

PRECURSOR ASSESSMENT REPORT of 2-bromo-4'-methylpropiophenone

This EUDA Precursor Assessment Report examines the evidence on 2-bromo-4'-methylpropiophenone, 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'-methylpropiophenone is a chemical precursor used for the production of mephedrone (4-methylmethcathinone or 4-MMC) – a synthetic cathinone stimulant drug that has been present in the drug market in the European Union (EU) since at least 2008. Mephedrone has been under EU control since 2010 and international control since 2015, following which a number of closely related new psychoactive substances emerged on the market. In the period 2021-2023 seizures of mephedrone in the EU have been close to an average of 960 kilograms per year.

Production of mephedrone in the EU seems to be focused primarily around Poland and the Netherlands. According to official data, at least 49 production or processing sites of mephedrone were dismantled in the EU between 2013 and 2022, of which 35 were found in Poland (12 only in 2022) and 9 in the Netherlands. Two additional sites were identified in open-source information (Poland and Austria). 2-bromo-4'-methylpropiophenone was seized in at least 37 illicit production sites, but it is likely that seizures of the precursor in these facilities are under-reported.

2-bromo-4'-methylpropiophenone is converted into mephedrone typically in a single-step chemical reaction. This method is straightforward and scalable, needing only basic equipment and minimal technical proficiency to be executed.

Reports of seizures of 2-bromo-4'-methylpropiophenone in the EU have been registered, however, it is still a non-scheduled substance and reporting is voluntary. At least 28 detections of 2-bromo-4'-methylpropiophenone were reported to the European Drug Precursor Database (EDPD) by 7 Member

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

States (Austria, Belgium, France, Germany, Hungary, Netherlands, Poland) between 2016 and 2023 totalling over 3.5 tonnes.

When known, shipments of the substance to the EU originated primarily in China, with destinations including France, Spain, United Kingdom and the Netherlands. Mislabelling was reported in several cases.

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

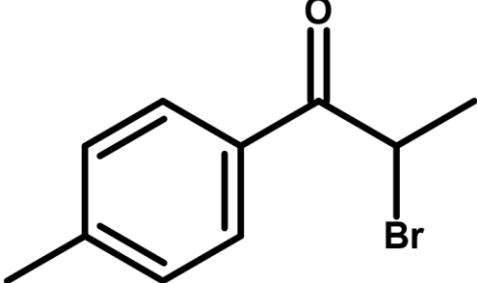
Scheduling considerations

Scheduling 2-bromo-4'-methylpropiophenone may contribute to the reduction of the availability of mephedrone 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. If 2-bromo-4'-methylpropiophenone is scheduled, and its non-brominated counterpart 4'-methylpropiophenone is freely available, this may motivate illicit drug producers to simply start from 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 in this scenario. Suffice to say, if a decision is taken to schedule 2-bromo-4'-methylpropiophenone, then 4'-methylpropiophenone should also be scheduled 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 mephedrone (such as 2-MMC or 3-MMC) or pyrrolidine-containing cathinones (alpha-PVP, alpha-PHP and alpha-PHiP) which could pose similar, or even more harms to people who use drugs.

These factors should be weighed against the risks of not scheduling of the substance. If 2-bromo-4'-methylpropiophenone remains freely available illicit drug producers may be enabled to continue producing mephedrone 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	2024-0004
Substance name	2-bromo-4'-methylpropiophenone
Abbreviation	2B4MPP
Chemical structure	 <p>Chemical structure of 2-bromo-4'-methylpropiophenone: A benzene ring with a methyl group at position 4 and a 4-bromo-2-methylpropiophenyl group at position 1.</p>
IUPAC name	2-Bromo-1-(4-methylphenyl)-1-propanone
InChI code	InChI=1S/C10H11BrO/c1-7-3-5-9(6-4-7)10(12)8(2)11/h3-6,8H,1-2H3
InChI Key	OZLUPIIIHOOPNQ-UHFFFAOYSA-N
SMILES	O=C(C1=CC=C(C=C1)C)C(Br)C
Other names	2-Bromo-1-(4-methylphenyl)propan-1-one; 2-Bromo-1-(<i>p</i> -tolyl)propan-1-one; 2-Bromo- <i>p</i> -methylpropiophenone; 4-Methylphenyl 1-bromoethyl ketone
Molecular formula	C ₁₀ H ₁₁ BrO
Molecular weight (g/mol)	227.1
EUDA Classification	Propiophenones
CAS RN	1451-82-7
CAS page link	https://scifinder-n.cas.org/searchDetail/substance/66ded27b7ae4e751265390d2/substance_Details
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)	0148968-5
ECICS link	https://ec.europa.eu/taxation_customs/dds2/ecics/chemicalsubstance_consultation.jsp?Lang=en&Cas=1451-82-7&Cus=&CnCode=&EcCode=&UnCode=&Name=&LangNm=en&NomenclatureSystem=&Inchi=&Inchikey=&Characteristic=&sortOrder=1&Expand=true&offset=0&viewVal=&isVisitedRef=false
EC number	696-162-0
REACH link	https://echa.europa.eu/substance-information/-/substanceinfo/100.225.418
Physical form (RT)	Solid crystalline substance

Colour	White/off-white to light yellow colour
Physical features	Distinctive smell
Associated with the production of	Mephedrone (4-methylmethcathinone, 4-MMC)
GHS Hazard Statements	H335 - May cause respiratory irritation H319 - Causes serious eye irritation H315 - Causes skin irritation

2. Evidence of use in the illicit production

2.1 Background

2-bromo-4'-methylpropiophenone is a substituted propiophenone, i.e., an aromatic ketone, substituted in the aryl moiety in the *para* position with a methyl group, and ‘brominated’ in the alkyl chain. According to the published literature (EMCDDA, 2011; Wrzesień, 2018), **2-bromo-4'-methylpropiophenone** is associated with the illicit production of **Mephedrone (4-methylmethcathinone, 4-MMC)**, 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).

Mephedrone is available on the EU drug market at least since 2008 (EMCDDA, 2011). It has been subject to a risk assessment by the EUDA in 2010 and, subsequently, controlled in the EU since December 2010 (²). Following the CND Decision 58/1 (³) its international control in Schedule II of the 1971 Convention on Psychotropic Substances of 1971 has entered into force at the end of 2015.

Mephedrone was one of the first synthetic cathinones to be detected in the European Union. Detections of mephedrone have been made by all 27 Member States, and have continued to occur despite its legal control. Although seizures of mephedrone reported to the EU Early warning system have been limited over the last few years (Figure 1), additional data reported to the EUDA suggests that in the period 2021-2023 seizures of mephedrone in the EU have been close to an average of 960 kilograms per year.

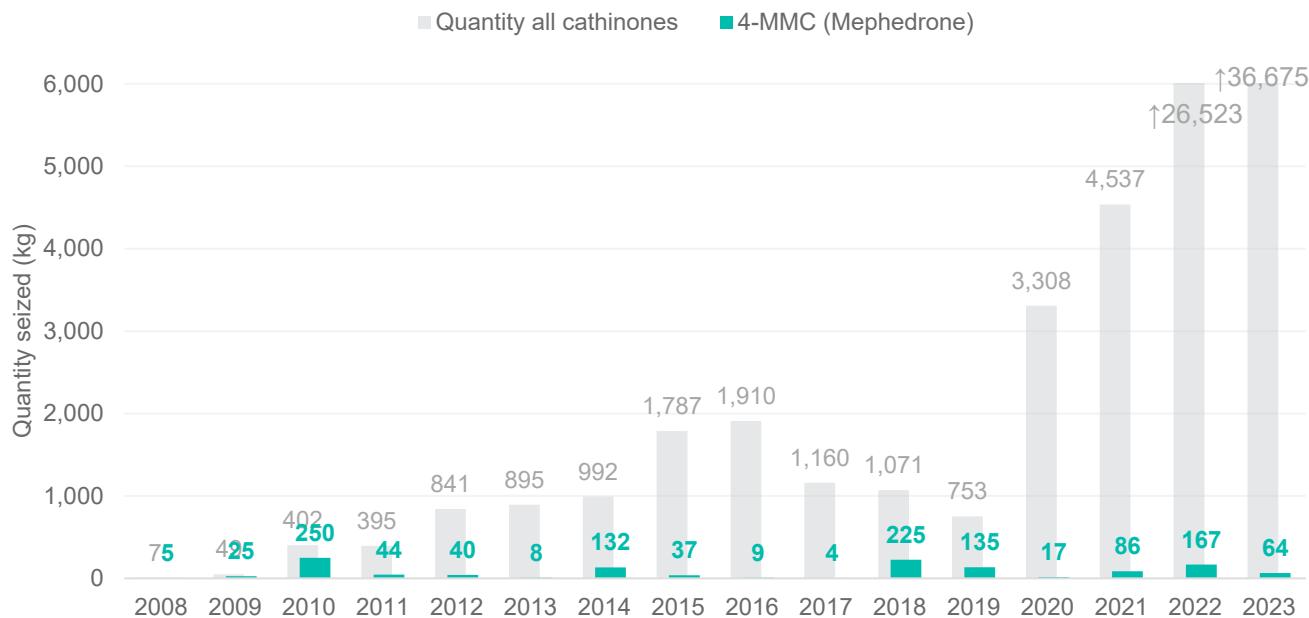
The main source of mephedrone to the EU at the time of its legal control were shipments from China (EMCDDA, 2011). Since then, a number of closely related ‘legal’ alternatives to mephedrone were detected on the market (3-MMC, 3-CMC, 4-CMC, among others). In addition, some mephedrone production has been reported in Europe, particularly focused around Poland and the Netherlands.

(²) 2010/759/EU: Council Decision of 2 December 2010 on submitting 4-methylmethcathinone (mephedrone) to control measures <https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32010D0759>

(³) Commission on Narcotic Drugs Report on the fifty-eighth session (5 December 2014 and 9-17 March 2015), E/2015/28 E/CN.7/2015/15

<https://www.unodc.org/documents/commissions/CND/CND Sessions/CND 58/E2015 28 ADVANCE UNEDITED VERSION.pdf>

Figure 1. Quantity of all synthetic cathinones and 4-MMC alone seized in the EU (2008-2023)



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 2013 and 2022, at least 49 sites have been reported as involved in production or processing of mephedrone in six Member States. These include 35 sites found in Poland, 9 in the Netherlands, 2 in Estonia, and one site in Belgium, in Czechia and in Spain. The number of dismantled labs suggests an increase in production over the last few years, with 47% of all sites reported being dismantled in 2021 (10 sites) and 2022 (13 sites).

Data on the quantity and the identity of precursors seized at these sites is not routinely captured by any of the data sources available. Nonetheless, in the large majority of cases (37 sites, 76% of all reports) across all the countries, 2-bromo-4'-methylpropiophenone was found at the site as the precursor chemical for mephedrone synthesis (in 11 cases from Poland the precursor was reported as 'not known', and in one Polish case 'pseudoephedrine' was reported as a precursor). Additional information sources including open-source information account for at least one additional production site in Austria in 2021 (EMCDDA, 2024) and one in Poland in 2024 (5).

(4) Information reported to the European Reporting Instrument on Sites Related to Synthetic Production (ERISSP).

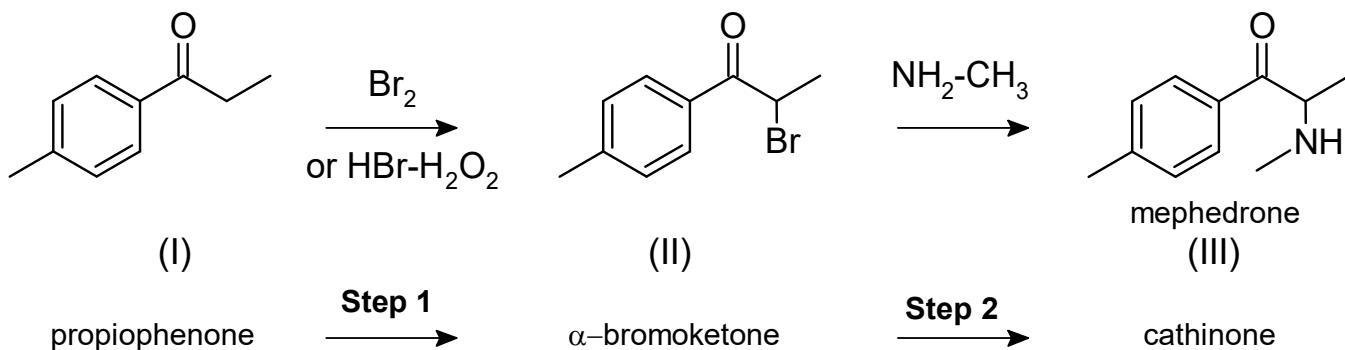
(5) <https://cbsp.policja.pl/cbs/aktualnosci/239993,Zlikwidowana-fabryka-mefedronu-i-rozpracowana-internetowa-siecdystrybucji-dzial.html?search=4413493620647>

2.2 General methods for the synthesis of cathinones and mephedrone

The synthesis of mephedrone was first described in 1929 (Saem de Burnaga Sanchez, 1929), but several methods exist for its synthesis, which are common to the synthesis of other cathinones (EMCDDA, 2022).

The simplest approach involves a two-step bromination-amination⁶ 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⁽⁶⁾ 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 mephedrone via the 'bromination-amination' pathway (Shalabi et al., 2017; Blough et al., 2014).



Step 1 uses 4'-methylpropiophenone (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'-methylpropiophenone (II). If isolated, this substance is a solid, crystalline substance with a white, off-white to light yellow colour and a distinctive smell. It is sparingly soluble in water but exhibits good solubility in various organic solvents such as chloroform and methanol. This substance causes serious eye irritation, causes skin irritation and may cause respiratory irritation.

The subject of this assessment, 2-bromo-4'-methylpropiophenone (II) is also available from chemical suppliers, meaning that the first step can be omitted, avoiding the use of bromine. Seizures of

⁽⁶⁾ 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.

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

The second step proceeds by reacting the 2-bromo-4'-methylpropiophenone (II) with an excess of methylamine or methylamine hydrochloride and an acid scavenger. The reaction is quenched with gaseous or aqueous hydrochloride providing the mephedrone 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

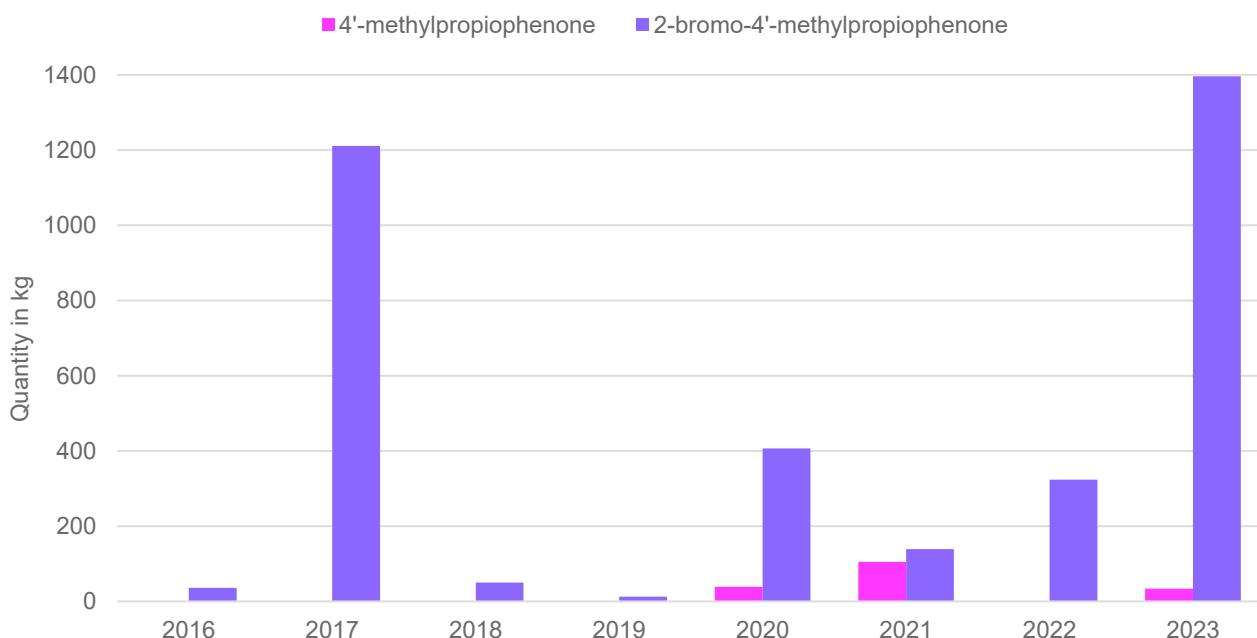
2-bromo-4'-methylpropiophenone is not a scheduled precursor and thus the reporting of its seizures and stopped shipments to the European Drug Precursors Database (EDPD) is voluntary, which may result in its de-prioritization in law enforcement activity and therefore data may not be recorded or reported (Singleton et al, 2018).

Between 2016 and 2023, 28 detections of 2-bromo-4'-methylpropiophenone were reported to the EDPD by 7 Member States (Austria, Belgium, France, Germany, Hungary, Netherlands, Poland) totalling over 3.6 tonnes (Figure 2). Of these, the large majority (2.8 tonnes, 78 %) were reported by the Netherlands, followed by Poland (0.6 tonnes, 16 %) and Austria (0.1 tonnes, 4 %).

The origin and/or provenance was reported for 14 out of 28 cases (corresponding to 65 kg out of 3.6 tonnes of material seized). In 13 the cases for which it was known, the origin was China or Hong Kong, in the remaining one the shipment had come from the Netherlands. Destinations reported included France (3 cases, 16 kg), the Netherlands (2 cases, 1.2 kg), Poland (1 case, 8 kg), Spain (3 cases, 3.3 kg) and the United Kingdom (4 cases, 37 kg).

Two of the seizures occurred in an illicit laboratory (Austria, 2021 and Poland, 2023). The majority of the remaining seizures appear to have been made by Customs authorities. In several cases 2-bromo-4'-methylpropiophenone was mis-declared (as 'butadiene acrylonitrile', 'Acrylonitrile butadiene rubber', 'Coating hydrophobic agent').

Figure 2. Quantities of Mephedrone precursors 4'-methylpropiophenone and 2-bromo-4'-methylpropiophenone seized in the EU, EU Drug Precursors Database, 2024.



4. Legitimate uses in the EU

2-bromo-4'-methylpropiophenone is commercially available as a reference standard for use in analytical laboratories⁽⁷⁾. It appears to have some applications in medicinal chemistry and organic synthesis. The full extent of its applications in pharmaceutical research would be difficult to evaluate.

No information about the legal trade of 2-bromo-4'-methylpropiophenone has been found.

5. Legal controls

2-bromo-4'-methylpropiophenone is not a controlled substance in any of the searched jurisdictions, except for Taiwan⁽⁸⁾. In Taiwan it is controlled under the Schedule 4 Controlled Drug Materials, Controlled Drugs Act (Item 14). The legislation also controls other halogenated derivatives of methylpropiophenone (including **2-chloro** methylpropiophenone, **2-fluoro**-methylpropiophenone and **2-iodo**-methylpropiophenone). No cathinone precursor with similar structure is scheduled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

⁽⁷⁾ <https://www.lgcstandards.com/FR/en/2-Bromo-4-methylpropiophenone-A-crystalline-solid-/p/CAY-39486>

⁽⁸⁾ 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.

6. Use, trafficking and distribution outside of the EU

According to an INCB's Report, information suggests that mephedrone manufacture is 'occasionally reported in Central Asian countries. However, while significant amounts of precursors are seized, their type is not usually specified. For example, INCB is aware of the dismantling of an alleged mephedrone laboratory in Kyrgyzstan in June 2023 involving the seizure of 2.2 tons of unspecified precursors and related laboratory equipment. The Board is also aware of illicit mephedrone manufacture in Taiwan Province of China' (INCB, 2024).

7. Conclusions and possible consequences of scheduling in the EU

The limited seizure data available suggests that 2-bromo-4'-methylpropiophenone is used in the European Union as a precursor in the synthesis of mephedrone. Production of mephedrone seems to commence from the second step of the two-step 'bromination-amination' reaction, which uses 2-bromo-4'-methylpropiophenone 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-4'-methylpropiophenone may lead to unpredictable outcomes. Some of the potential scenarios are listed below:

- **Scheduling 2-bromo-4'-methylpropiophenone may contribute to reducing the availability of mephedrone in the EU.** Inclusion of the chemical under EU controls might make its trade and use for illicit production of mephedrone more difficult and, thus, reduce the availability of mephedrone in the EU. Although 2-bromo-4'-methylpropiophenone appears to be the main precursor in illicit production of mephedrone, 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'-methylpropiophenone, while not scheduling its counterpart 4'-methylpropiophenone may motivate illicit drug producers to adapt the synthetic route to start from 4'-methylpropiophenone** 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 2-bromo-4'-methylpropiophenone, then 4'-methylpropiophenone should also be scheduled to avoid such a result.
- **Scheduling 2-bromo-4'-methylpropiophenone may result in different chemical routes being adapted by illicit drug producers.** Numerous alternative synthetic methods for mephedrone exist which avoid 2-bromo-4'-methylpropiophenone 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'-methylpropiophenone may result in the emergence of 'designer' cathinone precursors.** The scheduling of 2-bromo-4'-methylpropiophenone may motivate illicit drug producers to seek alternatives to the precursor, and import 'masked' alternatives of the final product mephedrone. [This section was redacted in the interest of public safety]

- **Scheduling 2-bromo-4'-methylpropiophenone may shift illicit drug production to different end-products.** Lack of access to the precursor necessary to produce mephedrone 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'-methylpropiophenone 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 4'-methylpropiophenone. These should be weighed against the risks of not scheduling the substance.

Not scheduling 2-bromo-4'-methylpropiophenone may enable illicit drug producers to continue producing mephedrone in EU territory. Synthetic cathinones such as mephedrone 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, mephedrone 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).

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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