EUDA
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PRECURSOR ASSESSMENT REPORT of 4′-methylpropiophenone

This EUDA Precursor Assessment Report examines the evidence on 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

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).

4′-methylpropiophenone is converted into mephedrone 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-4′-methylpropiophenone is made. To avoid this step, clandestine production often starts directly from the second step using the equally commercially available 2-bromo-4′-methylpropiophenone as a staring material to produce mephedrone.

Reports of seizures of 4′-methylpropiophenone 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-

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

4′-methylpropiophenone. At least 5 detections totalling over 282 kilograms and 220 litres of 4′-methylpropiophenone occurred in France, Poland and the Netherlands between 2020 and 2023, according to information reported to the European Drug Precursor Database (EDPD) and to the INCB.

When known, shipments of the substance to the EU originated primarily in China, with destinations including the Poland and Ukraine. 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′-methylpropiophenone in illicit production facilities are under-reported.

4′-methylpropiophenone has a legitimate use as an essential ingredient for the production of tolperisone, a centrally acting skeletal muscle relaxant used mainly for the treatment of pathologically increased muscle tone associated with certain neurological diseases. It is also commercially available as a reference standard for use in analytical laboratories.

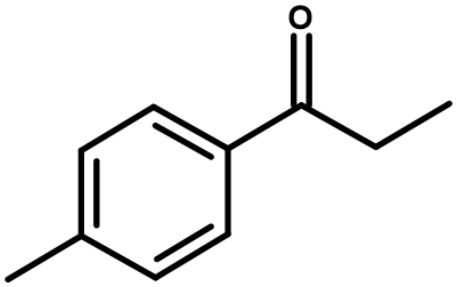
Scheduling considerations

Scheduling 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. These could possibly include the clandestine manufacture of 4′-methylpropiophenone, 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.

Scheduling the substance could also disrupt the availability of tolperisone, potentially impacting EU based production of this medicine (the extent of which is unknown) and the competitiveness of itsmanufacturers who could face competition from jurisdictions where access to 4′-methylpropiophenone is less restricted.

These risks should be weighed against the risks of not scheduling of the substance. For example, if 4′-methylpropiophenone remains freely available, and its brominated counterpart 2-bromo-4′-methylpropiophenone 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 4′-methylpropiophenone, then 2-bromo-4′-methylpropiophenone should also be scheduled to avoid such a result.

1. Substance description

PAR_ID	2024-0003
Substance name	4′-methylpropiophenone
Abbreviation	4MPP
Chemical structure	
IUPAC name	1-(4-methylphenyl)-1-propanone
InChI code	InChI=1/C10H12O/c1-3-10(11)9-6-4-8(2)5-7-9/h4-7H,3H2,1-2H3
InChI Key	PATYHUUYADUHQS-UHFFFAOYSA-N
SMILES	C(CC)(=O)C1=CC=C(C)C=C1
Other names	1-(4-methylphenyl)propan-1-one; 1-(p-tolyl)propan-1-one; p-Methylpropiophenone; para-methyldiphenylketone; Tolperisone Impurity 4
Molecular formula	$C_{10}H_{12}O$
Molecular weight (g/mol)	148.2
EUDA Classification	Propiophenones
CAS RN	5337-93-9
CAS page link	https://commonchemistry.cas.org/detail?cas_rn=5337-93-9&search=5337-93-9
HS/CN code	29143900
TARIC link	https://ec.europa.eu/taxation_customs/dds2/taric/goods_description.jsp?Lang=en&LangDescr=en&SimDate=20240710&Taric=29143900
CUS number (ECICS)	0038951-5
ECICS link	https://ec.europa.eu/taxation_customs/dds2/ecics/chemicalsubstance_consultation.jsp?Lang=en&Cas=5337-93-9&Cus=&CnCode=&EcCode=&UnCode=&Name=&LangNm=en&NomenclatureSystem=&Inchi=&Inchikey=&Characteristic=&sortOrder=1&Expand=true&offset=0&viewVal=
EC number	226-267-5
REACH link	https://chem.echa.europa.eu/100.023.879/identity?searchText=5337-93-9
Physical form (RT)	Oil

Colour	Clear colourless to yellow
Physical features	Oil with a distinct smell
Associated with the production of	Mephedrone (Synonyms: 4-methylmethcathinone, 4-MMC)
GHS Hazard Statements	H401 - Toxic to aquatic life H319 - Causes serious eye irritation H317 - May cause an allergic skin reaction H315 - Causes skin irritation H302 - Harmful if swallowed

2. Evidence of use in the illicit production

2.1 Background

4′-methylpropiophenone is a substituted propiophenone, i.e., an aromatic ketone, substituted in the aryl moiety in the *para* position with a methyl group. According to the published literature (EMCDDA, 2011; Wrzesień, 2018), **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.

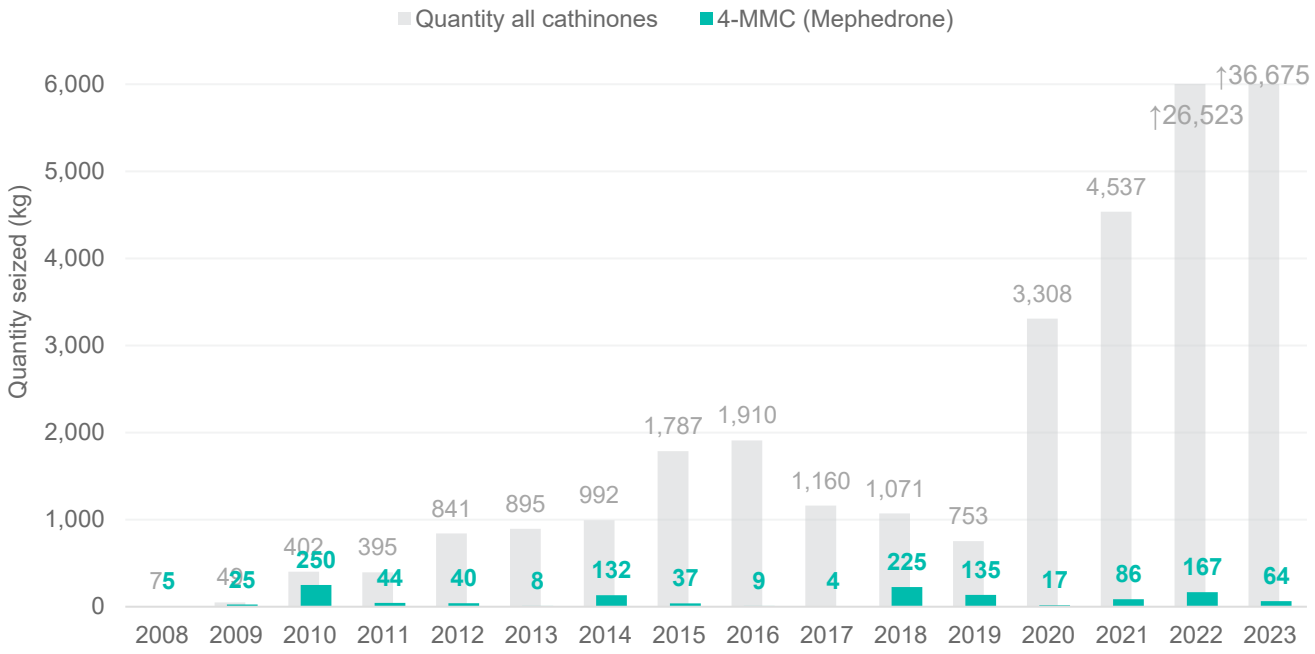
Mephedrone was one of the first synthetic cathinones to be detected in the European Union. Detections of mephedrone have been made by all 27 Member States, and have continued to occur despite its legal control. Although seizures of mephedrone reported to the EU Early warning system have been limited 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.

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

([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



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 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′-methylpropriophenone was indicated 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 in Poland in 2024 ([5]).

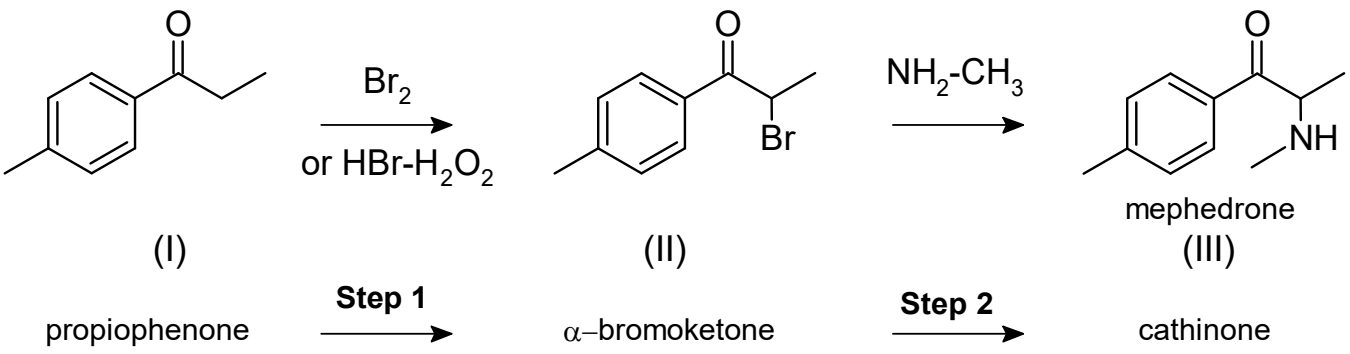
([4]) Information reported to the European Reporting Instrument on Sites Related to Synthetic Production (ERISSP).
([5]) https://cbsp.policja.pl/cbs/aktualnosci/239993,Zlikwidowana-fabryka-mefedronu-i-rozpracowana-internetowa-siec-dystrybucji-dzial.html?search=4413493620647

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-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 ([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 the subject of this assessment, 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.

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 precursors for synthetic cathinones tend

([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.

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).

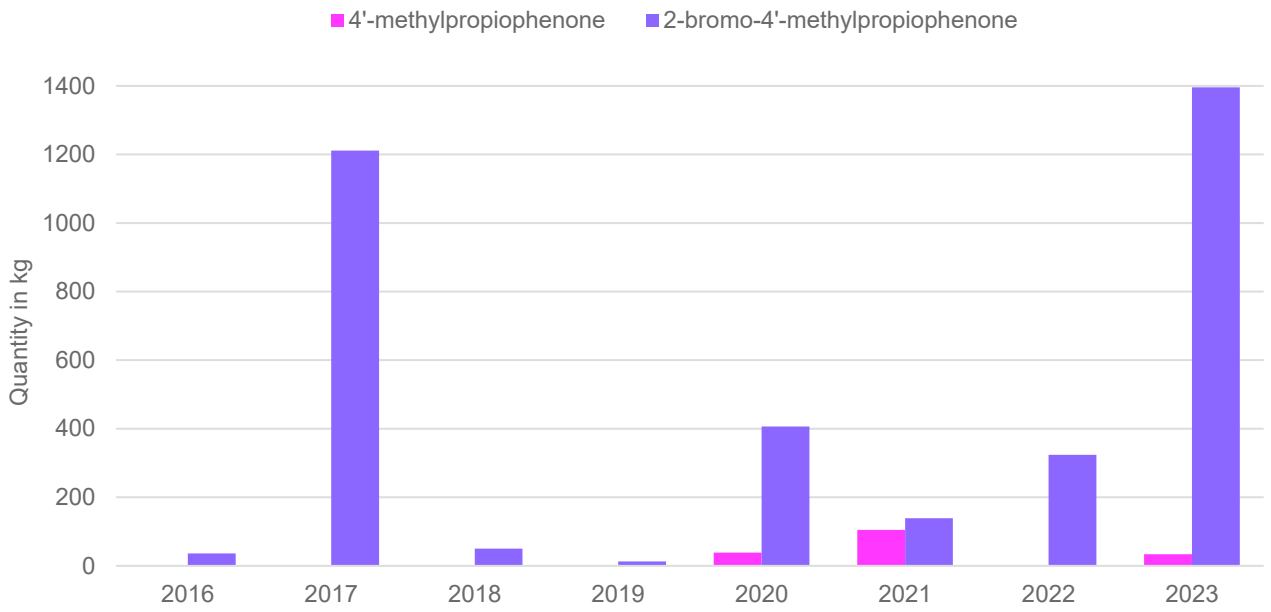
3. Evidence of trafficking in the EU

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).

There are reports of 5 detections totalling over 282 kilograms and 220 litres of 4′-methylpropiophenone occurring in 3 Member States (France, Netherlands and Poland) between 2020 and 2023. Three were reported to the European Commission's EDPD, whereas two were reported to the INCB.

Three detections of 4′-methylpropiophenone have been reported to the EDPD, two by Poland and one by France. Poland has reported a seizure of 38.6 kg of 4′-methylpropiophenone in 2020 and 34 kg in 2023, both seized in illicit laboratories where 4-MMC was produced. France reported a seizure of 105 kg in 2021 at Charles De Gaulle Airport, with the information provided in the case that the origin of the shipment was China, and the destination was Poland. These quantities are lower than the seizures of the brominated precursor of Mephedrone, 2-bromo-4′-methylpropiophenone (II), showing an apparent preference to import α-bromoketone intermediates (II) than propiophenones (I) needed for step 1 of the 'bromination-amination' synthesis (see Figure 2).

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

4′-methylpropiophenone is used as a precursor in the synthesis of a medicine tolperisone. Tolperisone is a centrally-acting muscle relaxant that has been used for the symptomatic treatment of spasticity and muscle spasm. According to the European Medicines Agency (EMA) ([7]), tolperisone-containing medicines have been authorised in several countries in the EU since the 1960s for the treatment of muscle spasms and spasticity caused by different conditions. These include neurological diseases (related to the brain or nerves, such as multiple sclerosis), locomotor diseases (related to the spine and large joints such as the hip), vascular diseases (related to the blood vessels), rehabilitation following surgery, and Little's disease (also known as cerebral palsy, a rare disease where there is damage to parts of the brain that control movement). Medicines containing tolperisone are available as tablets or solution for injection in Bulgaria, Cyprus, the Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, Romania and Slovakia, under various trade names. (EMA, 2012)

Four active Dossiers were found to be registered under the REACH Regulation ([8]) under Article 18 – intermediate, each with the estimated traded volume of 4′-methylpropiophenone between 10 and 1000 tonnes per year. The companies registered under REACH are based in Italy, Poland and Spain.

Apart from its use for the synthesis of tolperisone, 4′-methylpropiophenone is also commercially available as a reference standard for use in analytical laboratories ([9]). One of the applications of the reference standard is for example detecting impurities in the synthesis of tolperisone. 4′-

([7]) https://www.ema.europa.eu/en/medicines/human/referrals/tolperisone
([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/CG/en/p/TRC-M331175

methylpropiophenone appears to have wide applications in medicinal chemistry and organic synthesis. The full extent of its applications in pharmaceutical research would be difficult to evaluate.

5. Legal controls

Based on the available information, 4′-methylpropiophenone is not a controlled substance in any of the searched jurisdictions, except for Taiwan ([10]). In Taiwan it is controlled under the Schedule 4 Controlled Drug Materials, Controlled Drugs Act (Item 41). In the legislation, all isomers of methylpropiophenone (**2′-methyl**propiophenone, **3′-methyl**propiophenone and **4′-methylpropiophenone**) are controlled. No cathinone precursor with similar structure is scheduled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

6. Use, trafficking and distribution outside of the EU

It appears that 4′-methylpropiophenone is frequently seized in Central Asia and in the former Soviet Republics. According to an INCB Report, *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 4′-methylpropiophenone is not used to a significant extent in the European Union as a precursor in the synthesis of mephedrone. From the seizure data reported to the European Commission, production of mephedrone seems more often to commence from the second step of the two-step 'bromination-amination' reaction, using 2-bromo-4′-methylpropiophenone 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′-methylpropiophenone may lead to unpredictable outcomes. Some of the potential scenarios are listed below:

- ***Scheduling 4′-methylpropiophenone may reduce the availability of mephedrone in the EU.*** Inclusion of the chemical under the 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. Because the extent of use of 4′-methylpropiophenone in illicit production of mephedrone appears to be limited, the scale of this impact would be difficult to assess. Nevertheless, following the ban, the illicit production might shift to other starting materials, different synthetic routes or other end-products altogether.

([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.

- ***Scheduling 4'-methylpropiophenone may result in different chemical routes being adapted by illicit drug producers.*** Numerous alternative synthetic methods for mephedrone exist which avoid 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 4'-methylpropiophenone may result in its production by illicit drug producers.*** Rather than obtaining it commercially, 4′-methylpropiophenone may be produced in clandestine facilities. [This section was redacted in the interest of public safety]

- ***Scheduling 4'-methylpropiophenone may result in the emergence of 'designer' cathinone precursors.*** The scheduling of 4′-methylpropiophenone may motivate illicit drug producers to seek alternatives to the precursor, and import 'masked' alternatives of the final product mephedrone. Scheduling the 'masked' or 'protected' versions of 4-MMC (following a precursor assessment) may mitigate this risk. [This section was redacted in the interest of public safety]

- ***Scheduling 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 4'-methylpropiophenone poses a risk of hindering legitimate industries*****.** The substance has legitimate use in manufacture of pharmaceuticals and is legally traded in the EU, with four registrants declaring the volume of 10-1000 tonnes per year. Its scheduling could impact the production of tolperisone and its availability on the EU market, as well as its price (in case of reduced availability), in cases where the production of tolperisone occurs in the EU (information currently not available). Limiting the access to 4′-methylpropiophenone may motivate local pharmaceutical producers to shift the location of production of tolperisone 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 this medicine.

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 4'-methylpropiophenone, while scheduling its counterpart 2-bromo-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 4′-methylpropiophenone, then 2-bromo-4′-methylpropiophenone 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'-methylpropiophenone* may enable the production and trafficking of mephedrone, which 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.

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