

Methylone (bk-MDMA)

Critical Review Report

Agenda item 4.14

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014



**World Health
Organization**

Acknowledgments

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Policy Access and Rational Use Unit. The WHO Secretariat would like to thank the following people for their contribution in producing this critical review report: Wim Best, the Netherlands (literature review and drafting), Dr Caroline Bodenschatz, Switzerland (editing) and Mr David Beran, Switzerland (questionnaire report drafting).

Contents

Summary.....	7
1. Substance identification	8
A. <i>International Nonproprietary Name (INN)</i>	8
B. <i>Chemical Abstract Service (CAS) Registry Number</i>	8
C. <i>Other Names</i>	8
D. <i>Trade Names</i>	8
E. <i>Street Names</i>	8
F. <i>Physical properties</i>	8
G. <i>WHO Review History</i>	8
2. Chemistry.....	9
A. <i>Chemical Name</i>	9
B. <i>Chemical Structure</i>	9
C. <i>Stereoisomers</i>	9
D. <i>Synthesis</i>	9
E. <i>Chemical description</i>	9
F. <i>Chemical properties</i>	9
G. <i>Chemical identification</i>	10
3. Ease of convertibility into controlled substances	10
4. General pharmacology	10
4.1. <i>Pharmacodynamics</i>	10
4.2. <i>Routes of administration and dosage</i>	12
4.3. <i>Pharmacokinetics</i>	13
5. Toxicology	14
6. Adverse reactions in humans.....	14
7. Dependence potential.....	16
8. Abuse potential.....	16
9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use	17
10. Listing on the WHO Model List of Essential Medicines	17
11. Marketing authorizations (as a medicine)	17
12. Industrial use	17
13. Non-medical use, abuse and dependence	17
14. Nature and magnitude of public health problems related to misuse, abuse and dependence	17
15. Licit production, consumption and international trade.....	18
16. Illicit manufacture and traffic and related information	18
17. Current international controls and their impact	19
18. Current and past national controls.....	19
19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance	19
References.....	21
Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Methylone	23

Summary

Methylone ((3,4-methylenedioxy)methcathinone) is a synthetic cathinone. It is the beta-keto version of 3,4-methylenedioxymethylamphetamine (mdma). It was originally developed as a therapeutic for Parkinson's disease or depression by Shulgin. Use of methylone was first reported around 2005. Use/abuse has been reported from Japan, the USA and Europe. The effects and the mode of use reported have similarities with mdma, but its potency is less.

Reported toxic effects of methylone include tachycardia, hypertension, paranoia, anxiety, bruxism and muscle tension and aching. Some of these effects leading to hospital admissions. A number of analytically confirmed drug-related deaths have been reported.

Animal studies have indicated that methylone possesses an abuse or dependence potential but there are no human clinical data to support this.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

186028-79-5N (base, racemic mixture)

191916-41-3 (base, + stereo-isomer)

186028-80-8 (hydrochloride salt)

C. Other Names

Methylone, 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one, (3,4-methylenedioxy)methcathinone, bk-mdma, mdmc, β-keto-(3,4-methylenedioxyphenyl,N-methylamphetamine).

D. Trade Names

None.

E. Street Names

Only a limited number of street names for methylone can be found in the literature, like:

Ease, Explosion, Inpact, mdmcat. bk-MDMA, M1, Neocor, Room odorizer.

F. Physical properties

Methylone hydrochloride salt is a white or lightly coloured powder.

G. WHO Review History

Methylone was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that Methylone 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

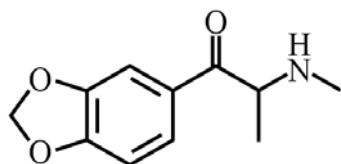
A. Chemical Name

IUPAC Name: (RS)- 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one

CA Index Name: methylone

B. Chemical Structure

Free base:



Molecular Formula: C₁₁H₁₃NO₃

Molecular Weight: 207.23 g/mol

C. Stereoisomers

Methylone contains a chiral centre at the C-2 carbon of the propane sidechain, so that two enantiomers exist: R-methylone and S-methylone.

Due to the similarity with 3,4-methylenedioxymethylamphetamine (MDMA) the S form is thought to be more potent than the R form.

D. Synthesis

A ring-substituted N-methylcathinone derivative, like methylone, is best synthesised by reacting the suitably substituted bromopropiophenone with methylamine; the result is always racemic. In the case of methylone, for example, 2-bromo-3,4-methylenedioxy-propiofenone can be prepared by reacting 3,4-methylenedioxypropiofenone with bromine.

E. Chemical description

Methylone ((3,4-methylenedioxy)methylcathinone) is a ring-substituted beta-keto-amphetamine related to methylcathinone and 3,4-methylenedioxymethylamphetamine (MDMA).

F. Chemical properties

Methylone hydrochloride salt is a white or lightly coloured powder. The powder is readily soluble in water.

G. Chemical identification

Gas-chromatography mass-spectrometry (GC-MS) and liquid chromatography with mass spectrometry-mass spectrometry (LC-MS/MS) techniques have been developed for the detection of methylone (Fornal, 2013, Reitzel et al., 2012).

Methylone does not give a colour reaction with the Marquis test.

3. Ease of convertibility into controlled substances

Methylone is not converted into controlled substances.

4. General pharmacology

4.1. Pharmacodynamics

In the mid-1990's methylone (mdmc) has been synthesized by Jacob and Shulgin (1996) as a potential treatment for Parkinson's disease and for depression.

Methylone is the beta-keto analog of N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (mdma). The effects are comparable to mdma, for instance stimulation, euphoria, empathogenic and entactogenic, but slightly milder.

Biochemical effects

Cozzi *et al.* (1999) tested the neurotransmitter uptake inhibition in vitro of methylone. The beta-ketone was threefold less potent than the nonketo drug MDMA, at inhibiting platelet serotonin accumulation, with IC(50) of 5.8±0.7 µM. Methylone was similar in potency to MDMA at catecholamine transporters individually expressed in transfected glial cells. For dopamine uptake, IC(50) was 0.82±0.17 µM, respectively; for noradrenaline uptake, IC(50) value was 1.2±0.1 µM, respectively. In chromaffin granules, IC(50) for serotonin accumulation was 166±12 µM for methylone, 10-fold higher than the respective value for MDMA. The results indicate that methylone potently inhibit plasma membrane catecholamine transporters but only weakly inhibit the vesicle transporter.

Simmler *et al.* (2013) determined the potencies of several cathinones to inhibit DA, NA and 5-HT transport into transporter-transfected HEK 293 cells, DA and 5-HT efflux from monoamine-preloaded cells.

Methylone, mephedrone, ethylone, butylone and naphyrone act as non-selective monoamine uptake inhibitors, similar to cocaine. Methylone, mephedrone, ethylone and butylone also induce the release of 5-HT, similar to MDMA. All the cathinones showed high blood-brain barrier permeability in an in vitro model; mephedrone and MDPV exhibited particularly high permeability.

Sogawa *et al.* (2011) examined the effects of methylone on the transporters for dopamine (DAT), norepinephrine (NET), and serotonin (SERT), using a heterologous expression system in CHO cells. Methylone inhibited the activities of DAT, NET, and SERT, in a concentration-dependent fashion with a rank order of NET > DAT > SERT. Methylone was less effective at inhibiting DAT and NET, but more effective against

SERT than was methamphetamine. The ability of methylone to inhibit monoamine transporter function, probably by acting as a transportable substrate, underlies the synergistic effect of methylone and methamphetamine.

In vitro studies using recombinant human monoamine transporters point in the same direction (Eshleman *et al.*, 2013). Mephedrone and methylone had higher inhibitory potency at uptake compared to binding and generally induced release of preloaded [³H]neurotransmitter from human dopamine (hDAT), serotonin (hSERT) and norepinephrine (hNET) transporters (highest potency at hNET), and thus are transporter substrates, similar to methamphetamine and mdma. In general these substituted methcathinones had low uptake inhibitory potency and low efficacy at inducing release via human vesicular monoamine transporters (hVMAT2). Furthermore these compounds were low potency h5-HT(1A) receptor partial agonists, h5-HT(2A) receptor antagonists, weak h5-HT(2C) receptor antagonists and have no affinity for dopamine receptors.

The primary mechanisms of action may be as inhibitors or substrates of DAT, SERT and NET.

Also in vivo methods employed by Baumann *et al.* (2012) showed similar results.

Methylone is a weak motor stimulant when compared with methamphetamine. Repeated administrations of mephedrone or methylone (3.0 and 10.0 mg/kg, s.c., 3 doses) caused hyperthermia but no long-term change in cortical or striatal amines, whereas similar treatment with MDMA (2.5 and 7.5 mg/kg, s.c., 3 doses) evoked robust hyperthermia and persistent depletion of cortical and striatal 5-HT.

Behavioral effects

López-Arnau *et al.* (2012) recorded locomotor activity in mice following different doses of cathinones (butylone, mephedrone and methylone).

All three cathinones (5-25 mg/kg) caused hyperlocomotion, which was prevented with ketanserin or haloperidol. Methylone was the most potent compound inhibiting both [(3) H]5-HT and [(3) H]dopamine uptake with IC(50) values that correlate with its affinity for dopamine and 5-HT transporter. The affinity of cathinones for 5-HT(2A) receptors was similar to that of MDMA.

Butylone and methylone induced hyperlocomotion through activating 5-HT(2A) receptors and increasing extra-cellular dopamine. They inhibited 5-HT and dopamine uptake by competing with substrate. Methylone was the most potent 5-HT and dopamine uptake inhibitor and its effect partly persisted after withdrawal.

Den Hollander *et al.* (2013) treated mice with a binge-like regimen of methylone (30 mg/kg, twice daily for 4 days) in order to investigate the possible long-term effects of this drug on a range of behavioral tests. Starting 2 weeks later, they performed behavioral tests of memory, anxiety and depression. Methylone had little effect on behavior or neurotransmitter levels in mice but produced a widespread depletion of 5-HT and 5-HTT levels in rats.

Marusich *et al.* (2012) evaluated the in vivo effects of several synthetic cathinones and compared them to those of cocaine (COC) and methamphetamine (METH). Acute

effects of methylenedioxyphyrovalerone, mephedrone, methylone, methedrone, 3-fluoromethcathinone, 4-fluoromethcathinone, COC, and METH were examined in male ICR mice on locomotor activity, rotorod, and a functional observational battery (FOB). All drugs increased locomotor activity, with different compounds showing different potencies and time courses in locomotor activity. Methylone decreased performance on the rotorod. The FOB showed that in addition to typical stimulant induced effects, some synthetic cathinones produced ataxia, convulsions, and increased exploration. These results suggest that individual synthetic cathinones differ in their profile of effects, and differ from known stimulants of abuse.

4.2. Routes of administration and dosage

Methylone can be administered through a variety of different routes, including oral, intranasal, intravenous, sublingual, and rectal administration.

However oral consumption appears to be the most popular route of administration (Erowid).

Intranasal dosage is the same as oral dosage but is not considered as rewarding and with a much shorter duration of action.

Methylone is generally available as pure crystals but also oral solutions are available (e.g. Explosion).

Oral dosages of methylone and activity:

Threshold	60 - 120 mg
Light	100 - 150 mg
Common	100 - 250 mg
Strong	160 - 270 mg
Very strong	250 + mg

Some users mention that increasing doses of methylone beyond 100-180 mg causes increased physical effects but does not substantially improve the empathic cognitive effects.

Timecourse of effects after oral dosages of methylone:

Onset	15 - 60 minutes
Coming Up	30 - 45 mins
Plateau	60 - 90 mins
Coming Down	60 - 120 mins
Duration	2 - 3.5 hours
Normal After Effects	6 - 24 hours
Total Duration	3 - 5 hrs

Bumping / boosting:

Methylone is sometimes used with a larger "attack" dose (first dose) and then smaller "bumps" to maintain the effects for a longer period.

These bumps are taken orally or insufflated and are often around 30 - 100 mg oral and 20-80 mg insufflated.

A re-dose of a third to a half of the normal dose usually extends the duration for another hour, a full-dose redose often extends the duration for another 1-2 hours.

4.3. Pharmacokinetics

López-Arnau *et al.* (2013) investigated the pharmacokinetics of methylone in rats. In order to provide a pharmacokinetic/pharmacodynamic model they also looked at the locomotor activity of the animals.

Methylone was administered to male Sprague-Dawley rats intravenously (10mg/kg) and orally (15 and 30 mg/kg). Plasma concentrations and metabolites were characterized by LC/MS and LC-MS/MS fragmentation patterns. Locomotor activity was monitored for 180-240 min.

The plasma concentrations after i.v. administration fit a two-compartment model.

After oral administration, peak methylone concentrations were achieved between 0.5 and 1h. The absolute bioavailability was about 80% and the percentage of methylone protein binding was of 30%.

They have identified four Phase I metabolites after oral administration. The major metabolic routes are N-demethylation, aliphatic hydroxylation and O-methylation of a demethylenate intermediate. A relationship between methylone brain levels and free plasma concentration yielded a ratio of 1.42 ± 0.06 . Methylone induced a dose-dependent increase in locomotor activity. The pharmacokinetic-pharmacodynamic model successfully describes the relationship between methylone plasma concentrations and its psychostimulant effect. A contribution of metabolites in the activity of methylone after oral administration is suggested.

Kamata *et al.* (2006) investigated the urinary metabolites of methylone in humans and rats. They administered methylone to rats and then analysed the urine specimens. Furthermore they also analysed the urine of some users. The techniques used were gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-electrospray ionization mass spectrometry (LC-ESI MS).

The following major metabolic pathways were found:

- side-chain degradation by N-demethylation to the corresponding primary amine, methylenedioxcathinone (MDC);
- demethylenation followed by O-methylation of either a 3- or 4-OH group on the benzene ring to produce 4-hydroxy-3-methoxymethcathinone (HMMC) or 3-hydroxy-4-methoxymethcathinone (3-OH-4-MeO-MC). Of these metabolites, HMMC was the most abundant in humans and rats. All formed metabolites were conjugated.

The same group (Katagi *et al.*, 2010) showed in a later study that also beta-keto reduction to the corresponding amino alcohols, 3,4-methylenedioxyephedrine and 3,4-methylenedioxyephedrine took place.

Pedersen *et al.* (2013) showed that cytochrome P450 2D6 (CYP2D6) was the main responsible enzyme for the in vitro Phase I metabolism of methylone, with minor contributions from CYP1A2, CYP2B6, and CYP2C19. The major metabolite was identified as dihydroxymethcathinone, and the minor metabolites were N-hydroxy-methylone, nor-methylone, and dihydro-methylone.

Forensic casework has been performed by Cawrse *et al.* (2012). They analysed four postmortem cases for methylone, mephedrone and MDPV, with drug levels quantitated in multiple biological matrices. All four cases had detectable levels of methylone, with heart blood concentrations between 0.060 and 1.12 mg/L. Analysis of several tissue samples shows that methylone does not sequester in a particular tissue type after death. The average liver-to-blood ratio was 2.68. Two different extraction methods, as well as analysis of derivatized and underivatized methylone, show that the drug is suitable for analysis in either method.

Another case is published by McIntyre *et al.* (2013). They describe a 19-year-old woman who was known to use drugs. She was found floating in the ocean 100 yards from the beach. When last seen she had said to a friend that she was going to get in the water. Autopsy findings were consistent with drowning. Postmortem blood initially screened positive for methamphetamine and cannabinoids by ELISA and was subsequently confirmed for methylone by a specific GC-MS SIM analysis following solid-phase extraction. Concentrations found in the peripheral blood, central blood and vitreous content were measured at 3.4 mg/L, 3.4 mg/L, and 4.3mg/L, respectively.

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of methylone.

6. Adverse reactions in humans

Adverse events

For drugs of abuse there is no formal registration system for adverse events. Information can be obtained by surveys, by searching on internet fora and by collecting information from national poison information services.

The following adverse events of methylone use have been mentioned:

Cardiovascular System:

Heart racing, palpitations,
Hypertension.

Central Nervous System:

Dizziness;
Paranoia, confusion;
Anxiety, fear;
Increased in body temperature;
Fatigue, loss of appetite.

Gastro-intestinal system:

Gastrointestinal discomfort;
Nausea, vomiting.

Musculoskeletal system:

Bruxism (teeth grinding), jaw tension;
Muscle tension and aching.

Miscellaneous:

Increased perspiration

Serious adverse events

Boulangier-Gobeil *et al.* (2012) report a case of methylone and ethcathinone poisoning with severe clinical toxicity.

A 22-year-old woman was brought to the emergency department following several episodes of tonicoclonic seizures, a few hours after ingesting "legal ecstasy". The patient needed intubation for recurrent seizures, and she was found to have severe hyponatremia (120 mmol/L) that was corrected with hypertonic saline. Furthermore she developed prolonged rhabdomyolysis (CK 34.537 U/L) that required a 6-day hospitalisation.

The seizures and the hyponatremia may be explained by the MDMA-like characteristics of methylone that may induce inappropriate secretion of antidiuretic hormone mediated via the serotonin system. The prolonged period of rhabdomyolysis may also be explained by excessive serotonin activity resulting in an increased motor hyperactivity.

Fatal intoxications

So far only a limited number of fatal intoxications with methylone have been reported, most of them originating from the USA.

Pearson *et al.* (2012) presented three fatal intoxications of methylone. Blood was analyzed with a routine alkaline liquid-liquid extraction and analyzed by gas chromatography coupled with a mass spectrometer (GC-MS). Methylone was identified by a full scan mass spectral comparison to an analytical standard of methylone. In all three fatalities, the deceased exhibited seizure-like activity and elevated body temperatures (103.9, 105.9 and 107°F) before death. Two of the three cases also exhibited metabolic acidosis. One of the three cases had prolonged treatment and hospitalization before death with symptoms similar to sympathomimetic toxicity, including metabolic acidosis, rhabdomyolysis, acute renal failure and disseminated intravascular coagulation. Peripheral blood methylone concentrations in the three fatal cases were 0.84, 3.3 and 0.56 mg/L. Their conclusion is that peripheral blood methylone concentrations in excess of 0.5 mg/L may result in death due to its toxic properties, which can include elevated body temperature and other sympathomimetic-like symptoms.

Warrick *et al.* (2012) report a case of a 24-year-old female who ingested a capsule containing methylone and butylone sold as "Ecstasy". The patient presented to the emergency department, comatose febrile, tachycardic, tachypnic, and hypertensive. On exam, she was diaphoretic, tremulous, hyperreflexic, and had sustained clonus. The patient progressed to multi-system organ failure and ultimately expired. The investigators obtained and analyzed both her urine and a capsule found on her person similar to the capsules ingested. In both samples, laboratory analysis identified only methylone and butylone.

Carbone *et al.* (2013) reported a case of sudden death related to methylone in a 19-year-old man. This is the first reported case of sudden cardiac death associated with methylone use. The amount of methylone detected postmortem (0.7 mg/L) is in line with the concentrations described by Pearson *et al.* (2012).

Kovács *et al.* (2012) present a fatal case related to the consumption of methylone. A 16-year-old boy suddenly lost his consciousness in a party. Resuscitation was unsuccessful. His previous history included cardiac malformation detected at infancy and bronchial asthma diagnosed one year before his death. Signs of sudden cardiac death were observed during autopsy. In addition, striated heart muscle damage was observed, which could be due to the use of an amphetamine-like substance. Methylone intake was proved in blood and liver extract using gas chromatography/mass spectrometry. The concentrations found were .272 mg/L in the blood and 387 ng/g in the liver.

Finally five cases to which methylone might have been contributed have been reported from the UK (personal communication John Corkery).

7. Dependence potential

No data available.

8. Abuse potential

Bonano *et al.* (2014) examined the behavioral effects of (±)-methcathinone, (±)-3,4-methylenedioxypyrovalerone (MDPV), (±)-3,4-methylenedioxymethcathinone (methylone), and (±)-4-methylmethcathinone (mephedrone) in rats using intracranial self-stimulation (ICSS). Male Sprague-Dawley rats with electrodes targeting the medial forebrain bundle responded for multiple frequencies of brain stimulation and were tested in two phases. First, dose-effect curves for methcathinone (0.1-1.0 mg/kg), MDPV (0.32-3.2 mg/kg), methylone (1.0-10 mg/kg), and mephedrone (1.0-10 mg/kg) were determined. Second, time courses were determined for effects produced by the highest dose of each compound.

MDPV, methylone, and mephedrone produced dose- and time-dependent increases in low rates of ICSS maintained by low brain stimulation frequencies, but also produced abuse-limiting depression of high ICSS rates maintained by high brain stimulation frequencies. Efficacies to facilitate ICSS were methcathinone \geq MDPV \geq methylone $>$ mephedrone. Methcathinone was the most potent compound, and MDPV was the longest acting compound.

Watterson *et al.* (2012) tried to determine the relative abuse liability of methylone by employing intravenous self-administration (IVSA) and intracranial self-stimulation (ICSS) paradigms in rats. They demonstrated that methylone (0.05, 0.1, 0.2, and 0.5 mg/kg/infusion) dose-dependently functions as a reinforcer, and that there is a significant positive relationship between methylone dose and reinforcer efficacy. Furthermore, responding during short access sessions (ShA, 2 hr/day) appeared more robust than previous IVSA studies with MDMA. However, unlike previous findings with abused stimulants (cocaine, methamphetamine), long access sessions (LgA, 6 hr/day) did not lead to escalated drug intake or increased reinforcer efficacy. Finally, methylone produced a dose-dependent, but statistically non-significant, trend towards reductions in ICSS thresholds. Together these results reveal that methylone may possess an addiction potential similar to or greater than MDMA, yet patterns of self-administration and effects on brain reward function suggest that this drug may have a lower potential for abuse and compulsive use than prototypical psychostimulants.

Gatch *et al.* (2013) tried to determine whether cathinone compounds stimulate motor activity and have discriminative stimulus effects similar to those of cocaine and/or methamphetamine. 3,4-Methylenedioxypropylamphetamine (MDPV), methylone, mephedrone, naphyrone, flephedrone, and butylone were tested for locomotor stimulant effects in mice and subsequently for substitution in rats trained to discriminate cocaine (10 mg/kg, intraperitoneally) or methamphetamine (1 mg/kg, intraperitoneally) from saline. All compounds fully substituted for the discriminative stimulus effects of cocaine and methamphetamine. MDPV and naphyrone produced locomotor stimulant effects that lasted much longer than those of cocaine or methamphetamine.

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

Not applicable.

10. Listing on the WHO Model List of Essential Medicines

Methylone is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

Methylone has never been marketed as a medicinal product.

12. Industrial use

Methylone has no industrial use.

13. Non-medical use, abuse and dependence

González *et al.* (2013) looked at the pattern of use of new psychoactive substances in a group of Spanish research chemical (RC) users. A total of 230 users participated. The most frequent RC's were hallucinogenic phenethylamines (2C-B 80.0%, 2C-I 39.6%) and cathinones (methylone 40.1%, mephedrone 35.2%). The most frequent combination of RC with other illegal drugs was with cannabis (68.6%). here is a specific RC user profile with extensive knowledge and consumption of substances, using different strategies to reduce risks associated to its consumption.

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

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

Caudevilla-Gálligo *et al.* (2013) described the presence and composition of synthetic cathinones in drug samples analyzed at a Drug Testing Service. Data were obtained from samples delivered as, or containing cathinones, between January 2010 and June

2012. Specimens were identified by combining thin layer chromatography and gas chromatography associated with mass spectrometry. Two hundred and thirty-seven (3.8%) of the 6199 samples were delivered as, or contained cathinones. 22 different cathinones were detected, alone or in different combinations. Methylone (24.9%), mephedrone (24.5%), 4-methylethcathinone (9.28%), and methylenedioxypropylone (6.8%) were the most common cathinones. These substances were also found in 80 (1.3%) of samples delivered allegedly containing drugs different from cathinones (mdma, amphetamines, ketamine, etc). Cathinone derivatives were markedly present in the Spanish drug market during the studied period.

Helander *et al.* (2013) collected information concerning the increasing use of new psychoactive substances. A project called 'STRIDA' was started to monitor the occurrence and trends of new psychoactive substances in Sweden. Another part of the project focused on collecting information about the clinical symptoms, toxicity and associated health risks of these new psychoactive substances. A liquid chromatographic-tandem mass spectrometric multi-component method has been developed, allowing for the determination of > 80 novel psychoactive compounds or metabolites thereof.

In their study they focused mainly on the particular drug substances identified and the population demographics of the initial STRIDA cases.

In urine and/or blood samples obtained from 103 consecutive cases of admitted or suspected recreational drug intoxications in mostly young subjects (78% were ≤ 25 years, and 81% were males) presenting at emergency departments all over the country, psychoactive substances were detected in 82%. The substances comprised synthetic cannabinoids, substituted cathinones (e.g. butylone, MDPV and methylone) and tryptamines, and also plant-based substances as well as conventional drugs-of-abuse. In 44% of the cases, more than one new psychoactive substance, or a mixture of new and/or conventional drugs were detected.

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

15. Licit production, consumption and international trade

There are no known uses of methylone as a research, industrial, agricultural or cosmetic compound, despite it being marketed as 'room odorizer', 'bath salt' or 'research chemical'.

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

16. Illicit manufacture and traffic and related information

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

17. Current international controls and their impact

Not applicable.

18. Current and past national controls

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

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

References

- Baumann MH, Ayestas MA Jr, Partilla JS, Sink JR, Shulgin AT, Daley PF, Brandt SD, Rothman RB, Ruoho AE, Cozzi NV. The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology*. 2012 Apr;37(5):1192-203.
- Bonano JS, Glennon RA, De Felice LJ, Banks ML, Negus SS. Abuse-related and abuse-limiting effects of methcathinone and the synthetic "bath salts" cathinone analogs methylenedioxypropylvalerone (MDPV), methylone and mephedrone on intracranial self-stimulation in rats. *Psychopharmacology (Berl)*. 2014 Jan;231(1):199-207.
- Boulanger-Gobeil C, St-Onge M, Laliberté M, Auger PL. Seizures and hyponatremia related to ethcathinone and methylone poisoning. *J Med Toxicol*. 2012 Mar;8(1):59-61.
- Caudevilla-Gálligo F, Ventura M, Indave Ruiz BI, Fornís I. Presence and composition of cathinone derivatives in drug samples taken from a Drug Test Service in Spain (2010-2012). *Hum Psychopharmacol*. 2013 Jul;28(4):341-4.
- Carbone PN, Carbone DL, Carstairs SD, Luzi SA. Sudden cardiac death associated with methylone use. *Am J Forensic Med Pathol*. 2013 Mar;34(1):26-8.
- Cawrse BM, Levine B, Jufer RA, Fowler DR, Vorce SP, Dickson AJ, Holler JM. Distribution of methylone in four postmortem cases. *J Anal Toxicol*. 2012 Jul;36(6):434-9.
- Cozzi NV, Sievert MK, Shulgin AT, Jacob P 3rd, Ruoho AE. Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur J Pharmacol*. 1999 Sep 17; 381(1):63-9.
- Den Hollander B, Rozov S, Linden AM, Uusi-Oukari M, Ojanperä I, Korpi ER. Long-term cognitive and neurochemical effects of "bath salt" designer drugs methylone and mephedrone. *Pharmacol Biochem Behav*. 2013 Jan;103(3):501-9.
- Erowid. Available from: <http://www.erowid.org> Accessed February 2014.
- Eshleman AJ, Wolfrum KM, Hatfield MG, Johnson RA, Murphy KV, Janowsky A. Substituted methcathinones differ in transporter and receptor interactions. *Biochem Pharmacol*. 2013 Jun 15;85(12):1803-15.
- Fornal E. Identification of substituted cathinones: 3,4-Methylenedioxy derivatives by high performance liquid chromatography-quadrupole time of flight mass spectrometry. *J Pharm Biomed Anal*. 2013 Jul-Aug;81-82:13-9.
- Gatch MB, Taylor CM, Forster MJ. Locomotor stimulant and discriminative stimulus effects of 'bath salt' cathinones. *Behav Pharmacol*. 2013 Sep;24(5-6):437-47.
- González D, Ventura M, Caudevilla F, Torrens M, Farre M. Consumption of new psychoactive substances in a Spanish sample of research chemical users. *Hum Psychopharmacol*. 2013 Jul;28(4):332-40.
- Helander A, Beck O, Hägerkvist R, Hultén P. Identification of novel psychoactive drug use in Sweden based on laboratory analysis--initial experiences from the STRIDA project. *Scand J Clin Lab Invest*. 2013 Aug;73(5):400-6.
- Jacob P 3rd and Shulgin AT. Novel n-substituted-2-amino-3',4'-methylene-dioxypropylphenones. WO 1996039133 A1, 1996.
- Kamata HT, Shima N, Zaitso K, Kamata T, Miki A, Nishikawa M, Katagi M, Tsuchihashi H. Metabolism of the recently encountered designer drug, methylone, in humans and rats. *Xenobiotica*. 2006 Aug;36(8):709-23.
- Katagi M, Zaitso K, Shima N, Kamata H, Kamata T, Nakanishi K, Miki A, Tsuchihashi H. Metabolism and Forensic Toxicological Analyses of the Extensively Abused D4esigner Drug Methylone. *TIAFT Bulletin* 2010; 40 (1): 30-36.
- Kovács K, Tóth AR, Kereszty EM. [A new designer drug: methylone related death].[Article in Hungarian] *Orv Hetil*. 2012 Feb 19;153(7):271-6.
- López-Arnau R, Martínez-Clemente J, Carbó MI, Pubill D, Escubedo E, Camarasa J. An integrated pharmacokinetic and pharmacodynamic study of a new drug of abuse, methylone, a synthetic cathinone sold as "bath salts". *Prog Neuropsychopharmacol Biol Psychiatry*. 2013 Aug 1;45:64-72.

- López-Arnau R, Martínez-Clemente J, Pubill D, Escubedo E, Camarasa J. Comparative neuropharmacology of three psychostimulant cathinone derivatives: butylone, mephedrone and methylone. *Br J Pharmacol*. 2012 Sep;167(2):407-20.
- Marusich JA, Grant KR, Blough BE, Wiley JL. Effects of synthetic cathinones contained in "bath salts" on motor behavior and a functional observational battery in mice. *Neurotoxicology*. 2012 Oct;33(5):1305-13.
- McIntyre IM, Hamm CE, Aldridge L, Nelson CL. Acute methylone intoxication in an accidental drowning--a case report. *Forensic Sci Int*. 2013 Sep 10;231(1-3):e1-3.
- Pearson JM, Hargraves TL, Hair LS, Massucci CJ, Frazee CC 3rd, Garg U, Pietak BR. Three fatal intoxications due to methylone. *J Anal Toxicol*. 2012 Jul;36(6):444-51.
- Pedersen AJ, Petersen TH, Linnet K. In vitro metabolism and pharmacokinetic studies on methylone. *Drug Metab Dispos*. 2013 Jun;41(6):1247-55.
- Reitzel LA, Dalsgaard PW, Müller IB, Cornett C. Identification of ten new designer drugs by GC-MS, UPLC-QTOF-MS, and NMR as part of a police investigation of a Danish internet company. *Drug Test Anal*. 2012 May;4(5):342-54.
- Simmler LD, Buser TA, Donzelli M, Schramm Y, Dieu LH, Huwyler J, Chaboz S, Hoener MC, Liechti ME. Pharmacological characterization of designer cathinones in vitro. *Br J Pharmacol*. 2013 Jan;168(2):458-70.
- Sogawa C, Sogawa N, Ohyama K, Kikura-Hanajiri R, Goda Y, Sora I, Kitayama S. Methylone and monoamine transporters: correlation with toxicity. *Curr Neuropharmacol*. 2011 Mar;9(1):58-62.
- Warrick BJ, Wilson J, Hedge M, Freeman S, Leonard K, Aaron C. Lethal serotonin syndrome after methylone and butylone ingestion. *J Med Toxicol*. 2012 Mar;8(1):65-8.
- Watterson LR, Hood L, Sewalia K, Tomek SE, Yahn S, Johnson CT, Wegner S, Blough BE, Marusich JA, Olive MF. The Reinforcing and Rewarding Effects of Methylone, a Synthetic Cathinone Commonly Found in "Bath Salts". *J Addict Res Ther*. 2012 Dec 1;Suppl 9. pii: 002.

Annex 1:

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

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 65 Member States answered the questionnaire for Methylone (bk-MDMA). Of these, only 32 respondents (AMR 6, EUR 22, SEAR 1, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that methylone was currently authorized or is in the process of being authorized/registered as a medical product in their country. Five respondents stated that this substance was used in research or as analytical standards. There was no stated use for animal/veterinary care

HARMFUL USE

Twenty-three respondents confirmed that there was recreational/harmful use of methylone with 8 reporting oral/ inhaling/sniffing, 6 stating only oral, 2 stating oral/injection, inhaling/sniffing and 1 stating inhaling/sniffing as common routes of administration. Seventeen respondents stated this was obtained via trafficking and one each reporting clandestine manufacturing, diversion plus trafficking and trafficking plus clandestine manufacturing. Common formulations available were reported as powder by 8, powder and tablet by 4, powder, tablet and liquid by 3, tablet only by 1 and liquid forms only by one. 4 respondents each stated that it was used only by the general population and only in clubs while two respondents stated its use was both in clubs and among general population.

Two respondents report overdose deaths, two and 18 respectively for 2012. The latter is for all cathinones. Emergency room visits are reported as two by one respondent and as about 20 by another, for 2012. One death is reported for 2010, and 4 emergency room visits in 2013 by one respondent. Five respondents reported withdrawal, tolerance and other adverse effects or medical illnesses. Hyperthermia and dehydration are described as prominent features. Other include several sympathomimetic features.

CONTROL

Of those with information on this substance, 29 reported that methylone was controlled under legislation that was intended to regulate its availability - 25 under “controlled substance act”, 2 under “medicines law” and 2 under “other” laws. Only 4 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving methylone, two reported clandestine manufacture where the product itself was synthesized. Four respondents reported processing into the consumer product, 16 reported trafficking, four reported diversion and 15 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	2,133 (14)	4,428 (14)
Total quantity seized (kg)	705.97 (12)	229.74 (14)
Total quantity seized (L)		1 (1)
Total quantity seized (tablets/pills)	2,881 (5)	56,430 (7)
Others seized	Wraps/ pieces/ bags	Wraps/pieces/bags

IMPACT OF SCHEDULING

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