessment Report examines the evidence on 2-bromo-4′-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-4′-chloropropiophenone is a chemical precursor used for the production of 4-CMC (Clephedrone or 4-chloromethcathinone) – a synthetic cathinone stimulant drug that has been present in the drug market in the European Union (EU) since at least 2014. 4-CMC has been under international control since 2020.

In the period 2014-2023 seizures of 4-CMC in the EU have been close to an average of 300 kilograms per year. However, from additional sources, it appears that the seizures in 2023 could have reached over 7.5 tonnes.

Production of 4-CMC in the EU seems to be focused primarily around Poland and, to a lesser extent, the Netherlands. According to official data, at least 33 production or processing sites of 4-CMC were dismantled in the EU between 2016 and 2022, of which 25 were found in Poland (10 in 2022), 6 in the Netherlands and 2 in Belgium. Eight additional sites in Poland were identified in open-source information.

2-bromo-4′-chloropropiophenone is converted into 4-CMC typically in a one-step reaction. This reaction is straightforward and scalable, needing only basic equipment and minimal technical proficiency.

Reports of seizures of 2-bromo-4′-chloropropiophenone in the EU have been registered, however, it is still a non-scheduled substance and reporting is voluntary. Between 2018 and 2024, 19 seizures of 2-bromo-4′-chloropropiophenone have been reported to the European Drug Precursors Database (EDPD) by 4 Member States (Germany, Luxembourg, the Netherlands and Poland), totalling over 4.5 tonnes. Additionally, 13 incidents occurring in the EU countries, totalling over 3.7 tonnes and 270 litres, were

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

reported to Precursors Incidents Communication System (PICS), some of which may be duplicated with data already reported to the EDPD.

When known, shipments of the substance to the EU originated primarily in China and India, with destinations including Poland and Germany. Mislabelling was reported in one case. At least eight seizures occurred in an illicit laboratory, but it is likely that seizures of 2-bromo-4′-chloropropiophenone in illicit production facilities are under-reported.

2-bromo-4′-chloropropiophenone is commercially available as a reference standard for use in analytical laboratories.

## Scheduling considerations

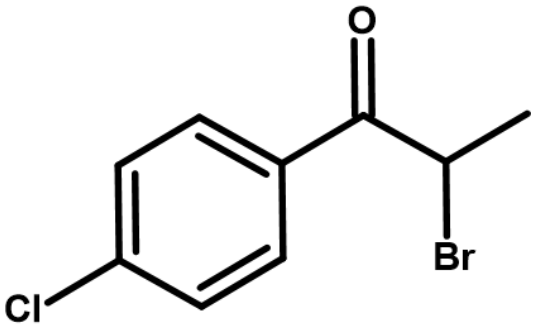
Scheduling 2-bromo-4′-chloropropiophenone may contribute to reducing the availability of 4-CMC in the EU and limit the generation of large profits for organised crime groups. However, the impact of this action would be difficult to assess. Alternative strategies can also be adopted by illicit drug producers. If 2-bromo-4′-chloropropiophenone is scheduled, and its non-brominated counterpart 4′-chloropropiophenone is freely available, this may motivate illicit drug producers to start the production from the previous step (‘bromination’), which poses serious public health risks for the individuals operating the illicit laboratories, 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. Suffice to say, if a decision is taken to schedule 2-bromo-4′-chloropropiophenone, then 4′-chloropropiophenone should also be considered for scheduling to avoid such a result.

Alternative synthetic routes could possibly include the use of ‘permanganate’ oxidation of suitable ephedrine analogues which can result in serious poisoning in people who use drugs or the emergence of other designer precursors such as ‘masked cathinones'. In addition, control may lead to a shift towards close chemical analogues of 4-CMC (such as 2-CMC and 3-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, or others cathinones (e.g. 4-BMC).

Scheduling 2-bromo-4′-chloropropiophenone is unlikely to impact legitimate industries, as the substance appears to have no known legitimate use in the sources consulted, outside of the use as a reference standard for analytical laboratories.

These factors should be weighed against the risks of not scheduling of the substance. For example, if 2-bromo-4′-chloropropiophenone remains freely available illicit drug producers may be enabled to continue producing 4-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** | 2025-0008 |
| **Substance name** | 2-bromo-4′-chloropropiophenone |
| **Abbreviation** | 2B4CPP |
| **Chemical structure** |   |
| **IUPAC name** | 2-Bromo-1-(4-chlorophenyl)-1-propanone |
| **InChI code** | InChI=1S/C9H8BrClO/c1-6(10)9(12)7-2-4-8(11)5-3-7/h2-6H,1H3 |
| **InChI Key** | SAKMPXRILWVZEG-UHFFFAOYSA-N |
| **SMILES** | C(C(Br)C)(=O)C1=CC=C(Cl)C=C1 |
| **Other names** | 2-bromo-1-(4-chlorophenyl)propan-1-one; α-Bromo-4′-chloropropiophenone; Bupropion Impurity 32 |
| **Molecular formula** | $C_9H_8BrClO$ |
| **Molecular weight (g/mol)** | 247.52 |
| **EUDA Classification** | Propiophenones |
| **CAS RN** | 877-37-2 |
| **CAS page link** | https://commonchemistry.cas.org/detail?cas_rn=877-37-2&search=877-37-2 |
| **HS/CN code** | N/A |
| **TARIC link** | N/A |
| **CUS number (ECICS)** | N/A |
| **ECICS link** | N/A |
| **EC number** | 814-935-4 |
| **REACH link** | https://echa.europa.eu/substance-information/-/substanceinfo/100.248.696 |
| **Physical form (RT)** | solid |
| **Colour** | white, off-white to pale beige colour |

| | |
|---|---|
| **Physical features** | Characteristic smell |
| **Associated with the production of** | Clephedrone (4-chloromethcathinone, 4-CMC) |
| **GHS Hazard Statements** | H402 - Harmful to aquatic life<br>H335 - May cause respiratory irritation<br>H332 - Harmful if inhaled<br>H319 - Causes serious eye irritation<br>H315 - Causes skin irritation<br>H312 - Harmful in contact with skin<br>H302+H332 - Harmful if swallowed or if inhaled<br>H302 - Harmful if swallowed |

# 2. Evidence of use in the illicit production

## 2.1 Background

2-bromo-4′-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 *para* position – and 'brominated' in the alkyl chain. According to the published literature (Wrzesień, 2018), **2-bromo-4′-chloropropiophenone** is associated with the illicit production of **4-CMC (Clephedrone, 4-chloromethcathinone)**.

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).

4-CMC has been available on the EU drug market since at least 2014 (EMCDDA, 2024). It has not been subject to a risk assessment by the EUDA, but it has been subject to a Critical Review by the Expert Committee on Drug Dependence (ECDD) (WHO, 2019). Following the CND Decision 63/9 ([2]) its international control in Schedule II of the 1971 Convention on Psychotropic Substances has entered into force in 2020.

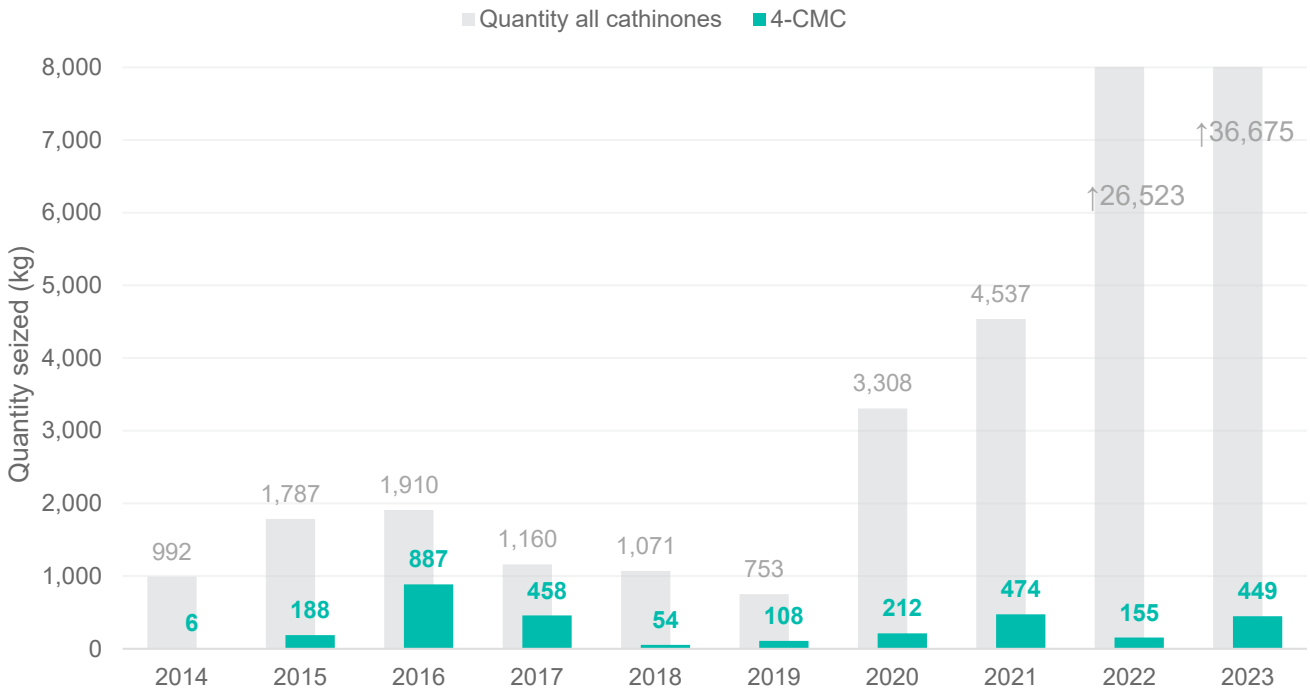
The appearance of 4-CMC on the drug market coincided with the control of mephedrone (4-MMC) in Europe, after the latter spread rapidly on the continent between 2009 and 2010 when it was being produced, distributed, and sold openly as a 'legal' stimulant (EMCDDA, 2022). At least in part, it appears that 4-CMC was introduced in the market as a non-controlled alternative to 4-MMC (EMCDDA, 2022). Detections of 4-CMC have been made by 25 Member States, and have continued to occur despite its legal control.

Although seizures of 4-CMC reported to the EU Early Warning System (EWS) have been limited over the last few years (Figure 1), averaging about 300 kg per year, additional data reported to the EUDA suggests that in 2023 seizures of 4-CMC in the EU have been close to 7.5 tonnes, primarily reported by Poland.

([2]) Commission on Narcotic Drugs Report on the sixty-third session (13 December 2019 and 2–6 March 2020), E/2020/28, E/CN.7/2020/15; https://documents.un.org/doc/undoc/gen/v20/019/56/pdf/v2001956.pdf

On multiple occasions the source of shipments of 4-CMC to the EU was reported to be China ([3]). 4-CMC production has been reported in Europe, particularly focused around Poland and the Netherlands.

**Figure 1.** Quantity of all synthetic cathinones and 4-CMC alone seized in the EU (2012-2023)




Source: EU Early Warning System on New Psychoactive Substances, 2024. Additional data was reported to the EUDA, via standard reporting (not shown).

Based on the data reported to the EUDA and Europol ([4]), between 2016 and 2022, at least 33 sites have been reported as involved in production or processing of 4-CMC in three Member States. These include 25 sites found in Poland, 6 in the Netherlands and 2 in Belgium. The number of dismantled laboratories suggests an increase in production over the last few years, with 42% of all sites reported being dismantled in 2022 (14 sites).

Data on the quantity and the identity of precursors seized at these sites is not routinely recorded in any of the data sources available. Nonetheless, in the large majority of cases reported from Poland (11 sites, 33% of all reports), 2-bromo-4′-chloropropriophenone was indicated as the precursor chemical used for 4-CMC synthesis.

Additional information sources including open-source information account for at least five additional 4-CMC production sites dismantled in Poland in 2023 and three in 2024 ([5]), including a large-scale illicit laboratory in April 2024, where 3.8 tonnes of 4-CMC and 20 tonnes of precursors and chemicals used in production were seized ([6]).

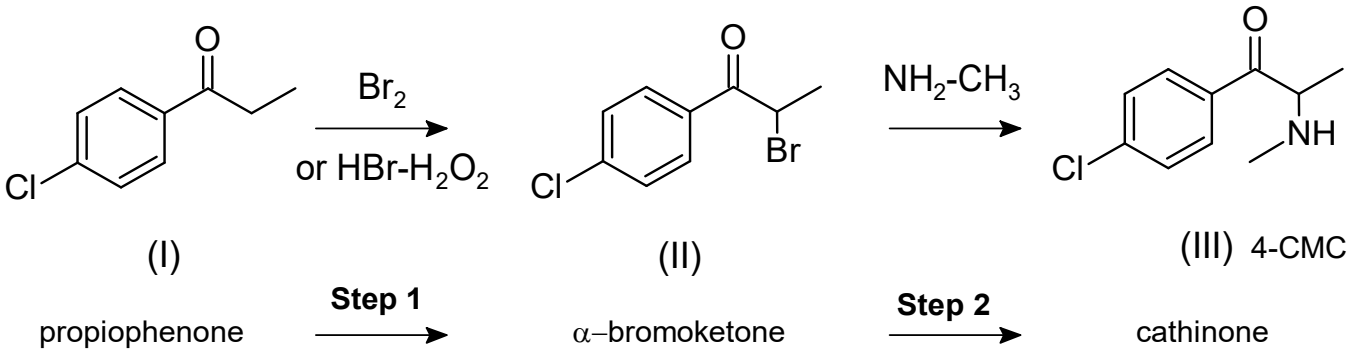
([3]) Based on the cases reported to the European Database on New Drugs (EDND)
([4]) Information reported to the European Reporting Instrument on Sites Related to Synthetic Production (ERISSP)
([5]) https://cbsp.policja.pl/cbs/szukaj?search=209529&sort=2&order=1&ile=20
([6]) https://cbsp.policja.pl/cbs/aktualnosci/244483,Ogromna-fabryka-krysztalu-zlikwidowana-przez-CBSP.html

## 2.2 General methods for the synthesis of cathinones and 4-CMC

Several methods exist for the synthesis of cathinones (EMCDDA, 2022). For ring-substituted cathinones such as 4-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.

The two-step 'bromination-amination' procedure starts with the bromination of a propiophenone 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) (Scheme 1). 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).

**Scheme 1.** Preparation of 4-CMC via the 'bromination-amination' pathway (Blough et al., 2014; Shalabi et al., 2017; Wrzesień, 2018).




Step 1 uses 4′-chloropropiophenone (I) as the starting material, obtained from direct synthesis or from commercial sources. 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. Using *N*-bromosuccinimide (NBS) in the presence of an acid catalyst avoids the use of bromine, which is sometimes the preferred approach for industrial-scale (pharmaceutical) production of these intermediates (II) (Reddy et al., 2010; see also Guha et al., 2015).

The reaction affords 2-bromo-4′-chloropropiophenone (II), the subject of this assessment. If isolated, this substance is a solid substance with a white, off-white to pale beige colour. It is sparingly soluble in chloroform and methanol. This substance is a lachrymatory agent, causes serious eye irritation, causes skin irritation and may cause respiratory irritation.

2-bromo-4′-chloropropiophenone (II) is also available from chemical suppliers, meaning that the first step can be omitted, avoiding the use of bromine. Seizures of precursors for synthetic cathinones tend

([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.

to reflect this, with larger quantities of α-bromoketone intermediates (II) being seized than propiophenones (I) (EMCDDA and Europol, 2024).

The second step (‘amination’) proceeds by reacting the 2-bromo-4′-chloropropiophenone (II) with an excess of methylamine or methylamine hydrochloride and an acid scavenger. The reaction is quenched with gaseous or aqueous hydrochloride providing the 4-CMC hydrochloride salt. The final product is then recrystallised to remove impurities, typically in large plastic trays that are characteristic findings in illicit cathinone production facilities (EMCDDA and Europol, 2024). This is a relatively straightforward option because the starting materials are commercially available or easily synthesised, it is scalable and straightforward (EMCDDA, 2011).

## 3. Evidence of trafficking in the EU

2-bromo-4′-chloropropiophenone is not a scheduled precursor and thus the reporting of its seizures and stopped shipments is voluntary at this point. Its legal status is likely to result in its de-prioritization in law enforcement activity and therefore data may not be recorded or reported (Singleton et al, 2018).

Two sources were examined for reports of 2-bromo-4′-chloropropiophenone trafficking, the European Commission’s EDPD and the INCB’s PICS. Between 2018 and 2024 ([8]), 19 cases (13 reports, some with multiple seizures) of seizures of 2-bromo-4′-chloropropiophenone have been reported to the EDPD by 4 Member States (Germany, Luxembourg, the Netherlands and Poland), totalling over 4.5 tonnes. Of these seizures, the majority (63 %) was reported by the Netherlands (2.8 tonnes, of which 2.3 tonnes were seized in 2024), followed by Germany (700 kg, 16 %), Luxemburg (500 kg, 11 %), and Poland (422 kg, 10 %).

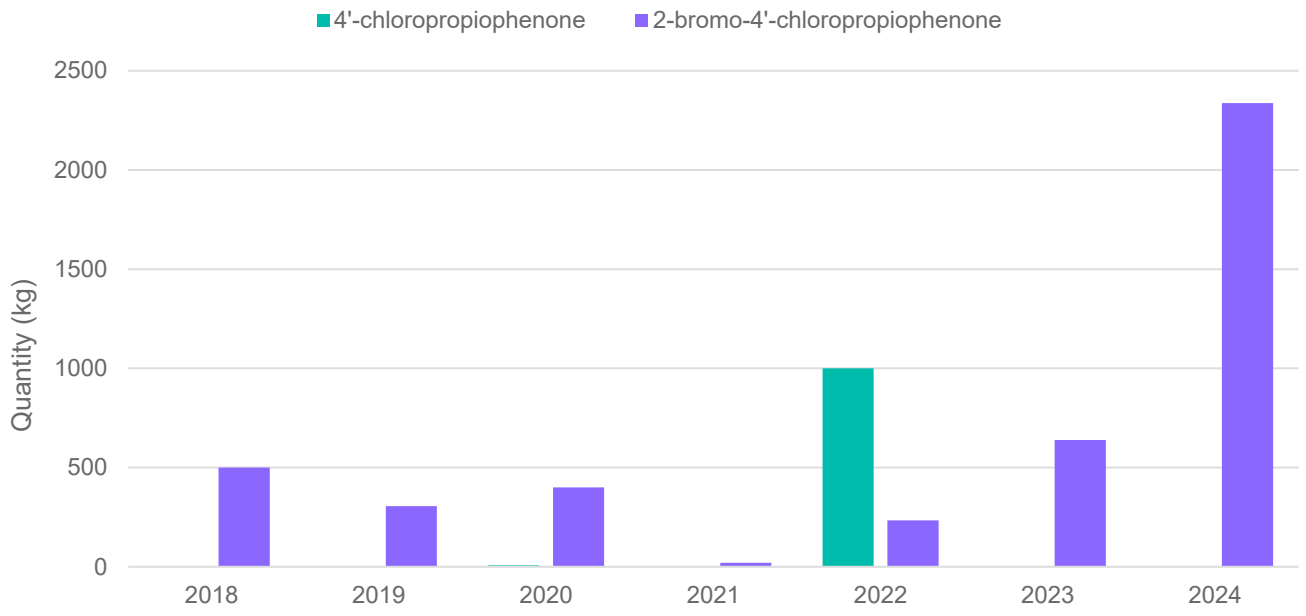
The origin and/or provenance of the seized material was reported for 4 out of 13 reports (corresponding to 1.5 tonnes out of 4.5 tonnes of material seized). In 3 of the cases for which it was known, the origin was China, and in one case from 2018 the shipment had come from India. Destinations reported included Germany (2 cases, 900 kg), the Netherlands (1 case, 300 kg), Poland (1 case, 400 kg).

At least three of those seizures occurred in illicit laboratories in Poland. In at least one case the shipment was misdeclared as ‘Medicines-Gen’.

Based on the seizure information it appears that 2-bromo-4′-chloropropiophenone (II) is the preferred starting material for the synthesis of 4-CMC, showing an apparent preference to import α-bromoketone intermediates (II) rather than propiophenones (I) needed for step 1 of the ‘bromination-amination’ synthesis (see Figure 2). Nevertheless, a large shipment of one tonne of 4′-chloropropiophenone has been reported by France in 2022, which suggests that substance could also be used as a starting material for production of 4-CMC.

([8]) Data collection for 2024 has not yet been finalised and can be subject to change.

**Figure 2.** Quantities of 4-CMC precursors 4′-chloropropiophenone and 2-bromo-4′-chloropropiophenone reported in seizures or stopped shipments in the EU, EU Drug Precursors Database, 2024




## 4. Legitimate uses in the EU

2-bromo-4′-chloropropiophenone is commercially available as a reference standard used in analytical laboratories ([9]). No information about the legal trade of 2-bromo-4′chloropropiophenone has been found in the European Chemicals Agency (ECHA) database.

The substance seems to have application in chemical synthesis and research, for examples it may be used as a substrate in the synthesis of 2-aminothiazoles, a group of compounds with antiviral properties and with various medicinal applications (Buchstaller, 2011). 2-bromo-4′-chloropropiophenone appears to have additional applications in medicinal chemistry and organic synthesis, however, the full extent of its applications in scientific research would be difficult to evaluate, and it is not the subject of this report.

## 5. Legal controls

Based on the available information, 2-bromo-4′-chloropropiophenone is not a controlled substance in any of the searched jurisdictions ([10]), except for Taiwan. In Taiwan, it is controlled under the Schedule 4 Controlled Drug Materials, Controlled Drugs Act (Item 39). In that legislation, all positional isomers of 2-bromo-chloropropiophenone (including also 2-bromo-**3′-chloro**propiophenone and 2-bromo-**2′-chloro**propiophenone) are controlled. No cathinone precursor with similar structure is scheduled under

([9]) https://www.caymanchem.com/product/40861/2-bromo-4'-chloropropiophenone
([10]) 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, Switzerland, Taiwan, UN (INCB), United Kingdom, United States of America, Wassenaar Arrangement, World Anti-Doping Agency.

the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

## 6. Use, trafficking and distribution outside of the EU

No information is available about the use, trafficking and distribution of 2-bromo-4′-chloropropiophenone outside of the EU.

## 7. Conclusions and possible consequences of scheduling in the EU

The limited seizure data available suggests that 2-bromo-4′-chloropropiophenone is used in the European Union as a precursor in the synthesis of 4-CMC. Production of 4-CMC in illicit facilities seems to preferably commence from the second step of a two-step 'bromination-amination' reaction, which uses 2-bromo-4′-chloropropiophenone as the main precursor, rather than from the previous step which requires 4′-methylpropiophenone. This is likely to be motivated by an attempt not only to simplify the synthesis procedure to one step but also to avoid handling the toxic chemical bromine.

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

- ***Scheduling 2-bromo-4'-chloropropiophenone may contribute to reducing the availability of 4-CMC.*** Inclusion of the chemical under EU controls might make its trade and use for illicit production of 4-CMC more difficult and, thus, contribute to reducing the availability of 4-CMC in the EU. Although 2-bromo-4′-chloropropiophenone appears to be the main precursor in illicit production of 4-CMC, the impact of scheduling 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.

- ***Scheduling 2-bromo-4'-chloropropiophenone, while not scheduling its counterpart 4'-chloropropiophenone may motivate illicit drug producers to adapt the synthetic route to start from 4'-chloropropiophenone*** i.e., start production in step 1 of the 'bromination-amination' procedure (see Scheme 1). This would imply that the 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 illicit laboratories, 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 environmental toxicity, environmental damage is likely to increase with an increasing use of bromine. Suffice to say, if a decision is taken to schedule 2-bromo-4′-chloropropiophenone, then 4′-chloropropiophenone should also be scheduled to avoid such a result.

- ***Scheduling 2-bromo-4'-chloropropiophenone may result in different chemical routes being adapted by illicit drug producers.*** Numerous alternative synthetic methods for 4-CMC exist which avoid 2-bromo-4′-chloropropiophenone and could potentially be used for production in case of its scheduling (Wrzesień, 2018). [This section was redacted in the interest of public safety]

- ***Scheduling 2-bromo-4'-chloropropiophenone may result in the emergence of 'designer' cathinone precursors.*** The scheduling of 2-bromo-4′-chloropropiophenone may motivate illicit drug producers to seek alternatives to the precursor, and import 'masked' alternatives of the final product 4-CMC. [This section was redacted in the interest of public safety]

- ***Scheduling 2-bromo-4'-chloropropiophenone may shift illicit drug production to different end-products.*** Lack of access to the precursor necessary to produce 4-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-4'-chloropropiophenone is unlikely to impact legitimate industries*****,** as the substance appears to have no known legitimate use in the sources consulted. Nevertheless, scheduling the substance might impact research, as it appears to have applications in medicinal chemistry and organic synthesis.

The information above appears to indicate that there are some risks to be considered concerning the scheduling of 2-bromo-4′-chloropropiophenone. These should be weighed against the risks of not scheduling the substance.

***Not scheduling 2-bromo-4'-chloropropiophenone may enable illicit drug producers to continue producing 4-CMC in EU territory*****.** Synthetic cathinones such as 4-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, as an analogy, mephedrone (4-MMC) powder costs 2.1 EUR per gram at wholesale level but can be sold at 22.5 EUR to the consumer (mark-up of approximately 20 EUR per gram) (EMCDDA, 2024).

Additional unintentional consequences may also occur due to a range of factors, derived from currently unpredictable market dynamics. This document should be viewed as part of a broader decision-making process, requiring ongoing evaluation as circumstances evolve.

## 8. References

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