EUDA
EUROPEAN UNION DRUGS AGENCY

Date issued: 18.12.2024

PRECURSOR ASSESSMENT REPORT of 3′-chloropropiophenone

This EUDA Precursor Assessment Report examines the evidence on 3′-chloropropiophenone, evaluating its licit use in the EU and the extent of its use in illicit production. This document was prepared on 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

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 of 3-CMC were dismantled in the EU between 2017 and 2024, of which nine were found in Poland. 3′-chloropropiophenone is converted into 3-CMC typically by means of a two-step process. This method is straightforward and scalable, needing only basic equipment and minimal technical proficiency to be executed. One of its main drawbacks is the need to use bromine, a particularly toxic and hazardous chemical, in the first step, when 2-bromo-3′-chloropropiophenone is made. To avoid this step, clandestine production often starts directly from the second step using the equally commercially available 2-bromo-3′-chloropropiophenone as a staring material to produce 3-CMC.

Reports of seizures of 3′-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-3′-chloropropiophenone. At least 5 seizures totalling over 1.3 tonnes of 3′-chloropropiophenone occurred in France and the Netherlands between 2016 and 2024, according to information reported to the

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

European Commission and to the INCB. When known, shipments originated outside the EU, primarily in China, with destinations including the UK, Poland, and the Netherlands. Mislabelling was reported in one case. At least one of the seizures occurred in an illicit laboratory, but it is likely that seizures of 3′-chloropropiophenone in illicit production facilities are under-reported.

3′-chloropropiophenone has a legitimate use as an essential ingredient for the production of bupropion, a medication used for the treatment of depression and smoking cessation. It is also commercially available as a reference standard for use in analytical laboratories.

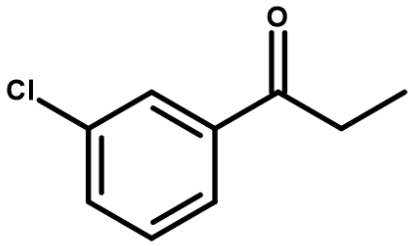
Scheduling considerations

Scheduling 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′-chloropropiophenone, the use of ‘permanganate’ oxidation of a suitable ephedrine analogue 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 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 substance could also disrupt the availability of bupropion, potentially impacting EU-based production of bupropion (the extent of which is unknown) and the competitiveness of its manufacturers who could face competition from jurisdictions where access to 3′-chloropropiophenone is less restricted.

These risks should be weighed against the risks of not scheduling of the substance. For example, if 3′-chloropropiophenone remains freely available, and its brominated counterpart 2-bromo-3′-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 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. Suffice to say, if a decision is taken to schedule 3′-chloropropiophenone, then 2-bromo-3′-chloropropiophenone should also be scheduled to avoid such a result.

1. Substance description

PAR_ID	PAR-2024-0001
Substance name	3′-chloropropiophenone
Abbreviation	N/A
Chemical structure	
IUPAC name	1-(3-Chlorophenyl)-1-propanone
InChI code	InChI=1S/C9H9ClO/c1-2-9(11)7-4-3-5-8(10)6-7/h3-6H,2H2,1H3
InChI Key	PQWGFUFROKIJBO-UHFFFAOYSA-N
SMILES	C(CC)(=O)C1=CC(Cl)=CC=C1
Other names	m-Chloropropiophenone; 3-Chlorophenyl ethyl ketone; 3'-chloropropiophenone; 1-(3-chlorophenyl)propan-1-one; 3-chlorophenone; 3'-chloroacetone; m-chloroproiophenone; Bupropion Impurity 22; MCPP
Molecular formula	C_9H_9ClO
Molecular weight (g/mol)	168.62
EUDA Classification	Propiophenones
CAS RN	34841-35-5
CAS page link	https://commonchemistry.cas.org/detail?cas_rn=34841-35-5&search=34841-35-5
HS/CN code	29147900
TARIC link	https://ec.europa.eu/taxation_customs/dds2/taric/goods_description.jsp?Lang=en&LangDescr=en&SimDate=20241004&Taric=29147900
CUS number (ECICS)	0040256-2
ECICS link	https://ec.europa.eu/taxation_customs/dds2/ecics/chemicalsubstance_consultation.jsp?Lang=en&Cas=34841-35-5&Cus=&CnCode=&EcCode=&UnCode=&Name=&LangNm=en&NomenclatureSystem=&Inchi=&Inchikey=&Characteristic=&sortOrder=1&Expand=true&offset=0&viewVal=&isVisitedRef=false
EC number	252-242-3
REACH link	https://chem.echa.europa.eu/100.047.478/identity?searchText=34841-35-5

Physical form (RT)	Solid: Crystalline ([2])
Colour	Colourless ([2])
Physical features	Odourless ([2])
Associated with the production of	Clophedrone (synonyms: 3-chloromethcathinone, 3-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

3′-chloropropiophenone is a substituted propiophenone, i.e., an aromatic ketone which is substituted in the aryl moiety – in this case with a chlorine in the *meta* position. According to published scientific literature (Blough et al., 2014; Shalabi et al., 2017) and law enforcement information, **3′-chloropropiophenone** is associated with the production of synthetic cathinones, namely of **3-chloromethcathinone (3-CMC)**.

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).

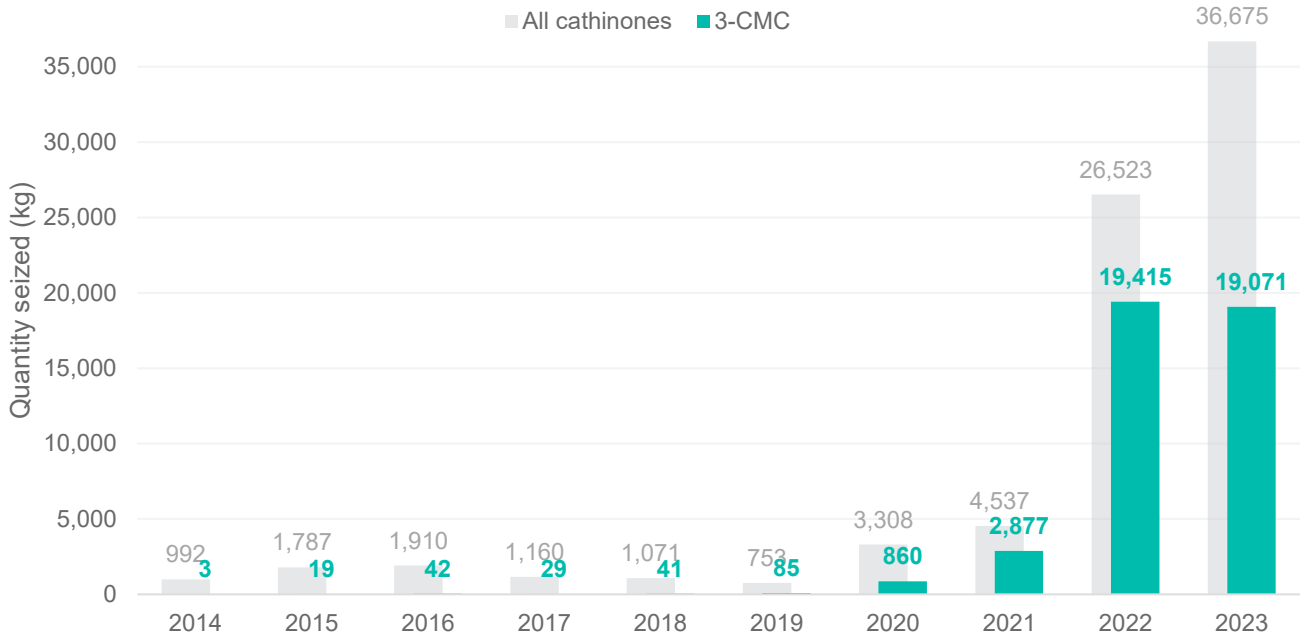
3-CMC has been available on the European drug market at least since September 2014 (EMCDDA, 2022). It has been subject of a risk assessment by the EUDA in 2021 (EMCDDA, 2022) and, subsequently, controlled in the EU in 2022 ([3]). Following the CND Decision 67/2 ([4]) its international control in Schedule II of the 1971 Convention on Psychotropic Substances of 1971 entered into force on 3 December 2024 ([5]).

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

([2]) https://chem.echa.europa.eu/100.047.478/dossier-view/c179735c-8049-4f69-9b81-22b65d48169f/IUC5-3d2613e7-7af6-4d53-b53f-0a11de066344_abcfd05a-94ea-4a14-815b-c14b10fcc524
([3]) 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
([4]) 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
([5]) https://documents.un.org/doc/undoc/gen/v24/035/96/pdf/v2403596.pdf

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 (EMCDDA, 2024).

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 (EUDA), 2024.

Based on the data reported to the EUDA, 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 2024, also in Poland ([6]) and one in the Netherlands in 2024.

Data on the quantity and the identity of precursors seized at these sites is not routinely captured by any of the data sources available, nor is the size of the production vessels known. Nonetheless, open-source information published by the Polish Police (PCBI), show that some of these sites appear to be large production facilities. For example, in at least one of the production sites in Poland, 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.

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-

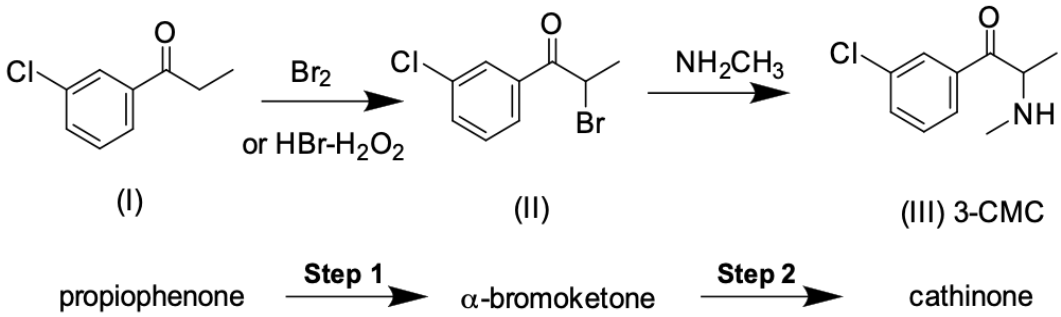
([6]) https://cbsp.policja.pl/cbs/aktualnosci/249227,Blisko-tona-narkotykow-wartych-43-mln-PLN-zabezpieczona-przez-CBSP.html

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)

Propiophenone precursors like 3′-chloropropiophenone (I) can be synthesized, but they are also commercially available from chemical suppliers and can be purchased in bulk. Since 3′-chloropropiophenone (I) is a key starting material for the synthesis of bupropion ([8]), it is presumably manufactured and commercially available on a large scale. Bromine ([9]), which is required for the ‘bromination’ step (step 1 in Scheme 1), is 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. This makes step 1 by far the most hazardous step of the process. 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 the intermediate (II) (Reddy et al., 2010; see also Guha et al., 2015).

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



One way to avoid the use of the bromine is to avoid the bromination step (step 1) altogether. Similar to 3′-chloropropiophenone (I), the α-bromoketone intermediate 2-bromo-3′-chloropropiophenone (II) is also available from chemical suppliers, meaning that the use of this precursor avoids the use of bromine as it reduces the number of steps needed to obtain the final product. Seizures of precursors for other

([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]) The interest in cathinones (and α-aminoketones in general) has motivated significant work aimed at developing efficient synthetic approaches to produce them. Some of this work is related to the synthesis of bupropion (Mehta, 1974; see also Perrine et al., 2000), an atypical antidepressant authorised in a number of Member States as an aid to smoking cessation and treatment of major depressive disorder.
([9]) Bromine can be commercially obtained as a liquid or prepared from a bromide salt (e.g. KBr), an acid (e.g. H_2SO_4), and an oxidizer (e.g. H_2O_2).

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).

Intermediate (II) is a lacrimatory agent. 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).

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 cathinones can be produced in series, simply by obtaining intermediate (II) in a large scale, subdividing it into lots and reacting each lot with a different amine to produce different cathinones (Collins, 2016).

3. Evidence of trafficking in the EU

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 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).

There are reports of at least 5 seizures totalling over 1.3 tonnes of 3′-chloropropiophenone occurring in two Member States (France and Netherlands) between 2016 and 2024. Two were reported to the European Commission's EDPD whereas three were reported to the INCB.

4. Legitimate uses in the EU

As indicated above (see section 2.2), 3′-chloropropiophenone is used in the pharmaceutical production of Bupropion, an atypical antidepressant used for treatment of major depressive disorder and an aid to smoking cessation. Bupropion is listed on the World Health Organization's List of Essential Medicines. In the US in 2022 it was the 21st most prescribed medication with the yearly volume of 25 million prescriptions, used by an estimated 6 million people ([10]). No similar statistics were found for the European population.

Eight active Dossiers were found to be registered under the REACH Regulation ([11]), two under Article 10 – full, with an estimated legal trade between 1 and 10 tonnes per year, and 6 under Article 18 – intermediate, with an estimated trade between 10 and 1000 tonnes per year. The companies registered under REACH are based in Estonia, Germany, Italy, Poland, Spain and Sweden.

Apart from its use for the synthesis of bupropion, 3′-chloropropiophenone is also available as a reference standard used in analytical laboratories ([12]). One of the applications of the reference standard

([10]) https://clincalc.com/DrugStats/Drugs/Bupropion
([11]) Under the REACH regulation, companies must register substances they import or manufacture in the EEA at 1 tonnes 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.
([12]) https://www.lgcstandards.com/DE/en/p/TRC-C379845

is for example detecting impurities in the synthesis of bupropion. 3′-chloropropiophenone appears to have wide applications in medicinal chemistry and organic synthesis, for example in the synthesis of thiazine derivatives with antimicrobial properties (Deepika, 2012). The full extent of its applications in pharmaceutical research would be difficult to evaluate.

5. Legal controls

Based on the available information, 3′-chloropropiophenone is not scheduled in any of the searched jurisdictions ([13]). 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 the EU

There is currently no available information about the use of 3′-chloropropiophenone outside of the EU.

It is possible that 3′-chloropropiophenone also has legitimate uses outside of the EU, particularly as a precursor in the production of bupropion, as a reference standard used in analytical laboratories and in pharmaceutical and chemical research.

7. Conclusions and possible consequences of scheduling in the EU

The limited evidence available suggests that 3′-chloropropiophenone is not used to a significant extent in the European Union as a precursor in the synthesis of 3-CMC. From the seizure data reported to the European Commission, production of 3-CMC seems more often to commence from the second step of the two-step ‘bromination-amination’ reaction, using 2-bromo-3′-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 3′-chloropropiophenone may lead to unpredictable outcomes. Some of the potential scenarios are listed below:

- ***Scheduling 3′-chloropropiophenone may reduce the availability of 3-CMC.*** 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 3′chloropropiophenone in illicit production of 3-CMC is 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.

- ***Scheduling 3′-chloropropiophenone may result in different chemical routes being adapted by illicit drug producers.*** Numerous alternative synthetic methods for 3-CMC exist which avoid 3′-chloropropiophenone and could potentially be used for production in case of its scheduling. [This section was redacted in the interest of public safety]

([13]) 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.

- ***Scheduling 3'-chloropropiophenone may result in local production by illicit drug producers.*** Rather than obtaining it commercially, 3′-chloropropiophenone may be produced in clandestine facilities, through one of the various ways available. [This section was redacted in the interest of public safety]

- ***Scheduling 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 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 3'-chloropropiophenone poses a risk of hindering legitimate industries.*** The substance has legitimate use in manufacture of pharmaceuticals and is legally traded in the EU, with 6 registrants declaring the volume of 10-1000 tonnes per year. Its scheduling could impact the production of Bupropion and its availability on the EU market, as well as its price (in case of reduced availability), in cases where the production of Bupropion occurs in the EU (information currently not available). Limiting the access to 3′-chloropropiophenone may motivate local pharmaceutical producers to shift the location of production of Bupropion to places outside the EU, where the chemical is not subject to such restrictions. This may impact the competitiveness of the EU-based pharmaceutical companies involved in the production of Bupropion.

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

Not scheduling 3'-chloropropiophenone, while scheduling its counterpart 2-bromo-3'-chloropropiophenone may motivate illicit drug producers to adapt the synthetic route to start from 3'-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 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 environmental toxicity, environmental damage is likely to increase with an increasing use of bromine. Suffice to say, if a decision is taken to schedule 3′-chloropropiophenone, then 2-bromo-3′-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.

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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