

# Mephedrone – an emerging drug of abuse in India

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Mephedrone (MEPH) is a synthetic derivative of cathinone, an alkaloid extracted from plant khat. Developed countries like UK, USA, Australia and Israel are the main places of MEPH abuse. Abuse of cathinone and MEPH in India has started recently. The young generation in metropolitan cities like Delhi, Mumbai, Ahmedabad and Panaji is being affected by its abuse. The increasing misuse of MEPH in India was due to its non-inclusion in the Narcotics Drugs and Psychotropic Substances (NDPS) Act, 1985 earlier. Due to the threat of MEPH abuse in the country, the Government of India included it in the NDPS Act from February 2015. Since then, the law enforcement agencies have taken strict action against MEPH users and traffickers.

In India, new drugs are rapidly emerging in the market and posing challenges for forensic toxicologists and law enforcement agencies. The seized drugs, urine and blood samples of the abusers are sent to forensic science laboratories for analysis. These samples are first screened by thin-layer chromatography, and then the confirmation and quantitation are done using modern instrumental methods. However, no studies are available in the literature on drug detection in saliva, sweat and other biological materials. Therefore a suitable technique needs to be developed for its detection in biological matrices. Particularly so for a country like India, this drug abuse is constantly increasing. In this article, we deal with the chemistry, pharmacodynamics, drug-herb interaction, metabolic fate (pharmacokinetics), related fatalities, abuse, effects and detection methods of MEPH, to create awareness about this drug abuse in India.

**Keywords:** Drug abuse, mephedrone, synthetic cathinone, traffickers.

MEPHEDRONE (MEPH) is a synthetic derivative of alkaloid cathinone and was first synthesized in 1929 during the discovery of the active principles of the plant khat (*Catha edulis*)<sup>1</sup>. Alkaloid cathinone is naturally found in the leaves of khat<sup>2-5</sup>. This plant is indigenous to the Arabian Peninsula and East Africa; its leaves are either chewed or brewed as tea<sup>4,6-9</sup>.

Mephedrone is marketed under different common street names such as meow-meow, M-cat, MEPH,

Meow/Miaow, plant food, kitty cat, bubbles, MMC hammer, MMCat, Ronzio, Fiskrens, Diablo, XXX, Crab, Miaow/Miaow, 4-methylmethcathinone, Blow, Mephedrone, Mephadrone, Snuff, Snow, Special Gold, Magic Powder, Flower Power, Charge+, Blue Magic Star, Cristal, Star, Blast, Dust, White, white magic, bounce, 4-MMC, MD<sup>2,10-13</sup>, Mephedrone + Ketamine, Roxy, Krabba (Sweden), Rush, Challenge, MD3, drone, Mefedron (Norway) and Plant feeder<sup>9</sup>.

The pure MEPH shows highly similar chemical structure to amphetamine and MDMA (3,4-methylenedioxy-methamphetamine). Yet it is less potent than an amphetamine. MEPH has been classified as a stimulant drug and grouped into new psychoactive substances (NPS). It is also defined as a class of drugs which produces effects similar to those of established illicit drugs<sup>11</sup>.

In early 2000, bath salts along with MEPH appeared in Israel. Since 2007, it is available in the markets and has gained rapid recognition in the United States and Europe<sup>14</sup>. It appeared in the illicit market as a designer drug with high tendency of abuse. The drug was produced by imitating the pharmacological and chemical properties or molecular structures of existing controlled substances or drugs. It was classified as 'legal highs', as the drug was not regulated and did not violate the existing law, but ultimately bypass the law. Few more examples of such drugs are 'beta-keto' (bk) designer drugs and 'bath salts' such as ethylone, butylone, methylone and mephedrone<sup>12,14-16</sup>.

In 2011, the US Drug Enforcement Administration placed three common synthetic cathinone drugs under immediate ban. In July 2012, MEPH and methylenedioxypropylvalerone (MDPV) were banned permanently by passing a legislation<sup>5</sup>. The European Monitoring Centre for drugs and drug addiction found that the United Kingdom was the capital of on-line trade of legal highs in Europe; nearly half of the websites selling these drugs were based in the UK. It was found that MEPH and its analogues were available for purchase on-line under new names<sup>6,14,17</sup>, even after the ban on MEPH in the UK<sup>2</sup>. This became a public concern because of MEPH status as a legal alternative to cocaine and ecstasy<sup>1,2,12</sup>. More recently, the market for new substances detected in seizures, shows their quick development and distribution. MEPH was initially marketed on-line as a plant food or 'research chemical' or plant fertilizer. MEPH is a white powder

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with a yellowish tinge and supplied in market in different forms (crystals, capsules, pills and tablets). It gives a distinct, unpleasant smell like stale urine<sup>9,11</sup>. Molecular modelling of MEPH indicates that it is more hydrophilic than methyl-amphetamines thus one may require higher doses for achieving a similar effect, because MEPH is less able to cross the blood–brain barrier (BBB)<sup>17</sup>.

Reports of serious toxicity and death after the use of MEPH have led to changes in its legal status; it has been legally restricted and banned in many countries including UK, Israel, Sweden, Denmark, Germany, Ireland, Finland, New Zealand and Australia<sup>9,18</sup>. In India, MEPH has been recently included in the NDPS Act, and banned from commercial sale<sup>19</sup>. It is also posing a new challenge for the law enforcement agencies and toxicological experts.

### Chemistry of mephedrone

Mephedrone is 4-methylmethcathinone (Figure 1) which is a substituted phenethylamine, and being a  $\beta$ -keto-amphetamine indicates that it is closely associated with cathinone known for its psycho-stimulant properties<sup>20</sup>. All known derivatives of cathinone have the nitrogen atom either as part of a pyrrolidine ring or *N*-alkylated<sup>6</sup>. The International Union of Pure and Applied Chemistry (IUPAC) has named it as (RS)-2-methylamino-1-(4-methylphenyl) propan-1-one (ref. 8). MEPH is also known by other names such as 4-methylephedrone, *N*-methylephedrone or *p*-methylephedrone, *p*-methylmethcathinone,  $\beta$ -keto (4,*N*-dimethylamphetamine), 2-aminomethyl-1-tolyl propan-1-one and 4-*N*-dimethylcathinone<sup>6</sup>. It has chiral centre, and therefore exists in two forms known as enantiomers – the S and R forms (Figure 1). The S form is more potent than the R form. MEPH differs from amphetamine-like compounds at the beta carbon<sup>7</sup>, the replacement of hydrogen atom with ketone converts methamphetamine to methcathinone (i.e. mephedrone)<sup>21</sup>. The presence of a ketone in the side chain gives a more planar structure to the methyl-cathinones, which is not present in the methyl-amphetamine series; this planarity may contribute to the toxicity<sup>17</sup>.

MEPH is synthesized by bromination of 1-tolyl-propan-1-one producing the 2-bromo-1-tolyl-propan-1-one racemic product, which is treated with aminomethane that displaces bromide resulting in a racemic 2-methylamino-1-tolyl-propan-1-one (mephedrone)<sup>17</sup>.

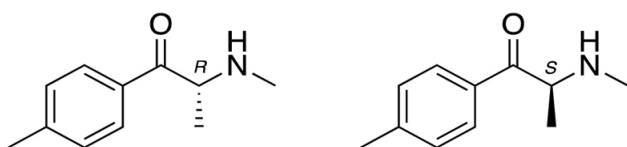


Figure 1. Chemical structure of R and S forms of mephedrone.

### Mephedrone abuse

The first evidence of MEPH use appeared on the Internet in 2007 (ref. 10). It was available for purchase on-line as plant food, but not for human consumption<sup>5</sup>. It produces a similar effect as other existing amphetamine-like stimulant drugs, which are controlled and regulated by laws. Therefore, it rapidly became popular among the users as it started being abused as a legal alternative. It can be administered in the body by oral route, snorting, inhalation or by injection. Maximum effect is produced by snorting or needle injection, as the drug enters the blood circulation and bypasses the first pass effect. MEPH is most commonly abused by ingestion or insufflation<sup>16</sup>. It is generally mixed with a drink or wrapped in a cigarette paper for smoking (known as ‘bombing’)<sup>9,11</sup>. Rectal administration of MEPH dissolved in water (enaema), smokable formulation and intravenous (IV) administration are some administration methods<sup>9</sup>. With the increasing incidence of seizure and abuse of MEPH in regions other than Europe, including Australia, Southeast Asia and North America, it came into the limelight and many countries amended their laws for regulating and controlling its use. According to a survey, 64% respondents in the UK cut down the use of MEPH after it had been brought under the law<sup>20</sup>.

### Herb–drug–food interaction

Herb–drug interaction can be defined as ‘the interaction occurs when a medication (certain drug) taken together with certain foods or herbal substances may produce unwanted side effects’<sup>22</sup>. Currently, very few studies have been reported on the possible interactions of mephedrone with other food and drugs. The combination of MDMA (3,4-methylenedioxymethamphetamine) with other drugs has been considered to contribute to possible long-term neurotoxicity and severe adverse events<sup>23</sup>. Furthermore, most mephedrone users accept concurrent illicit use or previous use of MDMA<sup>24,25</sup> so possible interactions of mephedrone with other psychoactive drugs, including MDMA are likely. MEPH is reported to have pharmacodynamic effect when it interacts with cannabis, tramadol, olanzapine, diazepam, fluoxetine, nelfinavir, citalopram, carbamazepine, haloperidol, moclobemide, diltiazem, caffeine and warfarine<sup>26</sup>. Angoa-Perez *et al.*<sup>27</sup> showed that while MEPH alone failed to produce any neurotoxic damage, it did enhance methamphetamine-induced neurotoxicity in dopamine nerve endings. It also enhanced the neurotoxic effects of MDMA and amphetamine on dopamine neurons, suggesting that a potentially dangerous interaction might occur when MEPH is taken with other recreational drugs.

Shortall *et al.*<sup>28</sup> studied the interaction of MEPH with caffeine; the latter altered the behavioural and

neurochemical effects of mephedrone. Recently, Cameron *et al.*<sup>29</sup> demonstrated that brain function could have serious adverse effects with the use of a combination of MDPV and MEPH.

MEPH interacts with bupropione, paroxetine, fluoxetine, quinidine, duloxetine, sertraline and terbinafine, and causes pharmacokinetic changes. Bupropione is an antidepressant with stimulant properties and is used for the treatment of methamphetamine dependence<sup>30</sup>. It is also effective in the treatment of nicotine dependence<sup>31</sup>, cocaine dependence<sup>32</sup>. It also inhibits the reuptake of DA, enhances residual DA neurotransmission and relieves methamphetamine abstinence symptoms. However, when it is taken in combination with MEPH, it increases the addiction effect<sup>33</sup>. Similarly, quinidine when taken with MEPH inhibits debrisoquine-specific isozyme (P450db), which shows genetic polymorphism in humans<sup>34</sup>.

MEPH is commonly consumed with alcohol; the combination produces an increase in the cardiovascular effects of MEPH and induces a more intense feeling of euphoria and well-being in comparison to MEPH and alcohol. MEPH reduces the drunkenness and sedation produced by alcohol<sup>35</sup>.

### Effects of mephedrone (pharmacodynamics)

The different types of effect experienced following the use of MEPH are psychoactive effect, physical effect, medical effect and toxicological effect.

#### *Psychoactive effect*

This produces changes in brain function and results in alteration in mood, perception or consciousness. Similar to other psychomotor stimulants, synthetic cathinones target plasma membrane transporters like norepinephrine (NET), dopamine (DAT) and serotonin (SERT). MEPH and methylone act as non-selective transporter substrates, thereby stimulating non-exocytotic release of norepinephrine, dopamine and serotonin<sup>36</sup>.

#### *Physical effect*

This is a change in the functioning of the body, as opposed to psychological or emotional effects. It includes headache, erratic heartbeats, convulsions and skin rashes; injecting MEPH can cause vascular and soft tissue damage. Regular use of MEPH may eventually cause difficulty in hearing, sleeping and muscle spasms. Synergic effects produced when MEPH is combined with other materials such as ice, speed or ecstasy, alcohol and cannabis. MEPH can be ingested in combination with other compounds such as methylone, MDPV, butylone, cocaine, ketamine, cannabis, kraton and Viagra<sup>9,11</sup>.

#### *Medical or clinical effect*

Side effects can be produced after the use of synthetic cathinone (mephedrone) that can last from hours to days, such as cardiovascular and neurological effects, and include agitation, confusion, fatigue, memory loss, aggression, myoclonus, mydriasis, combative behaviour, panic, disorientation, blackouts, paranoia, hallucinations, hypertension, breathing difficulties, excited delirium, hyperthermia, sweating and increased suicidal ideations. Synthetic cathinone users are often uncontrollable and violent, exhibiting paranoid behaviour and delusions; but with higher doses, hallucination and psychosis, and death have been reported in many cases. Similar and wide range of side effects have been reported in individuals admitted to hospitals<sup>18</sup>.

#### *Toxicological effect*

This includes potential peripheral neuropathy, immunological toxicity, nephrotoxicity, cardiotoxicity and respirotoxicity<sup>2,11</sup>. Sharing needles may also result in transmission of diseases and toxicological effect.

Repeated MEPH injections also rapidly decrease serotonin (5-hydroxytryptamine; 5HT) and dopamine transporter function. Repeated MEPH administration causes persistent serotonergic, but not dopaminergic deficits. MEPH has a unique pharmacological profile with both neurotoxic potential and abuse liability<sup>37</sup>.

Major effects produced by MEPH that are reported in the literature are as follows: cardiovascular – tachycardia, hypertension, diaphoresis, myocarditis, shortness of breath, cardiac arrest, palpitations; cognitive – improved alertness, concentration, amnesia; dermatological, musculoskeletal – trismus, increase in muscle tone; neurological – bruxism, insomnia, light headedness, tinnitus, seizures and nystagmus, mydriasis, numbness, blue/cold extremities and fever<sup>2,7,8,14</sup>. Acute intoxication includes craving, nausea, irritability, unusual sweat odour, paranoia and fear<sup>7</sup>.

#### *Withdrawal symptoms*

Stopping MEPH after long-term use produces withdrawal effects, including increased appetite, tiredness, cravings, stuffy nose, feeling depressed, feeling anxious, emotional, irritability, tear and difficulty in concentrating. Discontinuation of MEPH use results in dysphoria and agitation within a few hours, which is more severe than that of methamphetamine or cocaine, and is accompanied by an increase in muscle tone<sup>14</sup>.

MEPH produces an opposite electrophysiological effect through the human dopamine transporter (hDAT) expressed in oocytes. A recent analysis of the effects of MEPH and methylone in rats showed that these

drugs raised serotonin levels in a manner similar to MDMA<sup>37</sup>.

### Molecular pharmacology

Only a few studies investigating the molecular mechanisms of MEPH are available in the literature<sup>38,39</sup>. Due to the structural similarities and user substitution of MEPH for methcathinones and amphetamines, researchers initially hypothesized that MEPH may act through similar molecular processes as other psychostimulants. This hypothesis has been confirmed by several studies<sup>40–42</sup>. It is similar to phenethylamine, and exists in two stereoisomeric forms that may have different potencies. It contains a chiral centre at the C-2 carbon of the propane side chain, so that two enantiomers exist: S-mephedrone and R-mephedrone as mentioned earlier. Due to the similarity with cathinone, the S form is accepted to be more potent than the R form. Gregg *et al.*<sup>43</sup> showed that the R form is more dopaminergic and rewarding than the S form, in contrast to that observed with cathinone. Molecular modelling of mephedrone reveals that it is more hydrophilic than methyl-amphetamines, which accounts for the higher doses required to achieve a similar effect, because MEPH is less able to cross the blood–brain barrier (BBB).

### Metabolism of mephedrone (pharmokinetics)

The beta-keto (bk) designer drugs were metabolized by humans in analogy to corresponding amphetamines and reduced at the bk group to the corresponding alcohol. The bk drugs are mainly demethylated and subsequently *O*-methylated as well as *N*-dealkylated, and finally, the keto groups reduced. The MEPH is hydroxylated at the 4-methyl group followed by oxidation to the corresponding 4-carboxy metabolite. *N*-Demethylated finally reduced at the bk group to the corresponding alcohol<sup>44</sup>.

A study on the metabolism of the designer drug (MEPH) in urine was undertaken using gas chromatography–mass spectrometry (GC–MS). Seven phase-I metabolites of MEPH (Figure 2) were detected and identified in human urine<sup>15</sup>. Phase I reactions are *N*-demethylation, oxidation and reduction of the  $\beta$ -keto moiety, a human cytochrome P450 (CYP) enzymes CYP2B6, CYP2C19, CYP2D6 and CYP1A2 (ref. 20).

### Mephedrone fatalities

First clinical intoxication cases with new substances derived from cathinone were reported in Europe in 2007 and involved MEPH, a synthetic derivative of cathinone.

In Poland, a death was reported to be allegedly caused by mephedrone. Analysis of powder found in the pocket of the deceased was done using GC–MS and high-performance liquid chromatography with diode-array

detection (HPLC–DAD). MEPH was found to be of the same quality in all eight powder samples and the analysis of vitreous humour and blood samples<sup>45</sup>.

Four more deaths related to the abuse of MEPH were reported in the UK. The drug was detected and quantified in postmortem femoral venous blood by HPLC–DAD in all four fatalities. Among the four cases, one was attributed to the adverse effects of MEPH, with cardiac fibrosis and atherosclerotic coronary artery disease as a contributing factor. Another death was attributed to the combined effects of MEPH and methadone, the third one died due to combination of MEPH with alcohol and ecstasy and fourth died due to vehicular collision under influence of MEPH<sup>18</sup>.

In Scotland, four fatalities have been recorded by Torrance and Cooper<sup>46</sup>, who identified and quantified MEPH. All cases tested positive for MEPH using the in-house basic drug screen, and MEPH was recorded as the cause of death in the first two cases.

Dickson *et al.*<sup>47</sup> reported fatality of a 22-year-old man due to MEPH and intravenous (IV) heroin use. MEPH (0.50 mg/l) and morphine (0.06 mg/l) were found along with 6-acetylmorphine, codeine and doxylamine in the urine and blood of the deceased on GC–MS analysis.

Another fatality occurred in Hertfordshire, England where a teenager died and a 28-year-old woman became ill at a house party after MEPH abuse<sup>48</sup>. Even though

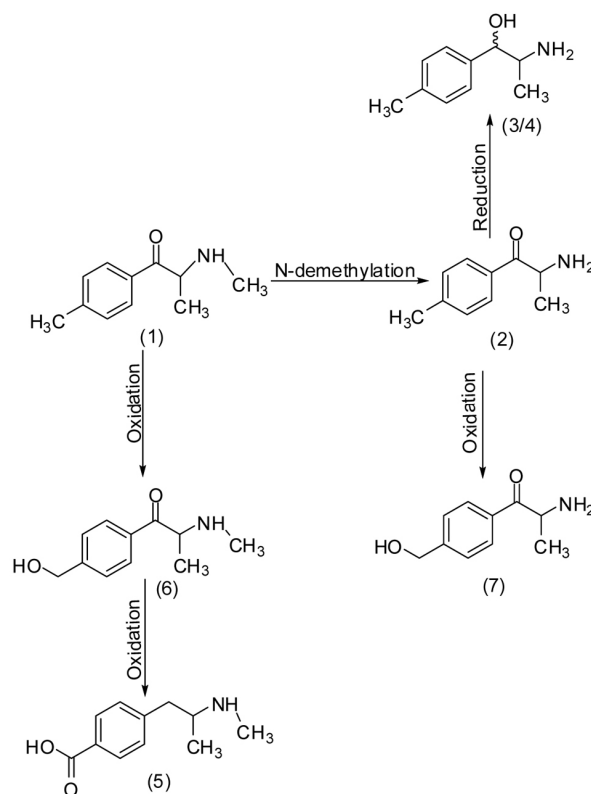


Figure 2. Phase-I metabolic pathway of mephedrone.

many fatalities have been reported with MEPH use, it is still available in the illicit drug markets and has also appeared on markets in developed countries, including the United States and Australia and is now emerging in India.

### Analysis of mephedrone

The number of cases of MEPH abuse has increased, which necessitate the demand for developing an effective and reliable method of analysis of the drug. Various analytical techniques are reported in the literature for analysis of mephedrone. In 2010, Gibbons and Zloh<sup>17</sup> performed 1D and 2D NMR, elemental analysis, high-resolution mass spectrometry and optical rotation studies of MEPH. Rambabu *et al.*<sup>49</sup> developed the RP-HPLC method for estimation of MEPH in bulk and its formulation that were purchased from the internet. Camilleri *et al.*<sup>50</sup> analysed four capsules in a hospital in South Australia anonymously delivered from an internet-based company using GC-MS, NMR and vapour phase infrared techniques. The capsules were found to contain the active components, including 2-fluoromethamphetamine, *N*-ethylcathinone, 4-methylmethcathinone (mephedrone) and alpha-phthalimidopropiophenone.

Power *et al.*<sup>51</sup> analysed a seized sample by GC-MS and found that it contained 4-methylmethcathinone (MMC) and benzocaine with traces of 2 and 3 MMC. They supported their GC-MS findings with NMR study. Martin *et al.*<sup>52</sup> reported GC-MS method for detection of chronic abuse of MEPH in hair samples. Detection was achieved in selected ion monitoring (SIM) mode ( $m/z$  254–119–210 for MEPH,  $m/z$  258–213 for MDMA-d5) using a 5973 mass selective detector (MSD) operating in the electron impact mode. Shaha *et al.*<sup>53</sup> developed a method for the quantitative analysis of MEPH and its two metabolites 4-methylnorephedrine and 4-methylephedrine in human hair using selected reaction monitoring (SRM) mode LC-MS/MS analysis.

Khreita *et al.*<sup>54</sup> synthesized and obtained chemical characterization data of the hydrobromide salt of two derivatives of MEPH, 4-methyl-*N*-benzylcathinone (4-MBC) and 4-methyl-*N*-ethylcathinone (4-MEC). They validated chromatographic method for their detection and quantification in a sample of legal high NRG-2, both in pure and adulterated form. Santali *et al.*<sup>55</sup> performed chemical synthesis and determined key physico-chemical parameters and the full structural elucidation of two salts – hydrobromide and hydrochloride of MEPH by IR, NMR, UV and MS. They also validated chromatographic methods (HPLC and GC-MS) for detection and quantification of the substance both in pure and adulterated form.

Verma *et al.*<sup>56</sup> reported the successful identification of MEPH (4-MMC) as a common component in all the exhibits of a case submitted to the Forensic Science Laboratory, Delhi, by the Department of Revenue Intelli-

gence (DRI), after a seizure suspected of clandestine manufacturing of illegal substances.

It has been reported that the methyl isomers of methcathinone (2-MMC, 3-MMC and 4-MMC (MEPH)) can be separated by GC-MS, without the requirement of chemical derivatation.

### Indian scenario

Prior to inclusion of MEPH in the NDPS Act (1985), several cases of MEPH abuse were registered under sections 328 IPC (causing hurt by means of poison, etc., with intent to commit an offence) and 284 IPC (negligent conduct with respect to poisonous substance) by the Mumbai police<sup>13</sup>. However this was not of much help to the police as it did not restrict the drug users and drug traffickers. As a result, the process was initiated for including MEPH in the NDPS Act, which was completed in February 2015. Now MEPH is being controlled in India by its inclusion under the NDPS Act, 1985 (ref. 57).

However, several cases of MEPH use are being reported in India, where it is becoming popular among youngsters in major cities like Mumbai, Ahmedabad and Panaji. In Mumbai it is called as the poor man's cocaine and it is commonly available over the Internet. The first case of MEPH use after its inclusion in the NDPS Act was registered in Maharashtra<sup>13</sup>. The number of MEPH-related cases has also increased in the past few months<sup>58</sup>. After inclusion of MEPH in the NDPS Act, the first major seizure was made in Delhi in February 2015 (ref. 59).

Forensic toxicology laboratories should be aware of the increasing misuse of synthetic cathinones and their implications in death and impairment cases. It is a continuous challenge for the forensic science laboratories to deal with clandestine manufacturers as they attempt to stay one step ahead of law enforcement. The substances abused are changing frequently in response to market trends and legislative controls; therefore it is an important challenge for forensic science laboratories, clinical toxicologists and investigating agencies to remain updated on the toxicological and pharmacological effects of these emerging agents.

### Conclusion

MEPH has become an important recreational drug in the recent past throughout the world as well as in India. It is easily available on the Internet at low cost with similar effects produced by the existing illegal drugs like amphetamine and MDMA. MEPH produces numerous effects following its use, including serious toxicological effects. Several fatalities have been reported throughout the world because of MEPH abuse. In India, many incidences have been reported on MEPH use in the recent past and its smuggling has become a big challenge before

the law enforcement agencies. It has now become possible in India for investigating agencies to prosecute an offender (users and traffickers) after inclusion of MEPH in the NDPS Act. Limited information is available on MEPH with reference to the Indian context more research needs to be done on its detection from body fluids like saliva, sweat and other biological matrices. Due to the emergence of this new drug in the Indian market, especially in metro cities, it is necessary to investigate this compound using standard analytical techniques for its estimation in suspected samples and to generate more data on this emerging drug.

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