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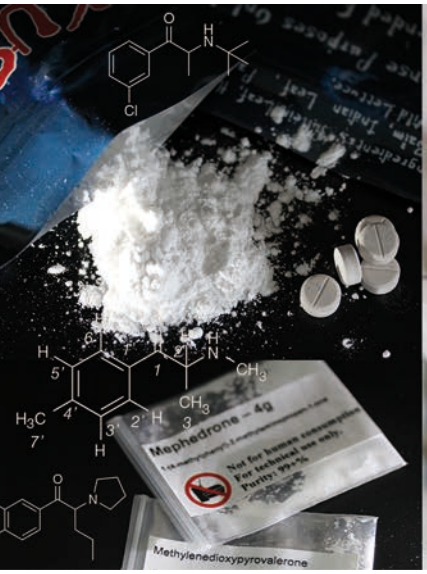

Recommended methods for the **Identification and Analysis of Synthetic Cathinones in Seized Materials**

MANUAL FOR USE BY NATIONAL DRUG ANALYSIS LABORATORIES

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Laboratory and Scientific Section
UNITED NATIONS OFFICE ON DRUGS AND CRIME
Vienna

Recommended Methods for the Identification and Analysis of Synthetic Cathinones in Seized Materials

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UNITED NATIONS
New York, 2015

Note

Operating and experimental conditions are reproduced from the original reference materials, including unpublished methods, validated and used in selected national laboratories as per the list of references. A number of alternative conditions and substitution of named commercial products may provide comparable results in many cases, but any modification has to be validated before it is integrated into laboratory routines.

ST/NAR/49

Original language: English

This publication has not been formally edited.

Publishing production: English, Publishing and Library Section, United Nations Office at Vienna.

Acknowledgements

UNODC's Laboratory and Scientific Section (LSS), headed by Dr. Justice Tettey, wishes to express its appreciation and thanks to Professor Niamh Nic Daeid of the Centre for Anatomy and Human Identification, University of Dundee, for the preparation of the first draft of this manual.

LSS would also like to thank Dr. Laurence Dujourdy of the Institut National de Police Scientifique, Lyon, France, and Ms. Katharine Konaris (ret.) of the State General Laboratory, Nicosia, Cyprus, for their expert reviews and valuable contribution.

The preparation of this manual was coordinated by Dr. Iphigenia Naidis, staff member of LSS, and the contributions of UNODC staff members Dr. Conor Crean and Ms. Susan Ifeagwu are gratefully acknowledged.

Contents

1. Introduction

1.1 Background

The emergence of new psychoactive substances (NPS), purported as "legal" alternatives to internationally controlled substances, was highlighted in the United Nations Office on Drugs and Crime (UNODC) publication *The challenge of new psychoactive substances* [1]. NPS are also commonly known as "designer drugs", "legal highs", "herbal highs" and "bath salts" and their emergence has resulted in the increased prevalence in forensic drug casework in recent years. This has given rise to both legal and analytical challenges, requiring the need for sensitive, reliable and reproducible methods to detect and identify these substances. However, this has been made more difficult by the lack of affordable chemical reference standards, appropriate analytical methodologies and scientific literature in this subject area.

Synthetic cathinones are a subgroup of NPS that can be considered to be derived structurally from cathinone, the principal active ingredient in the khat plant. Thus, synthetic cathinones are β-keto phenethylamines, and methcathinone, for example, is also known as β-keto amphetamine and has similar stimulant effects as amphetamine. There are a number of synthetic cathinones under international control. These include cathinone, methcathinone, cathine and pyrovalerone, which were all placed under international control before 2000. However, in the years that followed, a number of non-controlled synthetic cathinones appeared in drug markets, with methylone being the first synthetic cathinone to be reported to the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) in 2005. Mephedrone, first reported in 2007, became the most commonly used cathinone in the following years (although it had first been synthesized in 1928 [2]). Table 1 shows a number of other structurally diverse cathinones which have since emerged.

In response to the emergence of synthetic cathinones and other groups of NPS, many Member States have introduced national legislation. Following the scheduling decisions of the 58th Commission on Narcotic Drugs in 2015, mephedrone, methylone and methylenedioxypyrovalerone (MDPV) were all placed under international control and listed in Schedule II of the United Nations 1971 Convention on Psychotropic Substances (cathinone and methcathinone are listed in Schedule I, cathine in Schedule III and pyrovalerone in Schedule IV of the 1971 Convention).

1.2 Purpose and use of the Manual

The present Manual is one in a series of similar publications dealing with the identification and analysis of various classes of drugs under international control. These manuals are the outcome of a programme pursued by UNODC since the early 1980s, aimed at the harmonization and establishment of recommended methods of analysis for national drug analysis laboratories.

This Manual was prepared taking into account the Commission on Narcotic Drugs 2012 resolution 55/1, "Promoting international cooperation in responding to the challenges posed by new psychoactive substances", which encourages the United Nations Office on Drugs and Crime and other relevant international organizations, upon request, to provide Member States with technical assistance by supporting forensic and toxicological capability and to respond to the challenges posed by new psychoactive substances.

In accordance with the overall objective of the series, the present Manual suggests approaches that may assist drug analysts in the selection of methods appropriate for the sample under examination and provide data suitable for the purpose at hand, leaving room also for adaptation to the level of sophistication of different laboratories and various legal requirements. The majority of methods included in this manual have been presented in the published peer-reviewed scientific literature. **Any new method that is to be used in the reader's laboratory must be validated and/or verified prior to routine use.**

In addition, there are a number of more sophisticated approaches, but they may not be necessary for routine operational applications. Therefore, the methods described here should be understood as guidance; minor modifications to suit local circumstances should not affect the validity of the results. The choice of the methodology and approach to analysis, as well as the decision whether or not additional methods are required, remain with the analyst and may also be dependent on the availability of appropriate instrumentation and the level of legally acceptable proof in the jurisdiction within which the analyst works.

Attention is also drawn to the vital importance of the availability to drug analysts of reference materials and literature on drugs of abuse and the analytical techniques used for their identification. Moreover, the analyst must of necessity keep abreast of current trends in drug analysis, consistently following current analytical and forensic science literature.

UNODC's Laboratory and Scientific Section would welcome observations on the contents and usefulness of the present Manual. Comments and suggestions may be addressed to:

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All manuals, as well as guidelines and other scientific-technical publications, may be requested by contacting the address above.

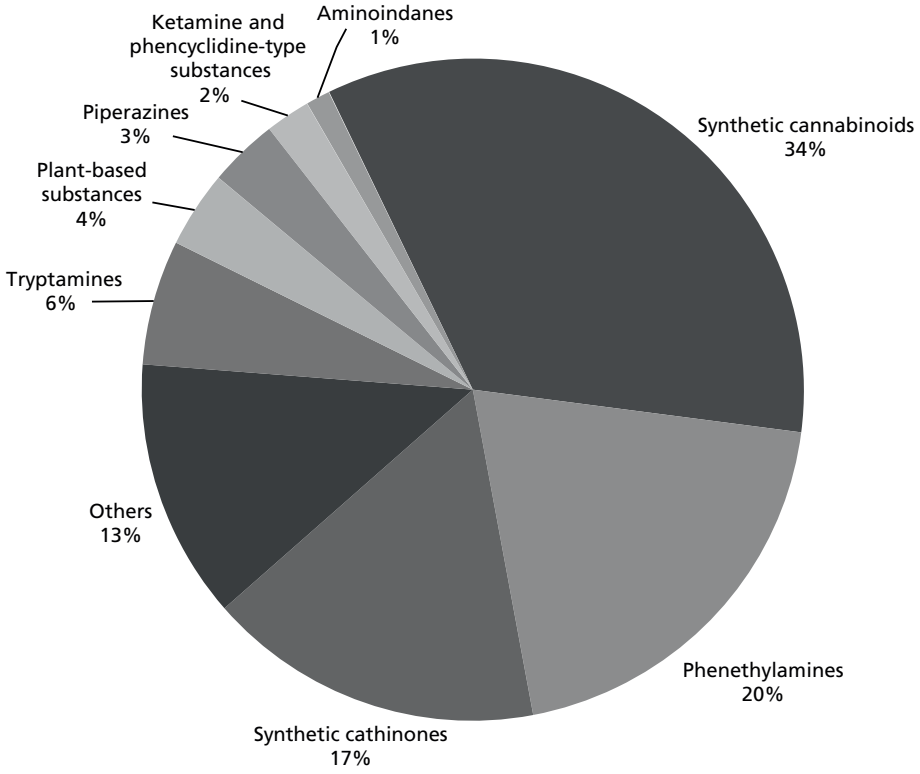
2. General aspects

2.1 Emergence of synthetic cathinones

The global emergence of synthetic cathinones as a group of new psychoactive substances was first highlighted in the UNODC publication *The challenge of new psychoactive substances* [1], in which 251 individual substances were reported to UNODC by 70 Member States and territories up to July 2012. The evolution and dynamic nature of the NPS market is illustrated by the fact that, as of July 2015, the number of countries reporting the emergence had increased to 95 and the number of substances to over 500 [3]. The majority of NPS, in terms of number of reports to UNODC in the period 2008-2015, were synthetic cannabinoids (34 per cent), followed by phenethylamines (20 per cent) and synthetic cathinones (17 per cent), as shown in figure I. With regard to individual synthetic cathinones, 97 have been reported to UNODC as of July 2015.

The increasing numbers of synthetic cathinones that have been reported to UNODC in recent years reflects the dynamic nature of the NPS market. The evolution can in part be considered as an attempt by the manufacturers to circumvent existing legislation. Following the control of mephedrone in a number of countries, other synthetic cathinones such as MDPV and more recently *alpha*-PVP have been marketed as alternatives [4, 5].

Figure I. Size of the different NPS substance groups, based on the individual substances reported to UNODC in the period 2008-2015 [3]



2.2 Description of the pure compounds

Synthetic cathinones normally present as white or off-white powders although they can come in a range of colours. Mephedrone, for example, commonly appears as white or yellow powder/crystals, with a distinct odour described as ranging from fishy to vanilla or bleach. Although primarily encountered as a powder, mephedrone has also been known to take the form of capsules/tablets of varying design [6]. Some of the more commonly encountered synthetic cathinones are presented in table 1.

Table 1. Commonly encountered synthetic cathinones

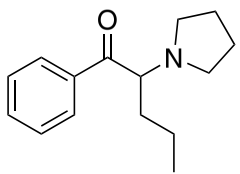
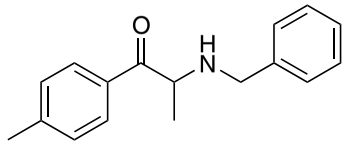
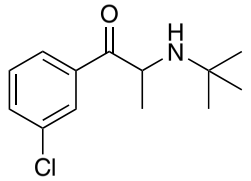
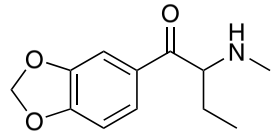
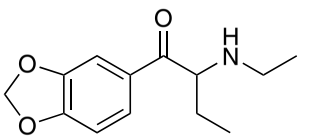
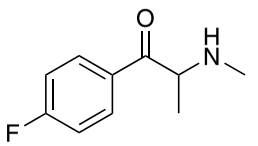
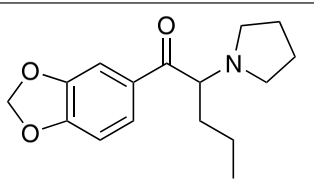
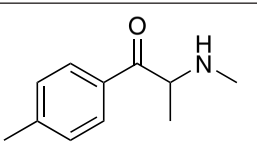
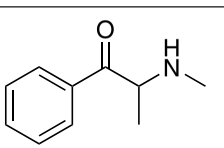
Common name/ abbreviation	*Chemical name*	*Structure*	*CAS number (where available)*
alpha-PVP	1-phenyl-2-(1-pyrrolidinyl)pentan-1-one		14530-33-7
Benzedrone, 4-MBC	4-methyl-*N*-benzylcathinone		36861-47-9
Bupropion	3-chloro-*N*-*tert*-butylcathione		34911-55-2
Butylone, βk-MBDB	1-(1,3-benzodioxol-5-yl)-2-(methylamino)-1-butanone		802575-11-7

Table 1. Commonly encountered synthetic cathinones *(cont.)*

Common name/ abbreviation	*Chemical name*	*Structure*	*CAS number (where available)*
Eutylone, βk-EBDB	1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-1-butanone		—
Flephedrone, 4-FMC	4-fluoromethcathinone		447-40-5
Methylenedioxypyrovalerone, MDPV	1-(1,3-benzodioxol-5-yl)-2-(1-pyrrolidinyl)-1-pentanone		687603-66-3
Mephedrone, 4-MMC	4-methylmethcathinone		1189805-46-6
Methcathinone	2-(methylamino)-1-phenylpropan-1-one		5650-44-2

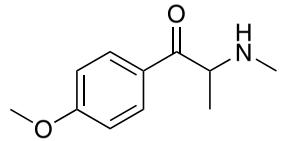
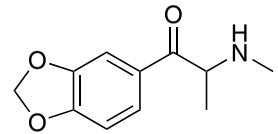
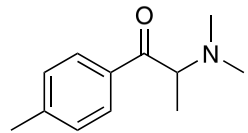
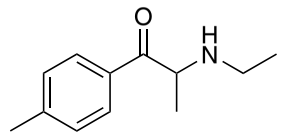
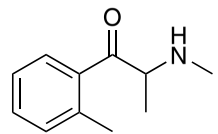
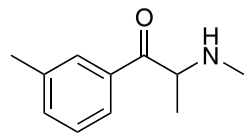
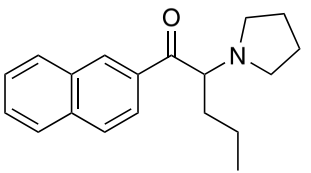
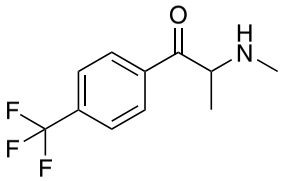
Methedrone, βk-PMMA	*Para*-methoxymethcathinone		530-54-1
Methylone, βk-MDMA	1-(1,3-benzodioxol-5-yl)-2-(methylamino)-1-propanone		186028-79-5
N-Methylmephedrone	4-methyl-*N*,*N*-dimethylcathinone		—
4-MEC	4-methyl-*N*-ethylcathinone		1225617-18-4
2-MMC	2-methylmethcathinone		—
3-MMC	3-methylmethcathinone		—

Table 1. Commonly encountered synthetic cathinones *(cont.)*

Common name/ abbreviation	*Chemical name*	*Structure*	*CAS number (where available)*
Naphyrone	1-(2-naphthalenyl)-2-(1-pyrrolidinyl)-1-pentanone		850352-53-3
4-TFMMC	4-trifluoromethylmethcathinone		—

2.3 Internet markets

According to the EMCDDA [7], most synthetic cathinones appearing on the European market for illicitly used drugs are reported to be synthesized outside Europe, with China and, to a lesser extent, India identified as the primary source countries. Since around 2006, there has been a shift in the illicitly used drug market from street-level drug dealers or "head shops" to a more widespread and readily-available virtual market on the Internet. This has significantly altered the pattern of trading with regards to the distribution, sales and marketing of NPS.

The Internet not only provides information about cathinones and other NPS but also serves as a globalized drug market for their distribution and sale [8]. The Internet provides a vast array of sources where materials can be advertised, including social networking websites, online head shops, discussion forums, blogs, etc. The advertising strategy is aggressive and involves giving those substances catchy product names such as "miaow miaow", "top cat", "bubbles" and "ivory wave". Online retailers can often provide ambiguous descriptions of their items, which are commonly sold as research chemicals, room odourizers, plant food, or bath salts, with a warning or disclaimer stating "not for human consumption" or "for research purposes only" [9]. The critical role played by the Internet is exemplified by the recreational use of mephedrone, a synthetic cathinone which is referred to as the most widely experienced "legal high" [10]. Data from Google trends [11] suggests that searches for the term "legal highs" worldwide began in 2006. An EMCDDA "snapshot" reported that the number of online shops offering "legal high" compounds in January 2014 was 650, in comparison to 314 in January 2011 and 170 in January 2010 [9, 12, 13]. The so-called "deep web" has also played an increasingly important role in recent years in anonymous online markets for the purchase of illicitly used drugs and NPS.

2.4 Use and abuse

Synthetic cathinones are commonly taken by insufflation (snorting) or orally. In recent years, the injection of synthetic cathinones has also been reported. Insufflation doses typically range from 20 to 80 mg, although they can be as low as 5 mg or as high as 125 mg in some cases, with peak effects experienced in less than 30 minutes. The peak effects of mephedrone, which requires a high dose when insufflated, have been reported to occur within 45 minutes to 2 hours after ingestion and effects are reported to last for up to 2 to 3 hours [6]. Users of NPS may often perceive them as safe and find them more attractive than traditional drugs of abuse. However the toxicity and health implications associated with these products are largely unknown [8]. Moreover, the descriptions on the package of these products regarding the constituents are often inaccurate and misleading. Identical packages have often been found to contain different psychoactive substances, thereby adding to the unpredictability of the effects of these products. A number of studies have demonstrated that these products may contain substances under international control and that the psychoactive constituents in the products are not consistent over time [14-16].

2.5 Pharmacology and toxicology

Some synthetic cathinones are structurally similar to the amphetamine-type stimulants amphetamine, methamphetamine and MDMA and are reported to have similar central nervous system (CNS) stimulant properties [17-20]. They can have a pronounced effect on the levels and action of neurotransmitters such as serotonin, dopamine and norepinephrine [17, 21-23]. Many cathinone derivatives have a single chiral centre and thus exist in two enantiomeric forms with differing potencies. For example, the *(S)*-enantiomers of cathinone and methcathinone have been reported as being more potent than the *(R)*-enantiomers [6].

Synthetic cathinones produce a variety of behavioural effects, and can affect locomotor activity, thermoregulation, learning and memory [17]. Short-term adverse effects reported following mephedrone use are variable and may include loss of appetite, blurred vision, anxiety, post-use depression, confusion, hallucinations, short-term psychosis and mania [24-26]. Similarly, clinical reports have noted that MDPV use can result in anxiety, paranoia, memory loss and aggression [17]. Intoxication by synthetic cathinones may also lead to severe adverse effects, including acute liver failure, acute kidney injury, high blood pressure and tremor [27, 28]. A number of synthetic cathinone users have also reported the development of tolerance, dependence or withdrawal symptoms with prolonged use [6].

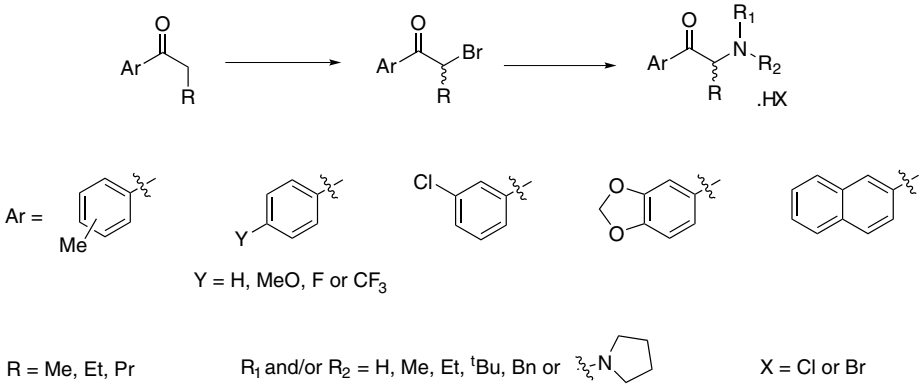
With regard to the metabolism of synthetic cathinones, mephedrone has been extensively studied and a number of metabolites have been characterized [25, 26, 29]. The major Phase I metabolites have been shown to be products of simple oxidative, reductive and *N*-dealkylation reactions [25]. The Phase I metabolites of mephedrone subsequently undergo extensive Phase II metabolism to form glucuronides as a prelude to excretion [29].

3. Illicit manufacture of synthetic cathinones

3.1 Synthesis of cathinone derivatives

The chemical synthesis of cathinones is facile and usually follows a two-step process. The initial synthesis is of an α-bromoketone (from the pre-requisite arylketone) followed by a nucleophilic substitution with an appropriate amine to give the corresponding freebase of the cathinone. Due to the instability of the freebase, the cathinones are conveniently isolated as their corresponding hydrochloride or hydrobromide salts [30]. The first reported synthesis of mephedrone was by Saem de Burnaga Sanchez in 1929 [31], where 1-tolylpropan-1-one was α-brominated and then reacted with methylamine to produce racemic 4-methylmethcathinone. This method could be adapted for the synthesis of a range of cathinones, including 2-MMC, 3-MMC, methcathinone, methedrone, methylone, flephedrone, *N*-methylmephedrone, eutylone, butylone, 4-MEC, 4-TFMMC and buproprion.

Figure II. Reaction scheme for the preparation of cathinone derivatives



These synthetic routes can be used in clandestine manufacture. However, if 4-methylephedrine is available, this can also be utilized via an oxidation step to produce 4-methylmethcathinone. This method is believed to be stereoselective if the reactant is a single enantiomer. However, due to the complexity of producing the pure enantiomers of 4-methylephedrine it is unlikely that this route is used routinely in clandestine laboratories. [19]

4. Qualitative and quantitative analysis of seized materials containing synthetic cathinones

4.1 Introduction

Generally, in attempting to establish the identity of a controlled drug or NPS in suspect material, the analytical approach must entail the determination of at least two uncorrelated parameters, one of which should provide information on the chemical structure of the analyte, for example infrared (IR), mass spectroscopy (MS), or tandem methods such as gas chromatography-mass spectroscopy (GC-MS). The choice of parameters in any particular case needs to be contextualized to the drug involved and the resources available. Judicial requirements may also dictate the analytical requirements.

4.2 Sampling

The principal reason for a sampling procedure is to permit an accurate and meaningful chemical analysis. Because most qualitative and quantitative methods used in forensic drug analysis laboratories require very small quantities of material, it is vital that these small quantities are representative of the bulk from which they have been drawn. Sampling should conform to the principles of analytical chemistry, as laid down, for example, in national pharmacopoeias or by regional or international organizations. For general aspects of qualitative sampling of multi-unit samples, refer to the *Guidelines on Representative Drug Sampling* (https://www.unodc.org/documents/scientific/Drug_Sampling.pdf) [32].

4.3 Extraction and sample preparation

Samples should be prepared according to their morphology as follows:

Powders: A solution should be prepared at a concentration of approximately 1mg/mL in methanol.

Tablets: A representative number of tablets (following the sampling procedure) should be ground to a fine powder and a solution prepared as for powders.

Capsules: The contents of a representative sample of capsules (following the sampling procedure) should be removed and a solution prepared as for powders.

Syringes or glassware: Should be washed with a minimum amount of methanol.

4.4 Presumptive colour tests

Presumptive tests are non-specific tests that can be used to identify which class of compounds a substance belongs to. However, they cannot be used to identify a specific compound within that class. Therefore, confirmatory tests must always be carried out in conjunction with these preliminary tests. Presumptive tests give a positive result simply by a colour change being observed on the addition of reagents to the substance of interest.

A negative control is required when undertaking presumptive testing to ensure that any colour change observed is due to the reaction between the substance and the reagents, and not to the reagents alone. In addition, it also ensures that the equipment being used is thoroughly clean with no possibility of contamination. A positive control should also be carried out on a reference standard or a known sample of the compound thought to be present in the sample to give an indication of the colour change that should occur.

One of the most suitable presumptive tests for synthetic cathinones is the Zimmerman test, which provides a clear and unambiguous response for both the hydrochloride and hydrobromide salts in most cases.

Zimmermann test reagents

A small amount of the sample to be tested should be added to a dimple well of a spotting tile and the reagents added sequentially. Positive and negative controls should be used. Any colour change or other noticeable effect occurring immediately on addition of the following reagents should be noted and observations made again after five minutes.

- Add 2 drops of 1% w/v 1,3-nitrobenzene in methanol, then
- Add 2 drops of 15% w/v potassium hydroxide in water.

The results observed with the Zimmermann test for a variety of cathinones are presented in table 2.

Table 2. Typical results obtained for a variety of cathinones using the Zimmermann test

Compound	*Immediate colour change*	*Colour after 5 minutes*
Benzedrone (4-MBC)	No colour change	Pale pink
Buproprion	No colour change	No colour change
Butylone	(After ~10 secs.) Very pale pink	Dark Purple
Eutylone	No colour change	Slight purple
Flephedrone	Light purple	Dark purple
MDPV	Yellow	Yellow
Mephedrone	Light purple	Dark red/purple
Methcathinone	Dark purple	Dark purple
Methedrone	(After a few secs.) Dark purple	Dark purple
Methylone	(After ~10 secs.) Light purple	Dark purple
N-methylmephedrone	(After ~20 secs.) Light purple	Light purple
4-MEC	(After ~10 secs.) Light purple	Purple with dark purple specs
2-MMC	Dark purple	Dark Purple
3-MMC	Purple	Dark purple
Napyhrone	Yellow	Darker shade of yellow
4-TFMMC	Dark purple	Dark purple

4.5 Microcrystal tests

Microcrystal tests are quick, simple, and extremely sensitive tests for the identification of substances. They involve the formation of crystals from the reaction of the target compound with a chemical reagent, followed by the analysis of the resulting crystals by means of a polarizing microscope and comparison with reference material. Usually photographs of known crystals or reference standards or known drug samples are treated similarly and compared.

Procedures have been reported using mercury chloride [33] and mephedrone was observed to form characteristic “paddlewheels and rosettes of blades” (figure III).

Reagent

The reagent is an aqueous solution of mercury chloride at a concentration of 10 g/L.

Drug standards should be prepared as aqueous solutions at concentrations of 10 g/L.

Method

An aliquot (10 μL) of the test solution (1 g/L) is mixed with 10 μL of the reagent on a glass slide. A plastic pipette is used to aid nucleation and crystal formation.

Figure III. "Paddlewheel and rosette of blade" shaped crystal observed during a microcrystalline test for mephedrone [34]

4.6 Thin layer chromatography (TLC)

TLC is a commonly used technique for the separation and identification of illicitly used drugs. It is inexpensive, rapid, sensitive and flexible in the selection of both the stationary and mobile phase and amenable to a wide variety of substances, in base and salt form, ranging from the most polar to non-polar materials. A retention factor (R_f) can be calculated for each compound within a sample to provide a tentative discrimination of compounds within a drug class.

$$Rf\ value = \frac{Distance\ from\ origin\ to\ sample\ spot}{Distance\ from\ origin\ to\ solvent\ front}$$

TLC is frequently used in the analysis of illicitly used drugs, as it is cheap, easy to use, gives a certain degree of specificity and is capable of simultaneous drug detection. As with presumptive tests, however, TLC is not considered a confirmatory test and is

only used as a screening method. In 1990, Lehmann et al. [35] proposed a method to identify cathinone from khat and this was corroborated by Lee in 1995 [36].

TLC plates (stationary phases)

Coating: Silica gel G with a layer thickness of 0.25 mm and containing an inert indicator, which fluoresces under UV light wavelength 254 nm (Silica gel GF_{254}).

Typical plate sizes: 20 x 20 cm, 20 x 10 cm, 10 x 5 cm (the latter should be used with the 10 cm side vertical with the TLC tank).

Solvent systems

The following solvent system should be prepared as accurately as possible by use of pipettes, dispensers and graduated (measuring) cylinders. The solvent system should be placed in a glass TLC tank for a sufficient time to allow vapour phase saturation to be achieved prior to the analysis.

Ethyl acetate, methanol and (25%) ammonia – (85:10:5 v/v/v).

Preparation of standard solutions

These should be prepared at a concentration of between 1 to 5 mg/mL in methanol (or according to laboratory protocol) and stored in a dark and cool place.

Sample solutions

Powders: A solution should be prepared at a concentration of approximately 1mg/mL in methanol.

Tablets: A representative number of tablets (following the sampling procedure) should be ground to a fine powder and a solution prepared as for powders.

Capsules: The contents of a representative sample of capsules (following the sampling procedure) should be removed and a solution prepared as for powders.

Spotting and developing

The samples, together with suitable negative and positive controls, should be applied as separate spots. Apply approximately 1 µL and 5 µL aliquots of the sample solution, 2 µL of the standard solution(s) and 2µL of solvent (as a negative control) onto the TLC plate. Spots should be applied carefully to avoid damaging the plate's surface.

Analytical notes

- The starting point of the run, i.e. the "spotting line", should be at least 2 cm from the bottom of the plate.
- The spacing between applications of sample (spotting points) should be at least 1 cm and spots should not be placed closer than 1.5 cm to the side edge of the plate.
- To avoid diffuse spots during development, the size of the sample spot should be as small as possible (2 mm) by applying solutions in aliquots rather than a single discharge.
- Allow spots to dry and place plate into solvent-saturated tank (saturation of the vapour phase is achieved by using solvent-saturated pads or filter paper as lining of the tank).
- Remove plate from the development tank as soon as possible after the solvent reaches the development line (10 cm from starting line) marked beforehand; otherwise, diffused spots will occur.

Visualization/detection

Plates must be dried prior to visualization. The solvent can be allowed to evaporate at room temperature or removed with a hot air blower. The plate should be viewed under UV light (254 nm) with any spots being noted before being sprayed with ninhydrin reagent (2%). The plate should then be placed into an oven at 80°C and until all spots have developed (~40 min.). Once removed from the oven, the spots should be marked with a pencil and then the R_f value calculated for each.

When TLC is carried out on substituted cathinone compounds, various colours and shapes of spots are observed. The spots produced by each compound vary in colour (black/blue/purple) when sprayed with ninhydrin reagent (2%) and viewed under UV light (table 3).

Table 3. TLC results for a variety of cathinone compounds (spray reagent ninhydrin 2%; UV = 254 nm)

Drug	*Spot colour under short λ UV light*	*R_f value*
Benzedrone (4-MBC)	Black line	0.83
Buproprion	Black line	0.60
Butylone	Light blue spot	0.20
Eutylone	Light blue spot	0.32
Flephedrone	Black spot	0.15
MDPV	Light blue spot	0.39
Mephedrone	Black spot	0.17

Drug	*Spot colour under short λ UV light*	*R_f value*
Methcathinone	Black spot	0.17
Methedrone	Black spot	0.14
Methylone	Faint spot	0.16
N-methylmephedrone	Black spot	0.33
4-MEC	Black spot	0.21
2-MMC	Black spot	0.18
3-MMC	Black spot	0.20
Naphyrone	Bright blue/purple spot	0.44
4-TFMMC	Faint line	0.27

Analytical notes

- R_f values are not always reproducible due to small changes in plate composition and activation in solvent systems, tank saturation or development distance. Therefore, the R_f values provided are indications of the chromatographic behaviour of the substances listed.
- It is essential that reference standards are run simultaneously on the same plate.
- For identification purposes, both the R_f value and the colour of the spots after spraying with the appropriate visualization reagents should always be considered.

4.7 Gas chromatography (GC) with mass spectrometry (MS)

Gas chromatography-mass spectrometry (GC-MS), one of the most commonly used hyphenated techniques for the identification of drug samples of forensic significance, can be used as a confirmatory test for the cathinones. It affords two independent means of analysis (chromatographic separation and mass fragmentation data). There is a wide range of instruments available and analysis should be undertaken using standard analytical capillary columns.

Preparation of the internal standard solution

Eicosane (or a similar n-alkane) can be used as an internal standard and prepared as a solution in methanol at a concentration of 1 mg/mL.

Preparation of the standard solution

A reference material or standard of the drug to be analysed should be accurately weighed and prepared at a concentration of 1 mg/mL in methanol, containing the internal standard.

Preparation of the sample solution

A representative sample of the drug to be analysed should be accurately weighed and prepared at a concentration of 1 mg/mL powdered sample in methanol, containing the internal standard.

There are various GC-MS methods emerging within the peer-reviewed literature for the analysis of cathinone compounds, and forensic science laboratories may adopt these or carry out the appropriate research to generate their own method. It is critical that, whatever method is used, it is appropriately validated. A general screening method is presented in this Manual.

GC-MS operating conditions		
GC oven conditions:	90°C for 1 minute, increased to 300°C at a rate of 8°C/min. and then held isothermal at 300°C for 10 minutes	
Column:	5% phenyl / 95% methyl silicone column (HP-5MS), 30 m length x 0.25 mm i.d., 0.25 µm film thickness	
Injection parameters:	2 µL aliquot of sample injected with a split ratio of 75:1	
	Injector temp.:	225°C
Carrier gas:	Helium, flow rate:	1.0 mL/min.
Detector:	Ionization mode:	EI mode, 70 eV
	Scan parameters:	TIC full scan 50-550 amu
	GC interface temp.:	300ºC
	MS source temp.:	230°C
	MS quadrupole temp.:	150°C

Identification using GC-MS is accomplished by comparing the retention time and mass spectrum of the analyte with that of a reference standard. All compounds identified by GC-MS and reported by the analyst must be compared to a current mass spectrum of the appropriate reference standard, preferably obtained from the same instrument, operated under the same conditions. Commercial or user-generated mass spectral libraries should be used for reference purposes only. Table 4 provides reference data from a GC-MS screen using methanol as the extracting solvent. The sample can be prepared without the need for derivitization using the method above [12].

Table 4. Molecular weight, GC retention times and major GC-MS ions for selected synthetic cathinones [12]

Compound	*Molecular weight*	*Approximate GC RT (mins.)*	*Major GC-MS ions (m/z)*
4-TFMMC	229.7	7.40	58.1, 95.0, 145.0, 173.0
Flephedrone	181.2	7.60	58.1, 75.0, 95.0, 123.0
Methcathinone	163.2	7.80	58.1, 77.1, 91.0, 105.0
2-MMC	177.2	8.70	58.1, 77.1, 91.1, 119.0
3-MMC	177.2	9.40	58.1, 77.0, 91.1,119.1
4-MMC (mephedrone)	177.2	9.70	58.1, 77.0, 91.1, 119.1
N-methylmephedrone	193.2	10.30	56.1, 72.1, 91.1, 119.0
4-MEC	191.3	10.50	56.0, 72.1, 91.0, 119.0
Buproprion	239.7	11.90	57.1, 75.0, 100.1, 139.0
PMMC (methedrone)	193.2	12.30	58.1, 77.0, 92.0, 135.0
Methylone	207.2	13.50	58.1, 91.0, 121.0, 149.0
Butylone	221.2	14.30	57.1, 72.1, 121.0, 149.0
Eutylone	235.2	14.90	58.1, 86.1, 121.0, 149.0
Benzedrone	253.3	18.20	65.0, 91.0, 119.0, 134.0
MDPV	275.3	18.80	65.1, 96.1, 126.1, 149.0
Naphyrone	281.4	20.80	55.1, 96.1, 126.1, 155.0

4.8 High performance liquid chromatography (HPLC)

HPLC is another major separation technique used in forensic drug analysis. Reversed phase chromatography is most commonly used for the analysis of drugs in seized materials and the most universal and versatile column is a bonded octadecyl silica column (C18). Column length, diameter, particle size, pore size and carbon load should be considered in the selection of the column. As there is a wide variety of stationary and mobile phases available to the analyst, all methods must be properly validated and/or verified prior to routine use. The following method was used for the identification of mephedrone and methylone in the presence of a number of common adulterants and also applied to the quantification of mephedrone [30].

Preparation of standard solutions

For the preparation of the calibration standard solutions, 2.0 mg of mephedrone was added to a 100 mL volumetric flask and dissolved in mobile phase to give a 20 µg/mL solution. This solution was then suitably diluted to give calibration standards ranging from 0.5 µg/mL to 10 µg/mL each containing nicotinamide (2.5 µg/mL) as internal standard.

Preparation of sample solutions

Solutions were prepared at a concentration of approximately 10 µg/mL of mephedrone and methylone.

Column:	HiChrom ACE 3 C-18, 150 x 4.6 mm i.d., 3 µm particle size Isothermal at 22°C
Mobile phase:	28:72 (v/v) methanol: 10 mM ammonium formate (adjusted to pH = 3.5 with formic acid)
Flow rate:	0.8 mL/min.
Detection:	Photodiode array-UV detector (258 nm for cathinones)
Injection volume:	10 µL
Internal standard:	Nicotinamide, 2.5 µg/mL

Results for mephedrone

Linear range: 0.5-10 µg/mL

Repeatability: RSD < 3%

Correlation coefficient: 0.993

Table 5. HPLC retention times for mephedrone and methylone in the presence of eight common adulterants [30]

Compound	*Retention time (t_R) in minutes (t_0 = 2.2 min.)*
Nicotinamide (IS)	2.67
Paracetamol	3.7
Caffeine	4.9
Methylone	6.4
Lidocaine	9.0
Mephedrone	9.8
Ketamine	11.1
Diamorphine	15.6
Cocaine	17.1
Benzocaine	34.4

4.9 Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

LC-MS/MS is a powerful confirmatory technique which combines the separation features of conventional HPLC with the detection capabilities of a tandem mass spectrometer, resulting in significantly increased selectivity. Its low limits of detection allow for trace analysis and the analysis of biological specimens such as blood and hair. With high sensitivity and selectivity, LC-MS/MS is suitable for both qualitative and quantitative analysis of synthetic cathinones in seized materials and biological specimens.

There are a number of methods in the scientific literature for the analysis of synthetic cathinones by LC-MS. The following is an example of a screening method for the separation and identification of seven cathinones [37].

LC-MS/MS operating conditions

LC:

Column:	Agilent Zorbax Eclipse XDB C-18, (75 mm x 4.6 mm id 3.5 µm)	
Mobile phase:	(A) 95% water, 5% acetonitrile, 0.1% formic acid	
	(B) 95% acetonitrile, 5% water, 0.1% formic acid	
Gradient:	Initial conditions;	90% A:10% B
	0-2 mins.;	Isocratic 90% A:10% B
	2-7 mins.;	Linear 90% A:10% B - 60% A:40% B
	7-9 mins.;	Isocratic 60% A:40% B
Flow rate:	0.6 mL/min.	
Column temp.:	Room temperature	
Injection volume:	5 µL	

MS/MS:

Instrument:	Agilent 6410A triple quadrupole
Detection mode:	Multiple Reaction Monitoring (MRM)
Ionization mode:	Positive electrospray ionization (ESI^+)
Capillary voltage:	2.5 kV
Drying gas temperature:	325 oC at 5 L/min.
Nebulizer pressure:	60 psi

Optimized collision energies (Ce) and fragmentor voltages (fv) for selected cathinones are given in the following table.

Table 6. Optimized MRM parameters for selected synthetic cathinones

Analyte	*Precursor ion* $[M+H]^+$	*Product ions* $[M+H]^+$		*Fragmentor voltage V*	*Collision energy V*	
		Transition I	*Transition II*		*Transition I*	*Transition II*
Mephedrone	178	160	144	90	10	36
Butylone	222	174	204	100	16	9
MDPV	276	126	135	125	27	27
Flephedrone	182	164	149	100	11	22
Methylone	208	160	132	90	16	30
Methedrone	194	176	161	90	8	18
4-methylethcathinone	192	174	144	100	11	32

4.10 Fourier transform infrared (FTIR) spectroscopy

The confirmation of the identity of a substance can be achieved by FTIR. Unequivocal identification of a synthetic cathinone is possible from each unique spectrum. For powders, considered to be reasonably pure, the infrared spectrum of the powder can be acquired using the KBr disc method.

Analytical notes

- The KBr disc method consists of grinding a dry sample to a very fine powder, then mixing about 2 mg of homogenized sample powder with 200 mg of carefully dried and ground KBr. After grinding, the mixture is pressed into a thin transparent disk.
- KBr should be "IR Grade" and dried at 105°C for a minimum of one hour. It can be stored in a desiccator containing a strong desiccant (silica gel) or left in the oven and removed when required.

Table 7. Infrared (IR) spectrum data (cm^{-1}) for selected synthetic cathinones[1]

2-FMC	*3-FMC*	*4-FMC*	*2-MMC*	*3-MMC*	*4-MMC*	*Methylone*	*Butylone*	*MDPV*	*Methcathinone*
3382	2947	2459	3443.5	3434.6	3416.6	3466.3	3455.9	3442.9	1691
2686	2685	1686	2895.6	2937.0	2916.8	2916.7	2936.2	3092.0	1496
2467	2439	1594	2741.9	2799.7	2739.6	2798.5	2791.2	2967.3	1245
1686	1698	1513	2450.8	2738.0	2450.7	2743.6	2717.4	2915.3	705
1607	1589	1471	2361.2	2445.5	2417.7	2457.1	2500.6	2800.4	
1476	1478	1410	1696.4	1686.4	1684.2	2359.4	2421.1	2614.4	
1459	1433	1363	1600.3	1603.7	1605.0	1679.6	1666.7	1685.9	
1450	1382	1301	1572.4	1585.0	1568.8	1602.7	1624.6	1611.0	
1397	1364	1238	1488.9	1464.1	1456.7	1502.7	1604.2	1507.2	
1337	1230	1208	1459.2	1421.7	1412.1	1451.1	1507.9	1491.0	
1292	1259	1166	1430.3	1381.0	1384.2	1422.5	1494.3	1469.3	
1277	1218	1113	1417.0	1348.6	1347.4	1382.9	1456.9	1436.8	
1194	1189	1029	1380.4	1297.3	1295.4	1348.9	1425.0	1413.2	
1210	1167	1006	1335.0	1260.0	1247.7	1299.2	1415.9	1375.9	
1099	1096	980	1299.7	1180.2	1214.6	1260.3	1364.6	1355.1	
1029	1043	902	1246.1	1154.5	1200.9	1195.9	1347.2	1286.9	
1042	1016	847	1200.4	1102.5	1189.3	1120.8	1332.1	1277.0	
1001	993	819	1095.4	1041.3	1125.9	1090.0	1264.7	1256.8	
977	896	765	973.4	1003.7	1095.7	1037.9	1120.4	1223.2	

[1]IR data for the isomers of fluoromethcathinone were generated using an ATR-3 top plate [38]. Data for 2-MMC, 3-MMC, 4-MMC, methylone, butylone, MDPV and methcathinone were obtained using KBr discs [13, 39, 40].

Table 7. Infrared (IR) spectrum data (cm^{-1}) for selected synthetic cathinones *(cont.)*

2-FMC	*3-FMC*	*4-FMC*	*2-MMC*	*3-MMC*	*4-MMC*	*Methylone*	*Butylone*	*MDPV*	*Methcathinone*
899	830	748	752.4	982.9	1050.0	1006.7	1102.5	1104.6	
828	796	684		894.6	1029.5	990.8	1038.7	1035.0	
785	757			804.5	1007.8	927.6	962.0	1004.8	
767	723			753.7	976.4	887.4	934.8	930.0	
758	674			720.2	889.4	879.4	877.6	918.4	
740					853.9	836.7	840.0	868.3	
					844.2	819.2	828.1	833.0	
					827.5	807.2	806.2	808.0	
					802.2	767.3	743.9	568.2	
					756.5	740.7			
					733.0	715.3			
					687.4				
					600.0				
					477.7				

4.11 Nuclear magnetic resonance (NMR) spectroscopy

Nuclear magnetic resonance spectroscopy is a powerful analytical technique that can be used for the elucidation of molecular structure and purity determination (under the correct analytical conditions). The complete functional group assignment of a molecule can be determined using NMR experiments involving 1-dimensional proton (^{1}H) and carbon (^{13}C) spectra and a combination of 2-dimensional correlation experiments including NOESY (Nuclear Overhauser Effect Spectroscopy), HMQC (Heteronuclear Multiple-Quantum Correlation). The structural assignment of mephedrone is shown in table 8.

Figure IV. Structure of mephedrone with labelling of molecular positions

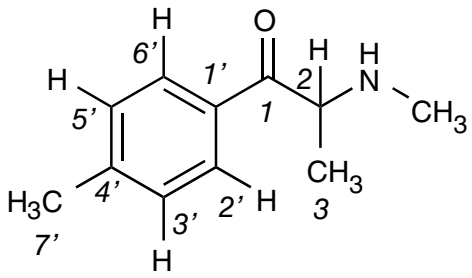


Table 8. Structural assignment of mephedrone, spectra carried out in deuterated methanol, ^{1}H spectrum (500 MHz), ^{13}C spectrum (125 MHz) [41]

Position	*^{1}H signal (ppm)*	*Signal multiplicity*	*Coupling constant (J, Hz)*	*^{13}C signal (ppm)*
1	–	–	–	196.6
2	5.09	quartet	7.2	60.5
3	1.57	doublet	7.2	16.3
1′	–	–	–	131.7
2′/6′	7.62	doublet	8.5	130.1
3′/5′	7.42	doublet	8.5	131.0
4′	–	–		147.6
7′	2.45	singlet	–	21.8
N-CH_3	2.77	singlet	–	31.7

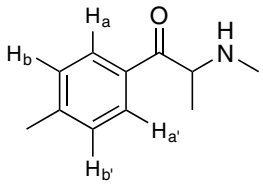
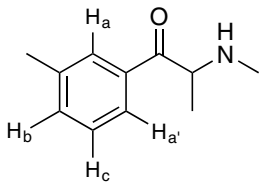
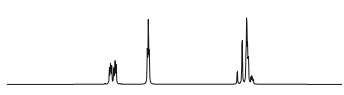
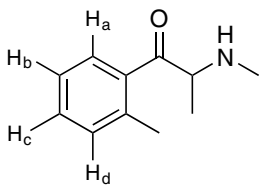
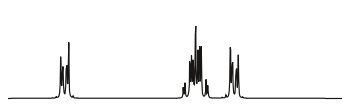
It should be noted that the absolute values of NMR chemical shifts, resolution of signal multiplicity and coupling constants can vary depending on a number of factors including but not limited to solvent, temperature and magnetic field strength of

the instrument. The NMR spectra of mephedrone in other solvents are also available in the literature [30, 42].

NMR for the discrimination of positional isomers

It is possible to use NMR spectroscopy to assist in the discrimination of positional isomers. 4-Methylmethcathinone (4-MMC), for example, is a 1,4-*para* substituted aromatic molecule with a symmetric distribution of protons on the aromatic ring. As such, the ^{1}H NMR signals of the aromatic protons show a splitting pattern characteristic of such an AA'/BB' system. 2-Methylmethcathinone (2-MMC) (1,2-*ortho* substituted system) and 3-methylmethcathinone (3-MMC) (1,3-*meta* substituted system) lack the symmetric distribution of aromatic protons in 4-MMC and thus generate more complicated splitting patterns, as shown in table 9.

Table 9. Predicted NMR splitting patterns of mephedrone and its positional isomers

Substance	*Structure*	*Predicted splitting pattern of aromatic protons*[2]
4-Methylmethcathinone		
3-Methylmethcathinone		
2-Methylmethcathinone		

Thus, 4-MMC can be easily discriminated from its positional isomers. However, it can be difficult to definitively discriminate between 2-MMC and 3-MMC without further complementary experiments. A similar analysis can be used to discriminate between para substituted cathinones and their ortho/meta positional isomers.

[2] Approximate splitting patterns calculated using ChemBioDraw Ultra™ software.

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V.15-05756