

PRECURSOR ASSESSMENT REPORT of 4'-chloropropiophenone

This EUDA Precursor Assessment Report examines the evidence on 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

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.

4'-chloropropiophenone is converted into 4-CMC typically by means of a two-step process. This method is straightforward and scalable, needing only basic equipment and minimal technical proficiency. One of its main drawbacks is the need to use bromine, a particularly toxic and hazardous chemical, in the first step, when 2-bromo-4'-chloropropiophenone is made. To avoid this step, clandestine production of 4-CMC often starts directly from the second step using the equally commercially available 2-bromo-4'-chloropropiophenone as a starting material.

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

Reports of seizures of 4'-chloropropiophenone in the EU have been limited, likely related to its status as a non-scheduled substance, as well as the preference towards starting production from the 2-bromo-4'-chloropropiophenone. At least 4 seizures and 1 stopped shipment, totalling over 1657 kilograms of 4'-chloropropiophenone occurred in 3 Member States (France, Netherlands and Poland) between 2020 and 2022, according to information reported to the European Drug Precursors Database (EDPD) and to the INCB.

Where known, shipments of the substance to the EU originated primarily in China, with destination to Poland. One shipment was also destined for the United Kingdom. Mislabelling was reported in one case. At least one of the seizures occurred in an illicit laboratory, but it is likely that seizures of 4'-chloropropiophenone in illicit production facilities are under-reported.

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

Scheduling considerations

Scheduling 4'-chloropropiophenone may contribute to the reduction of the availability of 4-CMC in the EU and limit the generation of large profits for organised crime groups. However, as a result, alternative strategies can be adopted by illicit drug producers. These could possibly include the clandestine manufacture of 4'-chloropropiophenone, 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 or 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.

Scheduling 4'-chloropropiophenone may impact legitimate industries to a limited extent, as the substance appears to have one active registration in the EU.

These factors should be weighed against the risks of not scheduling of the substance. For example, if 4'-chloropropiophenone remains freely available, and its brominated counterpart 2-bromo-4'-chloropropiophenone is subject to controls, this may motivate illicit drug producers to simply start from the first ('bromination') step, which carries serious public health risks for the individuals operating the illicit laboratories, and 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 4'-chloropropiophenone, then 2-bromo-4'-chloropropiophenone should also be considered for scheduling to avoid such a result.

Physical form (RT)	Solid, crystalline substance
Colour	White / off-white
Physical features	N/A
Associated with the production of	Clephedrone (Synonyms: 4-chloromethcathinone, 4-CMC)
GHS Hazard Statements	H411 - Toxic to aquatic life with long lasting effects H335 - May cause respiratory irritation H319 - Causes serious eye irritation H317 - May cause allergic skin reaction H315 - Causes skin irritation H302 - Harmful if swallowed

2. Evidence of use in the illicit production

2.1 Background

4'-chloropropiophenone is a substituted propiophenone, i.e., an aromatic ketone, substituted in the aryl moiety in the *para* position with a chlorine atom. According to the published literature (Wrzesień, 2018), **4'-chloropropiophenone** is associated with the illicit production of **4-CMC (Clephedrone, 4-chloromethcathinone)**, 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).

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.

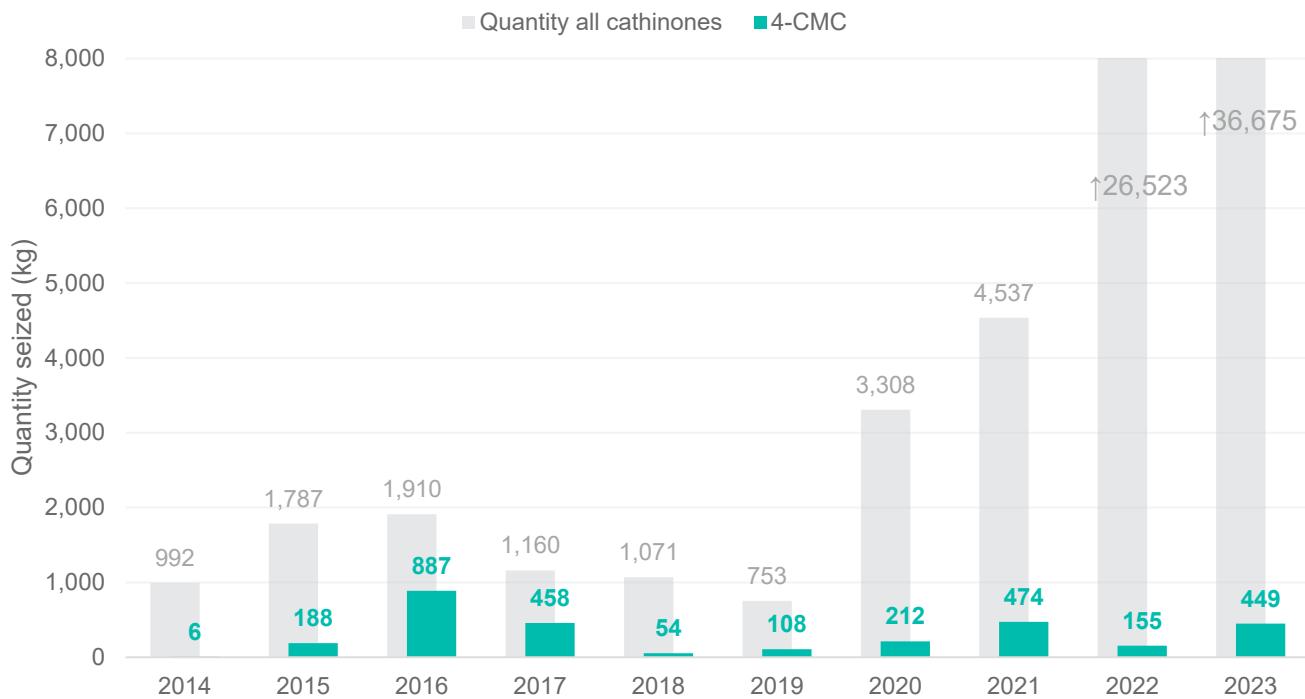
The appearance of 4-CMC on the drug market coincided with the control of mephedrone in Europe, after the latter spread rapidly on the continent between 2009 and 2010 when it was being produced, distributed, and sold openly as a 'legal' stimulant (EMCDDA, 2022). At least in part, it appears that 4-CMC 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 (2014-2023)



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 only 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'-chloropropiophenone, the precursor used in the second step of the synthesis and not assessed in this report, was indicated as the precursor chemical for 4-CMC.

Additional information sources including open-source information account for at least five additional production sites dismantled in Poland in 2023 and three in 2024⁽⁵⁾, including a large scale 4-CMC 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>

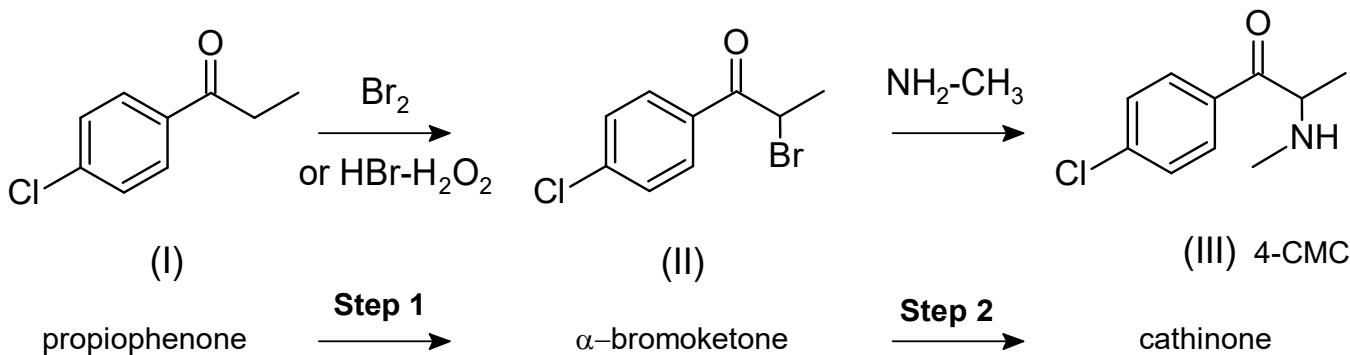
⁽⁶⁾ <https://cbsp.policja.pl/cbs/aktualnosci/244483,Ogromna-fabryka-kryształu-zlikwidowana-przez-CBSP.html>

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).



4-Chloropropiophenone (I), the subject of this assessment, is a solid, crystalline substance with a white to off-white colour. It is not soluble in water, and sparingly soluble in chloroform and methanol. This substance is harmful if swallowed, can cause serious eye irritation and skin irritation and may cause an allergic skin reaction. Step 1 (“bromination”) of the 4-CMC synthesis uses 4'-chloropropiophenone, 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). If isolated, this substance is a solid 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).

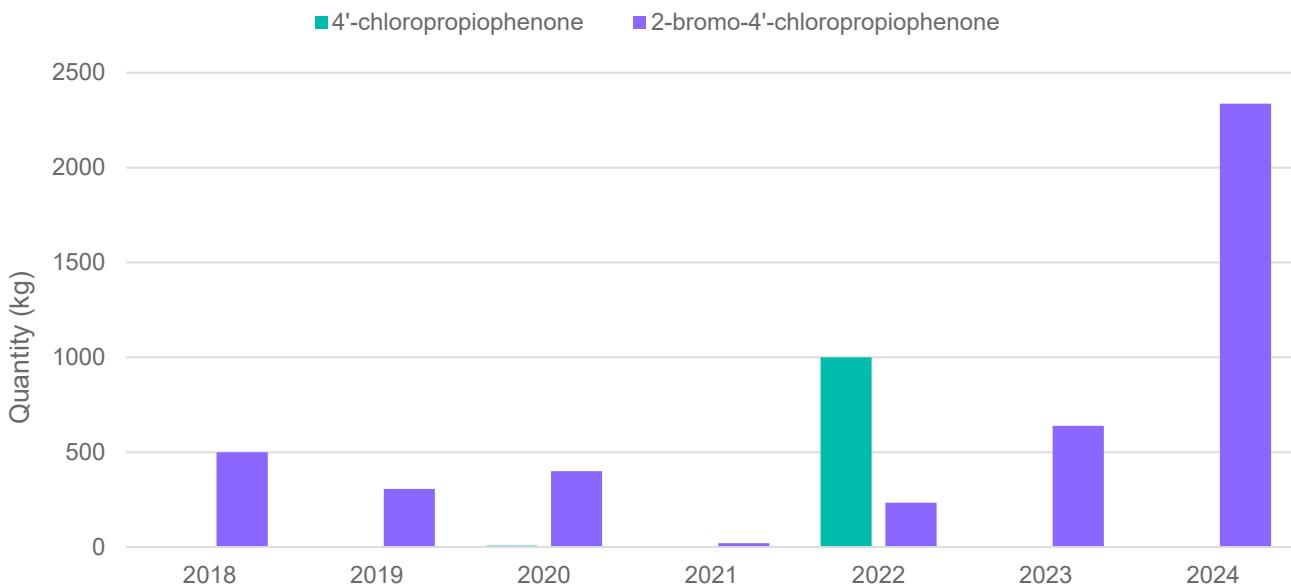
3. Evidence of trafficking in the EU

4'-chloropropiophenoneis 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 4'-chloropropiophenonетrafficking, the European Commission’s EDPD and the INCB’s PICS. Four seizures totalling over 657 kilograms of 4'-chloropropiophenoneoccurred in 3 Member States (France, Netherlands and Poland) between 2020 and 2022. One incident was reported to the EDPD, whereas three were reported to the INCB. In addition, one shipment reported to EDPD concerned 1 tonne of 4'-chloropropiophenoneoriginating in China and destined for Poland that was stopped by the French customs in 2022. No incidents of seizures or stopped shipments of 4'-chloropropiophenonehave been reported so far for 2023 nor 2024.

The seizure of 4'-chloropropiophenonereported to the EDPD occurred in Poland in 2020, where 7.3 kilograms of 4'-chloropropiophenonewere seized in an illicit laboratory. This quantity is much lower than the seizures of the brominated precursor of 4-CMC, 2-bromo-4'-chloropropiophenone (II), 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).

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

The estimated traded volume of 4'-chloropropiophenone in the EU is between 10 and 1000 tonnes per year, according to the data provided by the European Chemicals Agency (ECHA). One active Dossier was found to be registered under the REACH Regulation (8) under Article 18 – intermediate. The company registered under REACH is based in Poland.

4'-chloropropiophenone is also commercially available as a reference standard used in analytical laboratories (9). 4'-chloropropiophenone appears to have wide applications in medicinal chemistry and organic synthesis, particularly as an intermediate in the synthesis of pharmaceuticals, fragrances and agrochemicals. However, the full extent of its applications in pharmaceutical research would be difficult to evaluate, and it is not the subject of this report.

5. Legal controls

Based on the available information, 4'-chloropropiophenone is not a controlled substance in any of the searched jurisdictions (10). No cathinone precursor with similar structure is scheduled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

(8) Under the REACH regulation, companies must register substances they import or manufacture in the EEA at 1 tonne per year and above. As part of the registration, companies submit a so-called registration dossier to ECHA, with information on the identity, properties, classification and uses of the substance. ECHA publishes information from the registration dossiers as per REACH Article 119.

(9) <https://www.lgcstandards.com/GB/en/p/TRC-C379345>

(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 (INCBC), United Kingdom, United States of America, Wassenaar Arrangement, World Anti-Doping Agency.

6. Use, trafficking and distribution outside of the EU

No information is available about the use, trafficking and distribution of 4'-chloropropiophenone outside of the EU. However, a large shipment of 1 tonne of 4'-chloropropiophenone originating in China and destined for Poland, has been stopped by the French Customs in 2022, as reported to the EDPD.

7. Conclusions and possible consequences of scheduling in the EU

The limited seizure data available suggests that 4'-chloropropiophenone might be used to some extent in the European Union as a precursor in the synthesis of 4-CMC. From the seizure data reported to the European Commission, production of 4-CMC seems more often to commence from the second step of the two-step 'bromination-amination' reaction, using 2-bromo-4'-chloropropiophenone as the main precursor. 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 4'-chloropropiophenone may lead to unpredictable outcomes. Some of the potential scenarios are listed below:

- **Scheduling 4'-chloropropiophenone may contribute to the reduction of the availability of 4-CMC.** Inclusion of the chemical under the EU controls might make its trade and use for illicit production of 4-CMC more difficult and, thus, reduce the availability of 4-CMC in the EU. The extent of use of 4'-chloropropiophenone in illicit production of 4-CMC appears to be limited, and 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.
- **Scheduling 4'-chloropropiophenone may result in different chemical routes being adapted by illicit drug producers.** Numerous alternative synthetic methods for 4-CMC exist which avoid 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 4'-chloropropiophenone may result in local production by illicit drug producers.** Rather than obtaining it commercially, 4'-chloropropiophenone may be produced in clandestine facilities. [This section was redacted in the interest of public safety]
- **Scheduling 4'-chloropropiophenone may result in the emergence of 'designer' cathinone precursors.** The scheduling of 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 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 4'-chloropropiophenone poses limited risk of hindering legitimate industries.** The substance is legally traded in the EU in the volume of 10-1000 tonnes per year, based on the information provided by ECHA. It also appears to have applications as an intermediate in the synthesis of pharmaceuticals, fragrances and agrochemicals, and might be used in research.

The information above suggests that there are some risks to be considered concerning the scheduling of 4'-chloropropiophenone. These should be weighed against the risks of not scheduling the substance.

Not scheduling 4'-chloropropiophenone, while scheduling its counterpart 2-bromo-4'-chloropropiophenonemay 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 4'-chloropropiophenone, then 2-bromo-4'-chloropropiophenone should also be scheduled to avoid such a result.

Although bromine can be substituted by NBS, the use of the latter is not without its risks. NBS also decomposes over time and gives off bromine if not properly stored. Reactions involving NBS are exothermic, releasing heat, therefore precautions should be taken especially if used on a large scale.

In addition, **not scheduling 4'-chloropropiophenonemay enable the production and trafficking of 4-CMC, which 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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