4-Methylethcathinone (4-MEC)

Critical Review Report

Agenda item 4.15

(R/S)- 2-(Ethylamino)-1-(4-methylphenyl) propan-1-one
(4-methyl-N-ethylcathinone, 4-MEC)

Expert Committee on Drug Dependence

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World Health Organization

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Contents

Summary

(*R*/*S*)- 2-(Ethylamino)-1-(4-methylphenyl)propan-1-one, also known as 4-methylethcathinone or 4-MEC, has emerged in recent years as a recreational psychostimulant. Its synthesis was first published in 2010 as part of an analytical confirmation related to test purchases from online retailers. The first official notification submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by a European member state was 2010. Since then, it has been detected across the globe as a reflection of modern forms of trade within a globalised world. As was the case with many other emerging substances with psychoactive properties, commonly used terms include "legal highs", "bath salts" or "new psychoactive substances" (NPS) in the attempt to highlight the fact that many, if not most, did not originally fall under any legislative control and that detailed data on both pre-clinical and clinical levels were normally less well explored. 4-MEC appears to be among the most seized cathinone representatives. Currently, the available pre-clinical *in-vitro* data are limited but it is suspected that further studies may be underway. So far, 4-MEC was found to inhibit dopamine, norepinephrine and serotonin uptake transporters with equal potency. In addition, first evaluations have shown that it may also function as a serotonin releasing agent but not dopamine and norepinephrine. Further studies are needed to assess abuse liability and dependence potential.

1. Substance identification

A. International Nonproprietary Name (INN)

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B. Chemical Abstract Service (CAS) Registry Number

1225617-18-4 (free base)
1266688-86-1 (hydrochloride salt)
1359736-80-3 (hydrobromide salt)
1346747-06-5 (N-C_2D_5 free base)
1346602-57-0 (N-C_2D_5 hydrochloride salt)
1388142-29-7 (*R*-enantiomer free base)
1388142-30-0 (*S*-enantiomer free base)

C. Other Names

4-MEC, 4-methyl-*N*-ethcathinone, *p*-methyl-*N*-ethcathinone, 2-(ethylamino)-1-(*p*-tolyl)propan-1-one, 4-methylethcathinone.

D. Trade Names

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E. Street Names

4-MEC

F. Physical properties

4-MEC HCl is a white crystalline powder.

G. WHO Review History

4 MEC was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 4 MEC is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

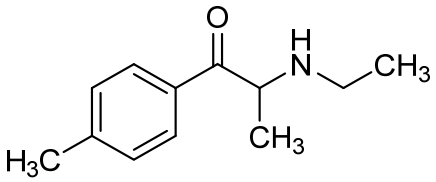
A. Chemical Name

IUPAC Name: (*R*/*S*)- 2-(ethylamino)-1-(4-methylphenyl)propan-1-one

CA Index Name:
(*R*/*S*)- 2-(ethylamino)-1-(4-methylphenyl)-1-propanone

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral centre

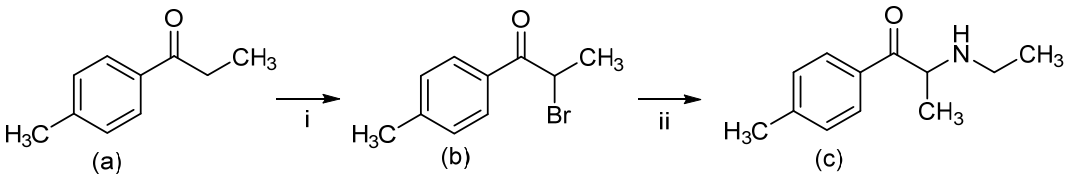
Molecular Formula: $C_{12}H_{17}NO$ (base)
Molecular Weight: 191.27 g/mol
Melting point: 191 °C (dec.)[1]
Boiling point: --
Fusion point: --

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-4-MEC and (*R*)-4-MEC, respectively. Currently, it appears that data about their optical rotation or potential to display distinguishable pharmacological properties have not been published. 4-MEC is most likely to be available as the racemic mixture.

D. Synthesis

The first synthesis of 4-MEC was published in 2010 by Brandt et al. following the scheme shown below.[2] This key procedure includes the α- bromination (step i) of the propan-1-one precursor (a) and formation of the 2-bromoppropan-1-one intermediate (b). Reaction with *N*-ethylamine (step ii) gives 4-MEC (c) which may then be converted into a range of salts. One of several alternatives may include the oxidation of the ephedrine-type (ethylamino)propan-1-ol precursor as well.



E. Chemical description

4-MEC, i.e. (*R*/*S*)- 2-(ethylamino)-1-(4-methylphenyl)propan-1-one, contains a 2-amino-1-phenylpropan-1-one nucleus which forms the structural basis for many cathinone-based substances that are known to interact with a range of targets found, for example, in the central nervous system.

F. Chemical properties

4-MEC HCl is a water-soluble white crystalline powder.

G. Chemical identification

4-MEC, as well as many other cathinones, has been repeatedly characterized in recent years. The first report that described its identification in a sample obtained from an internet supplier was published in 2010 by Brandt et al..[2] Confirmation was obtained from synthesis and analytical characterisation by gas chromatography-electron and chemical ionisation mass spectrometry (GC-EI/CI-MS) and ^{1}H, ^{13}C nuclear magnetic resonance spectroscopy (NMR). [2] In 2011, additional data were reported which included full scan ultraviolet (UV), electrospray ionisation (tandem) mass spectrometry, Fourier transform infrared (FTIR) and NMR data.[3] Several immunoassays have been described for the detection of 4-MEC and other cathinones. Under certain conditions, examples of cross-reactivity may occur.[4,5]

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

Similar to other well-established psychostimulants, a key principle involved in the molecular mechanisms of 4-MEC is the interaction with transport proteins that lead to the elevation of extracellular neurotransmitter levels, most notably, dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT), respectively.

However, an important question relates to the ability of a psychostimulant to act as a monoamine re-uptake inhibitor (e.g. cocaine-like) or as a substrate-type releaser (amphetamine-like). In the latter case, this may be achieved by transporter-mediated translocation of the drug into the cytoplasm in exchange of the monoamine which may be exacerbated by additional release from vesicular storage, thus leading to increasing monoamine availability for further release.[6] The key targets of interest normally include the evaluation of drug action at the dopamine (DAT), norepinephrine (NET) and serotonin (SERT) transporters. Recently published research demonstrated that when using using hDAT, hNET and hSERT expressed in HEK 293 cells, 4-MEC inhibited all three monoamine transporters with approximately equal potency similar to cocaine and also released 5-HT.[7]

4.1. Pharmacodynamics

In-vitro pharmacology

Receptor binding studies carried out at the National Institute of Mental Health's Psychoactive Drug Screening Program[8] revealed that 4-MEC acted as an inhibitor of monoamine transporter activity with K_i values of 565 nM (HEK-hDAT), 1668 nM (HEK-NET) and 1798 nM (HEK-SERT), respectively. Additional binding studies also confirmed appreciable affinity to the σ_2-receptor.[9]

In comparison, inhibition of monoamine uptake ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT) was reported by Simmler et al. at low micromolar levels (IC_{50} DAT = 4280 nM, IC_{50} NET = 2230 nM, IC_{50} SERT= 7930 nM).[7] Radioligand binding studies gave K_i values of 890 nM (HEK-hDAT), 6800 nM (HEK-hNET) and 7700 nM (HEK-hSERT), respectively.

Qualitative release studies (HEK 293 cells, hNET, hDAT, hSERT, loaded with [^{3}H]NE, [^{3}H]DA, and [^{3}H]5-HT), then exposed to 100 µM test substance) confirmed that 4-MEC was capable of releasing 5-HT whereas DA and NE release was not observed. Additional multi-target screens revealed a number of receptors with K_i values below 5 µM such as 5-HT_{2A} (3.8 µM), 5-HT_{2C} (5.2 µM).[7]

In-vivo pharmacology

Published animal data on 4-MEC do not appear to be currently available.

4.2. Routes of administration and dosage

Not applicable.

4.3. Pharmacokinetics

Published literature appears to be unavailable at the time of writing. There are indications that 4-MEC may suffer from instability in a number of biofluids when stored.[10,11]

5. Toxicology

Published literature reports appear to be currently unavailable at the time of writing.

6. Adverse reactions in humans

There appears to be limited data available in the published literature with regards to specific information about 4-MEC. Gil et al. described the detection of 4-MEC in three cases (Table 1). The detected blood levels were 152, 56 and 46 ng/ml, respectively. Two fatalities were involved but it was considered unlikely to be causally linked.[12] The authors also make reference to a case reported by Rojek et al. who described a fatal poisoning case with 4-MEC which included 4-MEC blood levels of 1267 ng/ml.[13] The same authors published a formal case report on postmortem analysis of blood following what appeared to be 4-MEC ingestion. The detected blood levels were given as 1200 ng/ml 4-MEC and 230 ng/ml amphetamine, respectively.[14]

7. Dependence potential

Data on dependence potential of 4-MEC appear to be currently absent from the literature.

8. Abuse potential

Detailed clinical studies in humans are not available in the scientific literature. Initial *in-vitro* studies indicate that 4-MEC shares some monoamine uptake/5-HT releasing properties but it seems unclear if this extends to abuse liability encountered, for example, with psychomotor stimulants such as methamphetamine or cocaine. More pre-clinical studies seem indicated.

Table 3. Summary of case reports on 4-MEC by Gil et al.[12]

Case 1

- 30 Year old male died in fatal traffic accident.
- White powder found in the driver's possession.
- Powder contained 4-MEC (51% purity)
- Blood analysis: 152 ng/ml 4-MEC and 0.12 g/dl ethanol
- Urine analysis: 122 ng/ml 4-MEC and 0.19 g/dl ethanol

Case 2

- Male user (age unknown) developed 'psychomotor agitation' following 'legal highs' intake and was found unconscious 5-6 hours following consumption.
- Cause of death considered ‘damage to important centers of the brain stem’.
- Blood analysis: 56 ng/ml 4-MEC, PMA (2347 ng/mL), PMMA (30 ng/mL), amphetamine (378 ng/mL), methamphetamine (48 ng/mL), tetrahydrocannabinol (THC, 1.3 ng/mL) and 11-nor-9-carboxy-THC metabolite (8.7 ng/mL)
- Urine analysis: PMA (50.1 µg/mL), PMMA (1.7 µg/mL), 4-MEC (14.3 µg/mL), amphetamine and THCCOOH (54.7 ng/mL).
- Analysis of stomach contents: detection of PMA, PMMA and 4-MEC.

Case 3

- 27 Year old male suspected to be in possession of 'narcotics'.
- White powder found in possession.
- Powder contained 4-MEC (78% purity).
- Blood analysis: 46 ng/ml 4-MEC

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Not known.

10. Listing on the WHO Model List of Essential Medicines

4-MEC is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

4-MEC is not marketed as a medicine.

12. Industrial use

Not known.

13. Non-medical use, abuse and dependence

Household surveys that specifically probe for prevalence of 4-MEC do currently not appear to be available in the published literature.

Oral dosage levels have been tentatively suggested to range between 15-50 mg (threshold) and 150-300+ mg (strong) whereas threshold levels obtained from nasal insufflation were suggested to range between 5-25 mg (strong: 100-200 mg). The total duration of intoxication may last between 2-5 hours (p.o.) or 2-3 hours via nasal insufflation.[15,16] As with many other synthetic cathinones, injection, inhalation, oral and rectal administration may also be encountered.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The Drug Enforcement Administration, after reviewing the scientific literature, 3-factor analysis, consultation of NFLIS, law enforcement, Customs and Border Protection and other sources, confirmed that 4-MEC appeared to be sufficiently prevalent to pose a public health risk.[17]

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

15. Licit production, consumption and international trade

No information available.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

As of 10.03.2014, reports have been received from the European early-warning system on new drugs that 4-MEC was encountered in seizures or as a used substance in Greece, Lithuania, Spain, Belgium, Norway, Italy, Austria, Turkey, Slovenia, Malta, Slovakia, Bulgaria, Croatia, Germany, Hungary, France, Czech Republic, Finland, Denmark, United Kingdom [18]. The Drug Enforcement Administration disclosed that 377 exhibits were reported for 4-MEC between January 2010 and December 2013 which was based on STRIDE (System to Retrieve Information from Drug Evidence) database queries. The National Forensic Laboratory Information System (NFLIS) registered 1952 reports containing 4-MEC between January 2010 and December 2013. Between April 2010 and November 2013, a total number of 78 encounters (shipments) with 4-MEC were identified by U.S. Customs and Border Protection.[17] 4-MEC was reported to be the most common substance found in pills sold as "ecstasy" in the region of Oceania.[19]

Responses obtained to the UNODC questionnaire on NPS (up to 2012) revealed that 4-MEC was ranked fourth with regards to numbers of reports (38) received. This was only superseded by mephedrone (68 reports), MDPV (61 reports), methylone (53 reports) whereas flephedrone was ranked fifth (35 reports).[20]

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Not applicable in terms of medical use.

18. Current and past national controls

The EMCDDA received confirmation that 4-MEC is controlled in the following countries [18]:

- Bulgaria via amendments to the National Drug Law; in force on 09 February 2011
- Czech Republic via amendment of the Act n. 167/1998 on addictive substances; came in force on 22 April 2011
- Denmark (as of 27 October 2011) controlled and included in Annex 1 to executive order no. 557 of 31 May 2011 on euphoriant substances issued by the Danish Ministry of Health and Prevention
- Estonia (as of 03 December 2011) controlled: first list of narcotic and psychotropic substances
- Finland: controlled as a medicinal product as of 22 October 2010
- France: controlled since 27 July 2012
- Germany (by adoption of the 26th Amending Regulation on Narcotic Drugs, i.e. the 26. Betäubungsmittelrechts-Änderungsverordnung, BtMÄndV); entered into force on 26 July 2012, permanently placed under schedule II (narcotics eligible for trade but not for medical prescription) of the German Narcotics Act (Betäubungsmittelgesetz, BtMG)
- Hungary (Act CLXXVI of 2011 on the amendment of certain health related acts; amended Act XXV of 1998 on human pharmaceuticals); addition to schedule 'A', the illegal drugs schedule
- Ireland (via generic definition, Misuse of Drugs Act 1977 (controlled drugs) (2011, S.I. No. 551 of 2011)
- Lithuania via amendment of Republic of Lithuania Law on the Control of Narotic Drugs and Psychotropic Substances
- Poland (as of 8 June 2011) amendment of the act of law on counteracting drug addiction from 15 April 2011
- Portugal (Portaria nº 154/2013, 17 April 2013)
- Slovenia via amendment of Decree on classification of illicit drugs, published on 22nd July 2013 in Official Gazette of RS No. 62/2013 and entered into force 15 days afterwards)
- Sweden: classified as narcotic since 01 September 2011)
- United Kingdom (via amendment of The Misuse of Drugs Act 1971 by generic definition as of 16 April 2010)
- Turkey confirmed control by way of Law on Control of Narcotic Substances no 2313; passed by Decision of the Council of Ministers on 22 May 2013.
- Greece and Malta: not controlled.

- The Russian Federation confirmed that 4-MEC is a controlled substance.
- USA: As of 7th March 2014, 4-MEC and nine other cathinones have been placed under temporary control (Schedule 1) of the Controlled Substances Act [17]
- Singapore, by way of generic definition, placed 4-MEC under temporary control (Misuse of Drugs (Amendment) Act 2012, No. 30 of 2012).
- New Zealand: controlled (Psychoactive Substances Act 2013).

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Not applicable.

References

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of 4 MEC

A total of 65 Member States answered the questionnaire for 4-Methylethcathinone (4-MEC). Of these, only 29 respondents (AMR 5, EUR 21, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that 4-MEC was currently authorized or in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in medical and scientific research or as analytical standard. There was no use stated for 4-MEC in animal/veterinary care

HARMFUL USE

Nineteen respondents confirmed that there was recreational/harmful use of 4-MEC; four reported that the common route of administration was oral, eight oral, inhaling/sniffing, two oral, injection, inhaling/sniffing, one each inhaling/sniffing, and injection. Thirteen respondents stated that the substance was obtained only via trafficking, one via diversion and trafficking, one via trafficking and clandestine manufacturing and one via clandestine manufacturing. The common formulations available were reported as powder by eight, powder and tablet by five, powder, tablet and liquid by one and liquid by one. When asked if 4-MEC was used by any special populations two responded that it was used by the general population and in clubs, three only in clubs and three only among general population. One respondent specifies youth. In 2012 18 deaths due to all cathinones were reported by one respondent as well as 4 emergency room visits by another. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by 4-MEC. These include hallucinations, delusions, palpitations, blurred vision, psychosis, dizziness, confusion, agitation and fits. (please refer to 4-FMC as well)

As reported by one respondent ‘a survey of college students in 2012 by the Monitoring the Future (MTF) showed that 0.2% of full-time college students used synthetic cathinone substances. The use of synthetic cathinone substances among 8th, 10th, and 12th grade students and young adults (non-college peers aged 19 to 28-years-old) was 0.8%, 0.6%, 1.3%, and 0.8%, respectively. According to a press release from the American Association of Poison Control Centers (AAPCC), there were 306 exposure calls related to synthetic cathinones in 2010, 6,137 calls in 2011, and 2,691 calls in 2012. 4-MEC, 4-MePPP, a-PVP, butylone, pentedrone, pentylone, 4-FMC, 3-FMC, naphyrone, and a-PBP are synthetic cathinones that emerged on the United States’ illicit drug market around the time of the temporary scheduling of mephedrone, MDPV, and methylone on October 21, 2011.4-MEC, 4-MePPP, a-PVP, butylone, pentedrone, pentylone, 4-FMC, 3-FMC, naphyrone, and a-PBP, like mephedrone, methylone, and MDPV, are popular recreational drugs. Evidence that these synthetic cathinone substances are being abused is indicated by law enforcement encounters of these substances. Forensic laboratories have analyzed drug exhibits received from state, local, and Federal law enforcement agencies and confirmed the presence of 4-MEC, 4-MePPP, a-PVP, butylone, pentedrone, pentylone, 4-FMC, 3-FMC, naphyrone, or a-PBP in these exhibits. STRIDE registered 1,732 drug exhibits pertaining to the trafficking, distribution and abuse of 4-MEC, 4-MePPP, a-PVP, butylone, pentedrone, pentylone, 4-FMC, 3-FMC, naphyrone, and

a-PBP from January 2010 to November 2013. Specifically, in 2010, STRIDE contains four reports related to 4-MEC and none for the other nine substances. However, in 2011, there were 205 reports related to these 10 substances, and in 2012, there were 1,302 reports. From January to November 2013 there were 221 reports (excluding naphyrone). National Forensic Laboratory Information System (NFLIS) registered over 8,000 reports from state and local forensic laboratories identifying these substances in drug related exhibits for the period from January 2010 to November 2013 across 42 states. Specifically, in 2010, NFLIS registered 13 reports from 5 states containing many of these synthetic cathinone substances. In 2011, there were 800 reports from 32 states related to these substances registered in NFLIS, in 2012 there were 5,485 reports from 41 states, and from January to November 2013 there were 2,509 reports from 41 states.

Another reported 'among cathinone derivatives, MDPV and 4-MEC – taking the place of mephedrone in 2011, after it was scheduled as an illicit drug – practically disappeared from the seizures in the first 3 months of 2012 following their reclassification as illicit drugs on 1 January 2012. Powders containing active substances 4-MEC generally had an active substance content of 15-85%, but most typically they occurred in an undiluted form.'

CONTROL

Of those with information on the substance, 26 reported that 4-MEC was controlled under legislation that was intended to regulate its availability - 18 under" controlled substance act", 4 under "medicines law", 2 under "analogue legislation", 1 under "generic legislation" and 1 as "other" type of legislation. Four respondents stated that there were challenges with the implementation of this legislation. On illicit activities related to 4-MEC, two respondents reported clandestine manufacture and one reported the synthesis of the product itself. Five respondents reported processing into the consumer product, 11 countries reported trafficking, 4 countries diversion and 12 countries an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	**2012 (number of respondents)**
Total number of seizures	1,047 (13)	1,694 (13)
Total quantity seized (kg)	330.65 (13)	273.54 (14)
Total quantity seized (l)	0.01	0.001 (1)
Total quantity seized (tablets/pills)	5,782 (6)	3,872 (4)

IMPACT OF SCHEDULING

Twenty-five respondents reported that if 4-MEC was placed under international control, they would have the laboratory capacity to identify the substance. It has no reported medical use.