3-Methylnmethcathinone (3-MMC)

Critical Review Report

Agenda Item 4.4

Expert Committee on Drug Dependence
Thirty-eighth Meeting
Geneva, 14-18 November 2016
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Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Policy Access and Use team. The WHO Secretariat would like to thank the following people for their contribution in producing this critical review report: Dr. Simon Elliott, United Kingdom (literature search, review and drafting) and Dr. Stephanie Kershaw, Geneva, Switzerland (editing and questionnaire report drafting).
3-Methylmethcathinone (3-MMC) was first encountered in Sweden in 2012, following the control in many countries of the related compound 4-MMC (4-methylmethcathinone, mephedrone) – a Schedule II substance under the 1971 Convention. It has appeared on drug websites selling “research chemicals” or branded products, predominantly in powder form. 3-MMC is a synthetic cathinone with stimulant properties similar to amphetamines. Effects following use include euphoria, excitement, feelings of empathy, stimulation and enhanced awareness. Reported adverse effects (including intoxication) include tachycardia, agitation, reduced level of consciousness, dilated pupils, hallucinations, diaphoresis, seizures and hyperthermia. There is no known or reported therapeutic use for 3-MMC and it is being used and abused for non-medical purposes. Such use has predominantly been reported in Europe with instances of non-fatal and fatal intoxications, but few only involving 3-MMC although that does not negate its contribution to toxicity. No animal or human study data relating to dependence potential for 3-MMC are available.
1. Substance identification
   
   A. International Nonproprietary Name (INN)
      Not applicable
   
   B. Chemical Abstract Service (CAS) Registry Number
      1246911-86-3 free base
      1246816-62-5 hydrochloride salt
   
   C. Other Chemical Names
      3-methylmethcathinone
      3-methyl-N-methylcathinone
      3-MMC
      Metaphedrone
      2-(methylamino)-1-(3-methylphenyl)-1-propanone
   
   A. Trade Names
      3-MMC
   
   B. Street Names
      3-Mephedrone, 3-MMC
   
   C. Physical Appearance
      The hydrochloride salt of 3-MMC is a white crystalline powder.
   
   D. WHO Review History
      3-MMC was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that 3-MMC 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: 2-(Methylamino)-1-(3-methylphenyl)-1-propanone
- CA Index Name: Not applicable

B. Chemical Structure

Free base:

![Chemical Structure Diagram]

- Molecular Formula: C\textsubscript{11}H\textsubscript{15}NO
- Molecular Weight: 177.24 g/mol

C. Stereoisomers

3-MMC contains a chiral centre at the C-2 carbon of the propane sidechain, so that two enantiomers exist: R-3-MMC and S-3-MMC. Due to the similarity with cathinone the S form is thought to be more potent than the R form.

D. Methods and Ease of Illicit Manufacturing

3-MMC is a structural isomer of 4-methylmethcathinone (4-MMC, mephedrone) for which various methods of synthesis exist.\textsuperscript{1} As part of studies on the chemical analysis of 2-MMC, 3-MMC and 4-MMC, Power et al described the synthesis of 3-MMC through reaction of 3-methylphenylbenzaldehyde with ethyl magnesium bromide, followed by oxidation with pyridinium chlorochromate (PCC) on silica gel and bromination with hydrobromic acid/hydrogen peroxide. This produces the 3-methylphenyl-bromo ketone, which was reacted with ethanolic methylamine in acetonitrile to produce 3-MMC free base. The free base was converted to its hydrochloride salts with ethereal hydrogen chloride.\textsuperscript{2}

E. Chemical Properties

- Melting point: 193.2 ± 0.2°C (hydrochloride salt)
- Boiling point: 280.5 ± 23.0°C at 760 mm Hg

Solubility: 3-MMC is sparingly soluble in PBS; slightly soluble in ethanol, dimethyl sulfoxide, and dimethyl formamide.
F. Identification and Analysis

Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) (the latter with and without high resolution mass-spectrometry) have been used for identification of 3-MMC, including in biological fluid.\textsuperscript{3-6} IR spectroscopy, gas chromatography-mass spectrometry (GC-MS) and proton/carbon NMR spectroscopy have been used to identify 3-MMC material.\textsuperscript{2,7} Furthermore, UV diode array detection can be used to differentiate between 3-MMC and related mephedrone (4-MMC).\textsuperscript{3}

3. Ease of Convertibility Into Controlled Substances

3-MMC is not readily converted into mephedrone (4-methylmethcathinone, 4-MMC) or other controlled substances.

4. General Pharmacology

Whilst there are some but limited studies regarding mephedrone, similar studies for 3-MMC are lacking. However, the general pharmacology of 3-MMC could be expected to be similar to mephedrone in that 3-MMC is also a β-ketoamphetamine stimulant drug of abuse with structural and mechanistic similarities to methamphetamine. Mephedrone has been found to stimulate dopamine release and block its reuptake through an interaction with the dopamine transporter (DAT).\textsuperscript{1,8} It also has some affinity for various serotonin receptor subtypes. Mephedrone was not found to have a neurotoxic effect on the dopamine or serotonin system when given alone but no such studies involving 3-MMC have been performed.

A. Routes of administration and dosage

3-MMC is generally administered by insufflation, inhalation, orally or by injection. Repeated administration in a single session has also been reported, often by different routes. Self-reported dosages range from 50 to 150 mg or more (250–500 mg), with many users reporting repeated administration to prolong the euphoric experience, leading to 0.5–2 g doses consumed during a single session or within a few hours.\textsuperscript{4,9,10} Specifically, a questionnaire-based study of self-reporting 3-MMC users in Slovenia found that 88.8% insufflated the drug and 42.6% used it orally; the study did not find any injecting users of 3-MMC. A large share of users (26.2%) reported using more than 1.5 g of 3-MMC in a single evening (n = 168) and over half of the respondents answered that they consumed more than 0.5 g of 3-MMC in a single evening. 43.6% stated going on binges and consuming new psychoactive substances uninterruptedly for more than 24 hours.\textsuperscript{10}

B. Pharmacokinetics

No human pharmacokinetic studies have been performed for 3-MMC but animal (pig) studies showed rapid absorption with a peak concentration achieved within 5–10 min after oral ingestion (3 mg/kg) and a plasma half-life of 0.8 hours.\textsuperscript{11} The bioavailability following oral administration was 7% (which was the same as for that reported for mephedrone in rats) and the authors postulated 3-MMC likely underwent extensive first-pass metabolism. 3-MMC tissue levels were below detectable levels (<0.5 µg/kg) 24 hours after the last oral
dosage. 3-MMC is metabolised to 3-methylephedrine and 3-methylnorephedrine as detected in human pubic hair.\(^5\)

Self-reporting users have stated that the first effects appear between 20 and 30 min after oral administration, the peak effects are observed after 50 min and last up to 3 to 4 hours.\(^9,12\)

Therefore, if these initial animal studies were to reflect that of humans, an apparent low oral bioavailability and short half-life may provide some support for the insufflated route of administration of the drug as well as re-dosing reported by users.

C. Pharmacodynamics

During the pig studies the authors reported no treatment-related mortality and morbidity was observed and no gross pathological findings were detected.\(^11\) Behavioural and other effects on the animals were not recorded/published, however, monitoring of daily feed intake showed a statistically significant reduction in intake following 3-MMC administration.

Previous studies regarding the related compound mephedrone had shown the drug to have a general pharmacological profile comparable to the other amphetamine type stimulants but milder.\(^1\) Whilst no pre-clinical or formal studies have been undertaken in humans, data from users and case reports (including clinically described intoxications) indicate that 3-MMC displays similar properties to mephedrone and amphetamines including euphoria, excitement, feelings of empathy, stimulation and enhanced awareness.\(^3,4\) Adverse effects following administration that have been reported are tachycardia, agitation, reduced level of consciousness, dilated pupils, hallucinations, diaphoresis, seizures and hyperthermia. Users have also reported insomnia, difficulties in concentrating and tingling in the arms and legs.\(^10,13\)

In a questionnaire of self-reporting users, the effects of 3-MMC were reportedly much softer and less “brutal” than mephedrone (4-MMC), and therefore preferable.\(^10\) Further user comparison of the two drugs can be found in internet forums with one user stating: \(^12\) “It's very easy to tell apart 3-MMC and 4-MMC, 3-MMC lacks the powerful buzz of 4-MMC when it comes up, and when it peaks, the overall feeling of well-being is somewhat "blurred" and much much less intense. What I like about 4-MMC is that surge of warmth and fullness in my head when it hits, with 3-MMC there is none. With 4-MMC I would start feeling cold in like 3 hours after a single dose, with 3-MMC it's almost instant. Re-dosing 3-MMC doesn't give any more empathogenic effects, actually 3-MMC is hardly empathogenic at all for me, often it would just produce some stimulation less pronounced but much dirtier than plain amphetamine with no willingness to talk, definitely not resembling methcathinone though (methcathinone is really a stimulant all the way - hard to fall asleep when it wears off, a lot like methamphetamine but less powerful and shorter living, more euphoric and more "chaotic" compared to amphetamine for me). Also, after binging with 3-MMC I wouldn't see trees as people etc., well, at least, it wasn't as psychotic. Also, I noticed that re-dosing 3-MMC made me nauseous at "satisfying" doses unlike 4-MMC. It's not really worth the load it puts on the heart, and it somehow pushes me away contrary to 4-MMC, so a lot less moreish too. I can't see it growing on me as mephedrone did, no way.”
5. Toxicology

No acute or chronic pre-clinical studies were identified that have examined the toxicity of 3-MMC in humans or animals. However, during pharmacokinetic pig studies the researchers stated that no treatment-related mortality and morbidity was observed and no gross pathological findings were detected. Histopathological examination in two animals in the treatment and the control groups revealed mild diffuse hepatocellular vacuolation. In addition, mild multifocal collapse of alveolar walls as well as multifocal mild mononuclear infiltration involving the alveolar and interlobular septa (Interstitium) were observed in two animals in the treatment group, while in one animal in the control group mild hyperplasia of bronchiolar associated tissue was observed. No abnormal histopathological changes were observed in all other tissue samples analyzed.

6. Adverse Reactions in Humans

Cases of 3-MMC Intoxication in Humans

Non-fatal Cases

In Sweden, between August 2012 and March 2014, 3-MMC was detected in 50 of the 786 cases included in the STRIDA project, with the peak occurring in August 2013. The age range of patients testing positive for 3-MMC was 17-49 years (median 24) and 76% of them were men. The 3-MMC concentration in serum ranged between 0.002 and 1.49 mg/L (median, 0.091 mg/L) and between 0.007 and 290 mg/L (median, 3.05 mg/L) in urine. Co-exposure to other new psychoactive substances and/or traditional drugs was very common, and 3-MMC mono-intoxication was found in 4 cases, representing 8% of the 3-MMC cases. The most frequent clinical features were tachycardia (48% of cases) and agitation (42%). Other features included a reduced level of consciousness (32%), dilated pupils (24%), hallucinations (20%), diaphoresis (12%), seizures (8%) and hyperthermia (6%). Most patients (60%) needed hospital care for only 1 day but in 8% of cases needed it for 3 days or longer.

In Poland, 3-MMC was detected in 1 non-fatal intoxication where 3-MMC was determined in the blood of a male at a concentration of 0.021 mg/L with benzoylecgonine at a concentration of 0.058 mg/L. No symptoms or other details were provided.

Fatal Cases

In 5 fatal intoxications involving 3-MMC in Poland, the following results were reported but 3-MMC was not the sole cause of death in any of the cases:

1. 3-MMC concentration in post-mortem blood was residual (<0.001 mg/L) with MDMA also being detected at an equally low concentration (0.033 mg/L). The deceased male had administered 3-MMC and then collapsed. He was taken to hospital but died the following day. The authors commented that the long time delay between drug administration and death, including emergency procedures performed at the hospital and the short half-life of 3-MMC may have resulted in the low concentrations found. The known instability of cathinones (including 3-MMC) especially in blood is also a consideration.
2. The deceased had administrated approximately 500 mg of 3-MMC and 400 mg of 5-APB (5-(2-aminopropyl)benzofuran) in combination with ethanol. The clinical manifestations included agitation, seizures, hypertension, tachycardia, hyperthermia and bradycardia. The patient did not recover and died around 4 hours after the use of drugs. The cause of death was cited as being acute cardiovascular collapse following mixed intoxication with new psychoactive substances and alcohol. Analysis of the post-mortem blood determined 3-MMC and 5-APB concentrations of 1.6 mg/L and 5.6 mg/L, respectively.\textsuperscript{3,4}

3. 3-MMC (0.022 mg/L) and 5-APB (0.146 mg/L) detected along with medicine containing potassium chloride which was found near the deceased. Potassium chloride was also found in the stomach (3.4 mg/g).

4. Fatality involved 3-MMC with 25I-NBOMe. The concentrations of 3-MMC and 25I-NBOMe were determined in post-mortem blood to be 0.011 and 0.003 mg/L, respectively. The deceased male had taken ‘legal highs’ and the cause of death was cited as acute respiratory failure caused by a massive pneumonia which occurred in the course of septic shock followed by multiple organ failure.

5. 3-MMC (0.003 mg/L) was present along with tramadol (therapeutic concentration at 0.563 mg/L) in post-mortem blood of a deceased found in an apartment.

In France, a fatality involving 3-MMC and GHB was reported.\textsuperscript{6} A 69-year-old man who was discovered dead at a friend’s home. 3-MMC and ‘poppers’ (alkyl nitrites) were found at the scene. Toxicological analysis in peripheral blood revealed the presence of 3-MMC (0.33 mg/L), pseudoephedrine (0.03 mg/L) and GHB (576 mg/L) with the GHB concentration being consistent with other cases of fatal intoxication. Testing for ‘poppers’ was negative. The detected drugs were also found in the deceased’s hair. Importantly, 3-MMC was measured to be at a higher concentration of 0.91 mg/L in the cardiac post-mortem blood, suggesting that 3-MMC may be prone to post-mortem redistribution.

In Norway, 3-MMC was identified in a fatality involving the synthetic opioid, AH-7921.\textsuperscript{15}

In the UK in July 2013, venlafaxine, amphetamine and 3-MMC were detected in post-mortem blood where the deceased was found hanging. There was evidence of the use of venlafaxine as well as cocaine and/or amphetamine. 3-MMC was found to be present at a concentration of 1.1 mg/L in post-mortem femoral blood, with venlafaxine at a concentration of 1.62 mg/L (and O-desmethylvenlafaxine at 2.77 mg/L).\textsuperscript{16} Of note is that associated and previous studies had observed an association with mechanical suicide (including hanging) and cathinone use.\textsuperscript{17}

7. Dependence Potential

A. Animal Studies

No studies were identified that have examined the dependence potential of 3-MMC in animals.

B. Human Studies

No studies were identified that have examined the dependence potential of 3-MMC in humans. User reports involving the structurally related compound, mephedrone, suggested
that mephedrone ‘dependence’ is associated with psychological rather than physical dependency similar to other stimulant drugs, such as MDMA and cocaine.\(^1\)

8. Abuse Potential

A. Animal Studies

No studies (e.g. drug discrimination or self-administration) were identified that have examined the abuse potential of 3-MMC in animals. The structurally related compound, mephedrone, exhibited a high level of self-administration in rat studies.\(^1\)

B. Human Studies

No studies were identified that have examined the abuse potential of 3-MMC in humans, however, analytically confirmed use and abuse of 3-MMC has been reported in users.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

No evidence has been found that 3-MMC has been therapeutically used.

10. Listing on the WHO Model List of Essential Medicines

3-MMC is not found on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

None known.

12. Industrial Use

No evidence has been found that 3-MMC has or is used in industry.

13. Non-Medical Use, Abuse and Dependence

In a self-reporting user questionnaire in Slovenia, 249 users (67.9% of respondents) had tried 3-MMC (compared to 37.3% for mephedrone) and had the highest share of frequent new psychoactive substance users.\(^10\) More than a quarter (26.8%) said they had been using it for more than a year and one-third (n=168) said they had used it in the past month. 28.4% of 3-MMC users had used it once or twice, while 20.7% said they had used it 40 or more times.

In Hungary, 2744 subjects were sampled in Budapest between July 2012 and June 2013, and 774 subjects in South-East Hungary between January 2012 and December 2013.\(^18\) Blood and urine samples were collected from subjects prosecuted for illicit and/or designer drug use and tested. 3-MMC was detected in 19 cases in the Budapest cohort and in 24 cases in the South-East Hungary cohort. The authors noted that 3-MMC was amongst those drugs which had replaced drugs that had been placed on a list of illicit substances in
Hungary. This was noticed as the frequency of detection was collated in 2 month intervals to allow time-trend mapping.

In Poland, between 2012 and 2014 3-MMC was the most frequent being found in 50 cases out of the 1058 analysed, as opposed to the next frequent α-pyrrolidinopentiophenone (α-PVP) found in 23 cases.\textsuperscript{19}

Overall, 3-MMC use and abuse has currently been reported in: France, Hungary, Norway, Poland, Sweden and the United Kingdom.

Also see 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**

3-MMC has been detected as part of driving under the influence of drugs (DUID) monitoring in various countries, including Poland, the UK and Germany.\textsuperscript{4,16,20}

In a Polish study, 66 of all 95 instances where 3-MMC was encountered were DUID investigations.\textsuperscript{4} Blood concentrations ranged from 0.001 to 0.171 mg/L. The group where 3-MMC was the only substance present was divided into cases with and without observed symptoms. In a subgroup of drivers who had no unequivocal symptoms (13 cases), the determined 3-MMC concentrations were in the range of 0.003–0.171 mg/L (median 0.012 mg/L). In the second subgroup (6 cases), observed effects included gaiety, verbosity, stuttering, fatigue, agitation, aggression, uncoordinated movements and tachycardia (100 bpm). The authors stated that the pupils of these individuals were recorded to be narrow, normal or wide and reaction to light normal or sluggish. In these cases, lower 3-MMC concentrations were determined in blood overall (between 0.011 and 0.030 mg/L) but the median was higher (0.024 mg/L). In cases where other drugs were present (mainly cannabinoids and amphetamine), observed effects were anxiety, depression, disorientation, verbosity, slurred speech, strange behaviour, unsteady gait, staggering and tachycardia (100–110 bpm). In some individuals, the facial skin was reddened and the pupils were wide or narrow, sluggishly reacting to light.\textsuperscript{4}

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

15. **Licit Production, Consumption and International Trade**

Not applicable.

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

16. **Illicit Manufacture and Traffic and Related Information**

Between 2013 and 2015, 162 seizures of substances purchased through the Internet and confiscated by police authorities in Italy were analyzed: 35 seizures (22%) were crystals of
3-MMC. The authors stated that although 3-MMC is subject to drug legislation in Italy, the shipments originated from the Netherlands where it was not controlled.\textsuperscript{21}

Seizures have been reported elsewhere throughout Europe with the first detection in Sweden in September 2012.\textsuperscript{22} It is often sold on the internet through websites advertising “research chemicals” and related products.

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

17. **Current International Controls and Their Impact**

3-MMC is not controlled under the United Nations conventions.

18. **Current and Past National Controls**

3-MMC is a controlled substance in China, Czech Republic, Estonia, Finland, Germany, Hungary, Ireland, Slovakia, Slovenia, Sweden, Turkey and the United Kingdom.

Also see 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**

None
References


22. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal (European Database on New Drugs) – accessed September 2016

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 44 Member States (4 AFR, 2 EMR, 25 EUR, 7 PAH, 1 SEAR and 5 WPR) answered the questionnaire for 3-Methylmethcathinone (3-MMC). Of these, 26 respondents (21 EUR, 3 PAH and 2 WPR) had information on this substance.

LEGITIMATE USE

There were 24 countries that reported no approved medical products containing 3-MMC for human or veterinarian indications.

3-MMC is not currently being used in any medical or scientific research (excluding use as an analytical reference standard) in 19 countries. Also there was no reported industrial use in 19 countries.

3-MMC was not reported to be used for any cultural, religious or ceremonial purposes in 21 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 17 countries that reported 3-MMC as being misused for its psychoactive properties (as a recreational drug). Common routes of administration are oral (9 countries), injection (3 country), sniffing (7 countries), inhalation (2 countries) and smoking (2 countries). The main route of administration for 3-MMC was reported as oral (5 countries) followed by sniffing (2 countries) and smoking (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (14 countries), followed by tablets (3 countries), liquid or solution for oral administration/use (2 countries) and injectable formulations (1 country). One country also reported plant material impregnated with the 3-MMC being used as a formulation.

There were 10 countries which reported that the source of 3-MMC for non-medical/non-scientific use was smuggling. One country commented that online shopping was another source of 3-MMC. Another country commented that 3-MMC was not frequently observed in the country but it is sometimes found by customs, usually when in transit to/from other European country.

Nightlife settings (1 country), youths or young adults (1 country) and the party scene (1 country) were specified as subpopulations known to misuse 3-MMC.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (2 countries), substantial (5 countries) or serious (3 countries).
For the countries that indicated a substantial or serious level of negative health-impact, they specified that it was due to the association of 3-MMC with adverse effects (e.g. seizures, cardiovascular collapses, transmission of communicable diseases through injection drug use) and fatalities. It was also commented that 3-MMC is a potent cathinone and it has been frequently discussed in forum posts that regular use can quickly lead to tolerance as well as craving.

Three countries reported emergency room/department visits related to the non-medical use of 3-MMC. A combined number of 16 cases in 2014 and 2 cases in 2015 where reported (two countries). The remaining country reported 61 hospital care visits, however, no further data was provided regarding the severity of the visits or the time frame.

The adverse effects which presented for 3-MMC at the emergency room/department included hyperthermia, wild behaviour, chest pressure, anxiety and high pulse.

In regards to the mortality rate, data was provided by 3 countries. The rate which included involvement of other substances was reported to be 12 cases in 2013 (in 11 cases 3-MMC was not reported as cause of death). The rate where it was unknown if other substances were involved was 1 case in 2015. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

**STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL**

There were 22 countries reported that 3-MMC was under national control. The legislation the control is based upon included Medicines Act (1 country), Controlled Substances Act (17 countries), Criminal Law Act (2 countries), Analog Act (1 country) and other specific legislation (3 countries stated that it was specific legislation for new psychoactive substances). Two countries reported that the control is a temporary provision (one commenced in 2012, the other 2015). There were no challenges to implementing controls for 3-MMC reported.

The scope of the controls includes production (18 countries), manufacturing (19 countries), exporting (18 countries), importing (21 countries), distribution (21 countries), use (13 countries) and possession (19 countries).

Reported illicit activities involving 3-MMC include manufacture of the substance by chemical synthesis (1 country), trafficking (12 countries), smuggling (1 country), diversion (1 country), domestic internet sales (1 country), internet sales from abroad (8 countries), internet sales from unknown locations (5 countries) and finally sales to people who use this substance (5 countries).

There were 16 countries which completed the section on the number of seizures. The combined number of seizures was 2 (2013), 537 (2014), 395 (2015) and 68 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If 3-MMC was placed under international control, 24 countries responded that they would have the capacity to enforce the control at the national level. There were 25 countries which responded that they would have the forensic laboratory capacity to analyse the substance.