EUDA
EUROPEAN UNION DRUGS AGENCY

Date issued: 19.12.2024

PRECURSOR ASSESSMENT REPORT of 3′-methylpropiophenone

This EUDA Precursor Assessment Report examines the evidence on 3′-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

3′-methylpropiophenone is a chemical precursor used for the production of 3-methylmethcathinone (3-MMC) – a synthetic cathinone stimulant drug that has been present in the drug market in the European Union (EU) since at least 2012. 3-MMC has been under EU control since 2022 and international control since 2023. The appearance of 3-MMC on the drug market coincided with the control of mephedrone (4-MMC) in Europe and, it appears that the substance was introduced in the market as a non-controlled alternative to 4-MMC (EMCDDA, 2022). Seizures of 3-MMC in the EU included a large multi-tonne incident shipped from India.

Production of 3-MMC in the EU seems to be limited, with only four reports of production or processing sites being dismantled in the Netherlands, France and Slovakia. No information was reported about the type or quantity of precursors seized at those sites, including whether any 3′-methylpropiophenone was recovered there. No detections of 3′-methylpropiophenone were reported by EU Member States to the data sources consulted.

Based on the scientific literature, 3′-methylpropiophenone can be converted into 3-MMC 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′-methylpropiophenone is made. To avoid this step, clandestine production of cathinones often starts directly from the second step using the equally commercially available brominated propiophenone, such as 2-bromo-3′-methylpropiophenone as a staring material to produce 3-MMC.

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

3′-methylpropiophenone is commercially available as a reference material for use in analytical laboratories.

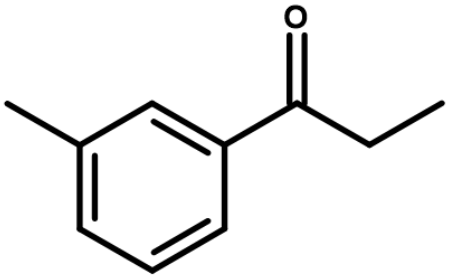
Scheduling considerations

Scheduling 3′-methylpropiophenone may contribute to reducing the availability of 3-MMC in the EU and to limit the generation of large profits for organised crime groups derived from its sale. However, based on the limited data available, the impact of this action would be difficult to assess, particularly because 3-MMC appears to be mainly imported to Europe in its final form. Alternative strategies can also be adopted by illicit drug producers. These could possibly include the clandestine manufacture of 3′-methylpropiophenone, or the use of alternative synthetic pathways such as the ‘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 3-MMC (such as 2-MMC or mephedrone) or pyrrolidine-containing cathinones (alpha-PVP, alpha-PHP and alpha-PHiP) which could pose similar, or even more harms to people who use drugs. This risk may be mitigated with the scheduling of the precursors associated with these substances.

Scheduling 3′-methylpropiophenone is unlikely to impact legitimate industries, as the substance appears to have no known legitimate use in the sources consulted, outside of the use as a reference standard for analytical laboratories.

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

1. Substance description

RAR_ID	2024-0005
Substance name	3′-methylpropiophenone
Abbreviation	3MPP
Chemical structure	
IUPAC name	1-(3-Methylphenyl)-1-propanone
InChI code	InChI=1S/C10H12O/c1-3-10(11)9-6-4-5-8(2)7-9/h4-7H,3H2,1-2H3
InChI Key	QHVNQIJBHWOZRJ-UHFFFAOYSA-N
SMILES	C(CC)(=O)C1=CC(C)=CC=C1
Other names	m-Methylpropiophenone; 3-MMC, 1-(m-tolyl)propan-1-one; Tolperisone Impurity 9; 1-(3-methylphenyl)propan-1-one
Molecular formula	$C_{10}H_{12}O$
Molecular weight (g/mol)	148.2
EUDA Classification	Propiophenones
CAS RN	51772-30-6
CAS page link	https://commonchemistry.cas.org/detail?cas_rn=51772-30-6&search=3-methylpropiophenone
HS/CN code	N/A
TARIC link	N/A
CUS number (ECICS)	N/A
ECICS link	N/A
EC number	257-405-2
REACH link	https://echa.europa.eu/substance-information/-/substanceinfo/100.052.170
Physical form (RT)	Liquid
Colour	Colourless to light-yellow

Physical features	Distinct smell
Associated with the production of	3-Methylmethcathinone (Synonyms: 3-MMC, Metaphedrone)
GHS Hazard Statements	H335 - May cause respiratory irritation H319 - Causes serious eye irritation H315 - Causes skin irritation H302 - Harmful if swallowed

2. Evidence of use in the illicit production

2.1 Background

3′-methylpropiophenone is a substituted propiophenone, i.e., an aromatic ketone, substituted in the aryl moiety in the *meta* position with a methyl group. According to the published literature (EMCDDA, 2022; Wrzesień, 2018), **3′-methylpropiophenone** is associated with the illicit production of **3-Methylmethcathinone (3-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).

3-MMC is available on the EU drug market at least since 2012 (EMCDDA, 2022). It has been subject to a risk assessment by the EUDA in 2021 and, subsequently, controlled in the EU since 2022 ([2]). Following the CND Decision 66/7 ([3]) its international control in Schedule II of the Convention on Psychotropic Substances of 1971 entered into force at the end of 2023.

3-MMC is a positional isomer of 2-MMC and mephedrone (4-MMC). The appearance of 3-MMC on the drug market coincided with the control of mephedrone in Europe, after the latter spread rapidly in Europe 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 3-MMC was introduced in the market as a non-controlled alternative to 4-MMC (EMCDDA, 2022).

Detections of 3-MMC were made by at least 23 Member States (EMCDDA, 2022). Judging from seizure data reported to the EU Early Warning System (Figure 1) 3-MMC appears to have re-emerged in 2020, following a decline in seizures which coincided with its legal control in China in 2015 which was then the main source country for the substance (EMCDDA, 2022). Over 2.8 tonnes of the 3-MMC were seized in the EU in 2022 ([4]). Most of this quantity (2.5 tonnes) were seized in one single incident in Spain, at

([2]) 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

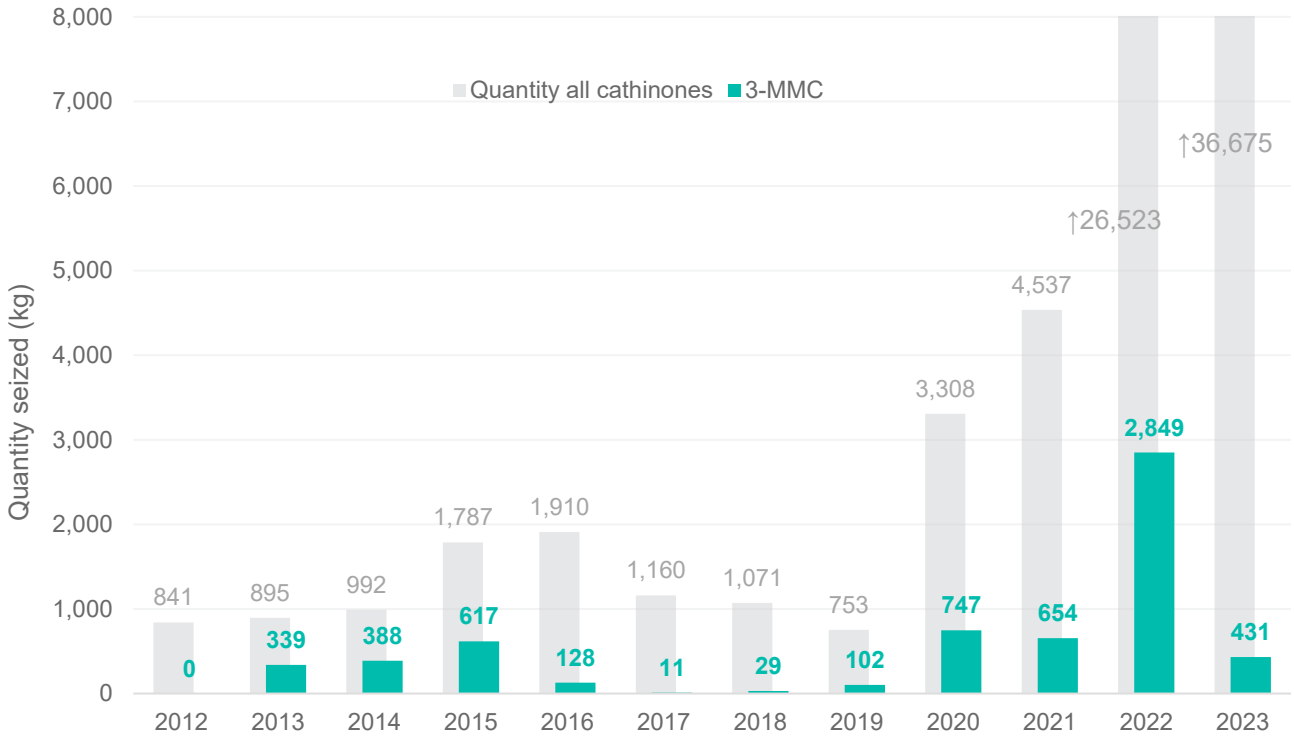
([3]) Commission on Narcotic Drugs Report on the sixty-sixth session (13-17 March 2023), E/2023/28, E/CN.7/2023/11; https://www.unodc.org/documents/commissions/CND/Drug_Resolutions/2020-2029/2023/Dec_66_5_2305857E.pdf

([4]) Additional data reported to the EUDA suggests that in 2023 seizures of 3-MMC in the EU have been close to 500 kg. 3-MMC was also reported in large quantities of tablets (16 250 units) in 2022 by Hungary. Some of these data may be duplicated with seizures reported to the EU Early Warning System.

Barcelona Airport, regarding a shipment originating in India. At present, India appears to be the main source of 3-MMC to the EU.

In addition, some 3-MMC production has been reported in Europe, particularly focused around the Netherlands.

Figure 1. Quantity of all synthetic cathinones and 3-MMC seized in the EU (2012-2023)



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

Based on the data reported to the EUDA and Europol ([5]), between 2013 and 2021, at least 4 sites have been reported as involved in production or processing of 3-MMC in three Member States. These include two sites found in the Netherlands (2017 and 2020), one in France (2021) and one in Slovakia (2013). Whereas the laboratory in Slovakia was considered an operational site, the two Dutch sites were considered storage and packaging plants (EMCDDA, 2022). No further information was provided for the French site.

Data on the quantity and the identity of precursors seized at these sites is not routinely captured by any of the data sources available and no information has been provided on the precursors used in the production of 3-MMC in the cases mentioned above.

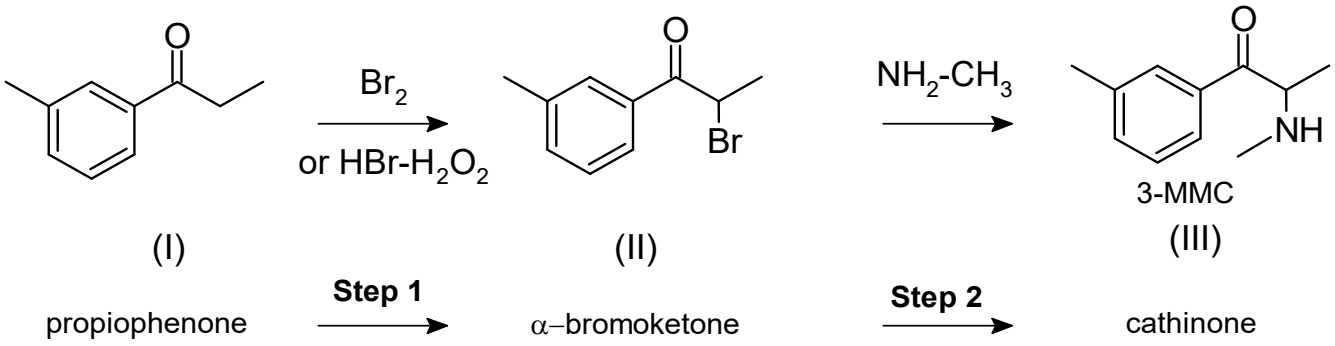
2.2 General methods for the synthesis of cathinones and 3-MMC

Several methods exist for the synthesis of 3-MMC, 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

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

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, 2022; 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, 2012; Wrzesień, 2018, Power et al., 2011).

Scheme 1. Preparation of 3-MMC via the ‘bromination-amination’ pathway (Power et al., 2011; Wrzesień, 2018).



Step 1 uses 3′-methylpropiophenone (I) (the subject of this precursor assessment) as the starting material, obtained from direct synthesis or from commercial sources – an oily, clear, colourless to light yellow liquid with a distinct smell. 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-3′-methylpropiophenone (II). If isolated, this substance is a fine white powder. It is sparingly soluble in water but exhibits good solubility in various organic solvents such as acetonitrile, chloroform, dichloromethane and ethyl acetate. This substance causes serious eye irritation, causes skin irritation and may cause respiratory irritation.

2-Bromo-3′-methylpropiophenone (II) is also available from chemical suppliers, meaning that the first step can be omitted, avoiding the use of bromine and reducing the number of steps needed to obtain the final product (3-MMC). Seizures of 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-3′-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 3-MMC hydrochloride salt. The final product is then recrystallised to remove impurities in large plastic trays that are characteristic findings in cathinone production facilities (EMCDDA and Europol, 2024). This is an advantageous option because the starting

([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.

materials are commercially available or easily synthesised, it is scalable and straightforward (EMCDDA, 2011).

In addition to the standard organic synthesis methods referred to above, chemically masked derivatives of 3-MMC, as well as synthetic cathinones in general, can also be produced in order to circumvent legal controls and/or avoid detection by law enforcement, such as customs agencies. The cathinone is chemically masked to produce a non-controlled substance which can then be converted back into the parent drug through relatively simple steps. For example, in 2019, Dutch Police seized 350 kilograms of chemically masked 3-MMC ([7]) at a site linked to a producer/distributor that had apparently imported the substance from India. The 3-MMC was masked as *N*-acetyl-3-MMC. It is presumed that this derivative was intended to be converted to 3-MMC, for example by acid hydrolysis using hydrochloric acid. Approximately 150 kilograms of 3-MMC were also seized at the site (CAM, 2021; EMCDDA, 2022).

3. Evidence of trafficking in the EU

3′-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).

As of December 2024, no seizures, stopped shipments or thefts of 3′-methylpropiophenone were reported to the EDPD or to the INCB. Therefore, the databases consulted do not provide evidence of trafficking of 3′-methylpropiophenone in the EU.

4. Legitimate uses in the EU

3′-methylpropiophenone has legitimate use as a reference material used in analytical laboratories ([8]). 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 its legal trade in the EU has been found.

5. Legal controls

Based on the available information, 3′-methylpropiophenone is not a controlled substance in any of the searched jurisdictions, except for Taiwan ([9]). In Taiwan it is controlled under the Schedule 4 Controlled Drug Materials, Controlled Drugs Act (Item 41). In the legislation, all isomers of methylpropiophenone (including **4′-methyl**propiophenone, **3′-methylpropiophenone**, **2′-methyl**propiophenone) 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.

([7]) It is unknown whether *N*-acetyl-3-MMC is hydrolysed to 3-MMC in human stomach acid. No information is available on the pharmacology or toxicology of this masked derivative.
([8]) https://www.sigmaaldrich.com/PT/en/product/fluorochempreferredpartner/fluh99c89070?context=bbe
([9]) 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

There is currently no information available on the seizures of 3′-methylpropiophenone outside of the EU.

7. Conclusions and possible consequences of scheduling in the EU

The data available suggests that 3′-methylpropiophenone is not used to a significant extent in the European Union as a precursor in the synthesis of 3-MMC, since no detections have been reported to the data sources consulted. Some detections may have occurred and not been reported, given that the substance is not scheduled.

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

- ***Scheduling 3'-methylpropiophenone may contribute to reducing the availability of 3-MMC in the EU.*** Inclusion of the chemical under the EU controls might make its trade and use for illicit production of 3-MMC more difficult and, thus, contribute to reducing the availability of 3-MMC in the EU. Because the extent of use of 3′-methylpropiophenone in illicit production of 3-MMC 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.

- ***Scheduling 3'-methylpropiophenone may result in different chemical routes being adopted by illicit drug producers.*** Numerous alternative synthetic methods for 3-MMC exist which avoid the use of 3′-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 3'-methylpropiophenone may result in its production by illicit drug producers.*** Rather than obtaining it commercially, 3′-methylpropiophenone 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'-methylpropiophenone may result in the emergence of 'designer' cathinone precursors.*** The scheduling of 3′-methylpropiophenone may motivate illicit drug producers to seek alternatives to the precursor, and import 'masked' alternatives of the final product 3-MMC. Seizures of chemically 'masked' 3-MMC have already been made in the EU. Scheduling the 'masked' or 'protected' versions of 3-MMC (following a precursor assessment) may mitigate this risk. [This section was redacted in the interest of public safety]

- ***Scheduling 3'-methylpropiophenone may shift illicit drug production to different end-products.*** Lack of access to the precursor necessary to produce 3-MMC 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'-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 3′-methylpropiophenone. These should be weighed against the risks of not scheduling the substance.

Not scheduling 3'-methylpropiophenone, while scheduling its counterpart 2-bromo-3'-methylpropiophenone may motivate illicit drug producers to adapt the synthetic route to start from 3'-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 chemical properties, environmental damage is likely to increase with an increasing use of bromine. Suffice to say, if a decision is taken to schedule 3′-methylpropiophenone, then 2-bromo-3′-methylpropiophenone should be scheduled at the same time 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 *3'-methylpropiophenone* may enable the production and trafficking of 3-MMC, which may generate large profits for organised crime groups**. For example, mephedrone powder costs 21 000 EUR per kilogram at wholesale level (equivalent to 2.1 EUR per gram) but can be sold at 22.5 EUR to the consumer (mark-up of approximately 20 EUR per gram) (EMCDDA and Europol, 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

CAM (Coördinatiepunt Assessment en Monitoring nieuwe drugs) (2021), Commissie Risicobeoordeling nieuwe drugs. *Risicobeoordeling 3-Methylmethcathinon (3-MMC)*. [Risk assessment 3-Methylmethcathinone]. RIVM-projectnummer: V/050091/21/SC. https://www.rivm.nl/publicaties/risicobeoordeling-3-methylmethcathinon-3-mmc

Carroll, F. I., Blough, B. E., Abraham, P., Mills, A. C., Holleman, J. A., Wolckenhauer, S. A., Decker, A. M., Landavazo, A., McElroy, K. T., Navarro, H. A., Gatch, M. B. and Forster M. J. (2009), 'Synthesis and biological evaluation of bupropion analogues as potential pharmacotherapies for cocaine addiction', *Journal of Medicinal Chemistry*, 52(21), pp. 6768–6781. https://doi.org/10.1021/jm901189z

EMCDDA (2011), *Report on the risk assessment of mephedrone in the framework of the Council Decision on new psychoactive substances*; Publications Office of the European Union, Luxembourg, ISBN 978-92-9168-457-1; doi: 10.2810/40800

EMCDDA (2015), *Perspective on drugs: Injection of synthetic cathinones*, https://www.euda.europa.eu/topics/pods/synthetic-cathinones-injection_en

EMCDDA (2016), *Report on the risk assessment of 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-pyrrolidinovalerophenone, α-PVP) in the framework of the Council Decision on new psychoactive substances*, Risk Assessments, Publications Office of the European Union, Luxembourg. https://www.euda.europa.eu/publications/risk-assessments/alpha-pvp_en

EMCDDA (2022), *Report on the risk assessment of 2-(methylamino)-1-(3-methylphenyl)propan-1-one (3-methylmethcathinone, 3-MMC) in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended)*, Publications Office of the European Union, Luxembourg. https://www.euda.europa.eu/publications/risk-assessments/3-mmc_en

EMCDDA and Europol (2024), *EU Drug Market: New psychoactive substances — In-depth analysis*; https://www.euda.europa.eu/publications/eu-drug-markets/new-psychoactive-substances/distribution-and-supply/synthetic-cathinones_en

Guha, S., Rajeshkumar, V., Kotha, S. S. and Sekar, G. (2015), 'A versatile and one-pot strategy to synthesize α-amino ketones from benzylic secondary alcohols using N-bromosuccinimide', *Organic Letters*, 17(3), pp. 406–409. https://doi.org/10.1021/ol503683q

Mehta N, inventor; Burroughs Wellcome Co USA, assignee. Meta chloro substituted-alpha-butylamino-propiophenones. United States patent US 3,819,706. 1974 Jun 25.

Power, J. D., McGlynn, P., Clarke, K., McDermott, S. D., Kavanagh, P., and O'Brien, J. (2011), 'The analysis of substituted cathinones. Part 1: chemical analysis of 2-, 3-and 4-methylmethcathinone', *Forensic Science International*, *212*(1-3), 6-12.

Reddy, Y. T., Reddy, P. N., Reddy, M. N., Rajitha, B. and Crooks, P. A. (2010), 'Convenient and scalable process for the preparation of bupropion hydrochloride via efficient bromination of m-chloropropiophenone with N-bromosuccinimide', *Synthetic Communications*, 40(11), pp. 1566–1573. https://doi.org/10.1080/00397910903097351

Saem de Burnaga Sanchez, J. (1929), 'Sur un homologue de l'ephédrine', *Bulletin de la Societé Chimique de France* 45, pp. 284–286.

Singleton, N., Cunningham, A., Groshkova, T., Royuela, L., and Sedefov, R. (2018), ‘Drug supply indicators: Pitfalls and possibilities for improvements to assist comparative analysis’, *International Journal of Drug Policy*, 56, 131-136. https://www.sciencedirect.com/science/article/abs/pii/S0955395918300380

Wrzesień, W., Stanaszek, R., Zuba, D. and Byrska, B. (2018), ‘Clandestine laboratory producing mephedrone (4-MMC) and clephedrone (4-CMC) – substance identification and hazard analysis’, *Problems of Forensic Sciences*, 115, pp. 287–309.