

Mephedrone

Critical Review Report

Agenda item 4.12

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Summary

Mephedrone (4-methylmethcathinone) is a synthetic cathinone. Mephedrone has never been licensed as a medicine, also no other legitimate uses are known. Although new on the market of recreational substances the history of mephedrone goes back to 1929 when its synthesis was published.

The product started its way on the market around the time when the availability of 3,4-methylenedioxymethylamphetamine decreased. Use of mephedrone was first reported around 2007 and since then increasing especially in Europe. This has led to a risk assessment by the EMCDDA in 2010 (EMCDDA, 2011). Meanwhile use/abuse has also been reported from Australia and the USA.

The effects and the mode of use reported have similarities with (meth)amphetamine, cocaine and 3,4-methylenedioxymethylamphetamine, but its potency is less than (meth)amphetamine. The overall profile shows a molecule with unique pharmacological properties. Not a new kid on the block, nevertheless the study into its pharmacology and toxicology started only recently.

Reported toxic effects of mephedrone include soar nose/nosebleeds after snorting, tachycardia, hypertension, agitation, paranoia, hallucinations and insomnia. Some of these effects leading to hospital admissions. A number of analytically confirmed drug-related deaths have been reported.

Animal studies have indicated that mephedrone possesses an abuse or dependence potential but there are no human clinical studies to support this. There are reports to suggest that some individuals with a particularly high dose and/or frequent use of mephedrone develop significant 'cravings' for it. There is one confirmed report of mephedrone dependence in a patient from Scotland.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable.

B. *Chemical Abstract Service (CAS) Registry Number*

1189805-46-6 (base)

1189726-22-4 (hydrochloride salt)

C. *Other Names*

Mephedrone, 4-methylmethcathinone, N-methylephedrone, β -keto-(4,N-dimethylamphetamine), 4,N-dimethylcathinone, p-methyl-methcathinone, 2-aminomethyl-1-tolyl-propan-1-one.

D. *Trade Names*

None.

E. *Street Names*

A number of street names for mephedrone can be found in the literature, like: bubbles, blow, Charge+, Cristal bath, Crush, Dark+, doves, kata, Fisk, Fiskrens, Flower Magic Powder, Flower Power, kati, Ketones, krabba, Kräfta, Lax, mef, Meffe, mefi, Mefko, mefo, mephisto, miaow miaow, meow meow, miaou miaou, Magic, MMC Hammer, moonshine, plant feeder, plant food, Raka, Real Euphoria, Recharge, Rocket fuel. Rush, Special Diamond, Special Gold, Special Original, Star Dust, Subcoca-1, top cat, Tornado, Torsk, Volt, White Gold, White Aroma Crystals, zsuzsi ronizio.

F. *Physical properties*

The base is a yellowish liquid at ambient temperature.

Mephedrone hydrochloride salt is a white or lightly coloured powder.

G. *WHO Review History*

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

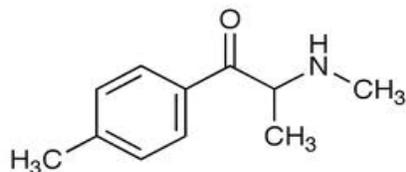
A. *Chemical Name*

IUPAC Name: (RS)-2-methylamino-1-(4-methylphenyl)propan-1-one

CA Index Name: Mephedrone

B. Chemical Structure

Free base:



Molecular Formula:	C ₁₁ H ₁₅ NO
Molecular Weight:	177.242 g/mol
Melting point:	66.61° C
Boiling point:	269.51° C

C. Stereoisomers

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

Due to the similarity with cathinone the *S* form is thought to be more potent than the *R* form.

D. Synthesis

The synthesis of mephedrone, mentioned as ‘toluyl-alpha-monomethyl-aminoethylcetone’, was first described by Saem de Burnaga Sanchez (1929). The main synthetic route involves α -bromination of 4-methylpropiophenone followed by reaction of the resulting compound (4-methyl-2-bromopropiophenone) with methylamine hydrochloride and triethylamine in an acidic scavenger to produce 4-methylmethcathinone. The reaction is then quenched with gaseous or aqueous hydrogen chloride providing the hydrochloride salt that needs to be recrystallised. The resulting product is always racemic.

There is the potential for other synthetic routes including oxidation of the substituted ephedrine analogue (4-methylephedrine) with potassium permanganate or potassium dichromate in a solution of diluted sulphuric acid. The precursor can be obtained in a specific enantiomeric form, ensuring that the synthesis is stereoselective.

Alternative synthetic methods, though more cumbersome, have been described in the literature such as the Hartung-Munch procedure.

E. Chemical description

Mephedrone (4-methylmethcathinone) is a beta-keto-amphetamine related to cathinone and methcathinone.

F. Chemical properties

The base is a yellowish liquid at ambient temperature.

Mephedrone hydrochloride salt is a white or lightly coloured powder. The powder is readily soluble in water and therefore can be dissolved prior to oral/ rectal use or injection.

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 mephedrone (Camilleri et al., 2010, Meyer et al., 2010, Gibbons and Zloh, 2010). The mass-spectrometry technique does not distinguish between the various methyl-methcathinone isomers. However, nuclear magnetic resonance spectroscopy allow the isomers to be differentiated.

Mass spectral data for mephedrone (m/z): 58 (base peak, 100 %).

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

3. Ease of convertibility into controlled substances

Mephedrone is not converted into controlled substances.

4. General pharmacology

In 2014 mephedrone will celebrate its 85th anniversary. But its pharmacology and toxicology have only recently been investigated. Mephedrone (4-methylmethcathinone) is a β -ketoamphetamine stimulant drug of abuse with structural and mechanistic similarities to methamphetamine.

4.1. Pharmacodynamics

Biochemical effects

Martínez-Clemente *et al.*, (2012) were one of the first to start investigations into the pharmacological targets of mephedrone in rats to establish the basis of the mechanism of action of this drug. They performed several *in vitro* experiments studying the effect of mephedrone on monoamine uptake and the displacement of several specific radioligands. In isolated synaptosomes from rat cortex or striatum, mephedrone inhibited the uptake of serotonin (5-HT) with an IC₅₀ value lower than that of dopamine (DA) uptake (IC₅₀=0.31±0.08 and 0.97±0.0 5µM, respectively). Moreover, mephedrone displaced competitively both [³H]paroxetine and [³H]WIN35428 binding in a concentration-dependent manner (K_i values of 17.55±0.78µM and 1.53±0.47 µM, respectively), indicating a greater affinity for DA than for 5-HT membrane transporters. The affinity profile of mephedrone for the 5-HT₂ and D₂ receptors was assessed by studying [³H]ketanserin and [³H]raclopride binding in rat membranes. Mephedrone showed a greater affinity for the 5-HT₂ than for the D₂ receptors.

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 3,4-methylenedioxymetamphetamine. 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.

Due to its numerous mechanistic overlaps with methamphetamine and the cathinone derivatives Angoa-Pérez *et al.*, (2012) decided to start a study into the neurotoxicity of mephedrone. They treated mice with a binge-like regimen of mephedrone (4 × 20 or 40 mg/kg) and examined the striatum for evidence of neurotoxicity 2 or 7 days after treatment. Although mephedrone caused hyperthermia and locomotor stimulation, it did not lower striatal levels of dopamine, tyrosine hydroxylase or the dopamine transporter under any of the treatment conditions used. Furthermore, mephedrone did not cause microglial activation in striatum nor did it increase glial fibrillary acidic protein levels. These results strongly suggest that mephedrone does not cause neurotoxicity to dopamine nerve endings of the striatum.

One of the most powerful actions associated with mephedrone is the ability to stimulate dopamine (DA) release and block its re-uptake through its interaction with the dopamine transporter (DAT). Although mephedrone does not cause toxicity to DA nerve endings, its ability to serve as a DAT blocker could provide protection against methamphetamine-induced neurotoxicity like other DAT inhibitors.

To test this possibility, Angoa-Pérez *et al.*, (2013a) treated mice with mephedrone (10, 20, or 40 mg/kg) prior to each injection of a neurotoxic regimen of methamphetamine (four injections of 2.5 or 5.0 mg/kg at 2 h intervals). The integrity of DA nerve endings of the striatum was assessed through measures of DA, DAT, and tyrosine hydroxylase levels. The moderate to severe DA toxicity associated with the different doses of methamphetamine was not prevented by any dose of mephedrone but was significantly enhanced. Mephedrone also enhanced the neurotoxic effects of amphetamine and 3,4-methylenedioxymethamphetamine on DA nerve endings. In contrast, nomifensine protected against methamphetamine-induced neurotoxicity. As mephedrone increases methamphetamine neurotoxicity, the present results suggest that it interacts with the DAT in a manner unlike that of other typical DAT inhibitors.

The effects of mephedrone on serotonin (5HT) nerve endings are not fully understood, with some investigators reporting damage while others conclude it does not. Therefore Angoa-Pérez *et al.*, (2013b) performed another study to investigate if mephedrone given alone or with methamphetamine or MDMA damages 5HT nerve endings of the hippocampus.

The status of 5HT nerve endings in the hippocampus of female C57BL mice was assessed through measures of 5HT, serotonin transporter (SERT) and tryptophan hydroxylase 2 (TPH2). Mephedrone alone did not cause persistent reductions in the

levels of 5HT, SERT or TPH2. Methamphetamine and MDMA alone caused mild reductions in 5HT but did not change SERT and TPH2 levels. Combined treatment with mephedrone and methamphetamine or MDMA did not change the status of 5HT nerve endings to an extent that was different from either drug alone. Mephedrone does not cause toxicity to 5HT nerve endings of the hippocampus. When co-administered with methamphetamine or MDMA toxicity is not increased as is the case for dopamine nerve endings when these drugs are taken together.

To summarize: mephedrone is a stimulant of dopamine release and blocks its re-uptake through an its interaction with the dopamine transporter (DAT).

Furthermore it has some affinity for various serotonin receptor subtypes. And although expected mephedrone does not have a neurotoxic effect on the dopamine or serotonin system when given alone.

Functional effects

The cardiovascular effects of mephedrone were characterized in rats by Varner et al. (2013). A group of 12 rats received radio telemetry probes which were used to measure the changes in mean arterial pressure (MAP) and heart rate (HR). Mephedrone was compared with metamphetamine. Mephedrone (0.01-9 mg/kg, i.v.) elicited increases in MAP and HR that were very similar to those elicited by methamphetamine (0.01-9 mg/kg, i.v.). The tachycardia and pressor responses to mephedrone (3 mg/kg) were blocked by the β -blocker atenolol (1 mg/kg, i.v.) and the α 1, α 2-blocker phentolamine (3 mg/kg, i.v.), respectively.

Repeated administrations of mephedrone (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 (Baumann et al., 2012).

Shortall *et al.*, (2013a) examined the acute effects of several cathinones (cathinone, methcathinone, mephedrone) on rectal and tail temperature of rats and compared it with MDMA. In individually housed rats at normal room temperature, MDMA caused sustained decreases in rectal and tail temperature. Mephedrone caused a transient decrease in rectal temperature, which was enhanced by α (1) -adrenoceptor and dopamine D(1) receptor blockade, and a prolonged decrease in tail temperature. Cathinone and methcathinone caused sustained increases in rectal temperature.

To summarize: mephedrone has a pharmacological profile comparable to the other amphetamine type stimulants but milder.

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. Mephedrone-induced hyperlocomotion was dependent on endogenous 5-HT.

In this study mephedrone was found to be the cathinone derivative with highest affinity for vesicular monoamine transporter-2 causing the inhibition of dopamine uptake. The affinity of these three cathinones for 5-HT(2A) receptors was similar to

that of MDMA. Vesicular content played a key role in the effect of mephedrone, especially for 5-HT uptake inhibition. The potency of mephedrone in inhibiting noradrenaline uptake suggests a sympathetic effect of this substance.

Den Hollander *et al.*, (2013) treated mice with a binge-like regimen of mephedrone (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. Mephedrone reduced working memory performance in the T-maze spontaneous alternation task.

Shortall *et al.*, (2013b) studied the behavioral effects of mephedrone in rats. Young-adult male Lister hooded rats received i.p. cathinone (1 or 4 mg/kg), mephedrone (1, 4 or 10mg/kg) or MDMA (10mg/kg) on two consecutive days weekly for 3 weeks. Locomotor activity (LMA), novel object discrimination (NOD) and conditioned emotional response (CER) were measured following intermittent drug administration. Cathinone (1, 4 mg/kg), mephedrone (10mg/kg) and MDMA (10mg/kg) induced hyperactivity following the first and sixth injections and sensitization to cathinone and mephedrone occurred with chronic dosing. All drugs used impaired NOD and mephedrone (10mg/kg) reduced freezing in response to contextual re-exposure during the CER retention trial. At the doses examined, mephedrone, cathinone, and MDMA induced similar effects on behaviour and failed to induce neurotoxic damage when administered intermittently over 3 weeks.

Huang *et al.*, (2012) compared the relative locomotor stimulant effects of mephedrone (MMC) (1-10 mg/kg, s.c.) and 3,4-methylenedioxy pyrovalerone MDPV (0.5-5.6 mg/kg, s.c.) with d-methamphetamine (MA; 0.5-5.6 mg/kg, s.c.) and 3,4-methylenedioxy methamphetamine (MDMA) (1-7.5 mg/kg, s.c.). They used locomotor activity (voluntary wheel running) as a model. The study was performed with a group of eight male Wistar rats. Compared to counts of wheel rotations after saline, a biphasic change in the pattern of counts was observed after injections of MA and MDPV, with relatively higher counts following lower doses and lower counts following the highest dose. However, monophasic, dose-dependent reductions in counts were observed in response to injections of MDMA and 4-MMC. Thus, voluntary wheel running yielded the same categorical distinctions for these drugs as did prior experiments testing the effects of these drugs on monoaminergic neurotransmission.

Gregg *et al.*, (2013) tested the hypothesis that prior mephedrone (MEPH) exposure enhances the locomotor-stimulant effects of cocaine and methamphetamine (METH) in rats. For cocaine experiments, rats were pretreated with saline, cocaine (15 mg/kg), or MEPH (15 mg/kg) for 5 days and then injected with cocaine after 10 days of drug absence. For METH experiments, rats were pretreated with saline, METH (2 mg/kg), or MEPH (15 mg/kg) and then injected with METH after 10 days of drug absence. Cocaine challenge produced greater locomotor activity after pretreatment with cocaine or MEPH than after pretreatment with saline. METH challenge produced greater locomotor activity after METH pretreatment than after saline pretreatment; however, locomotor activity in rats pretreated with MEPH or saline and then challenged with METH was not significantly different. The locomotor response to MEPH (15 mg/kg) was not significantly affected by pretreatment with cocaine (15 mg/kg) or METH (0.5, 2 mg/kg). The present findings that cocaine-induced locomotor activation is enhanced by prior MEPH exposure suggests that MEPH cross-sensitizes to cocaine and

increases cocaine efficacy. Interestingly, MEPH cross-sensitization was not bidirectional and did not extend to METH, suggesting that the phenomenon is sensitive to specific psychostimulants.

After intranasal mephedrone use humans have reported psychomotor speed improvement suggestive of classic stimulant properties. Limitations of the user group (which was impaired on some tasks) prompted Wright et al. (2012) to perform a controlled laboratory investigation. They trained adult male rhesus monkeys to perform tasks from the non-human primate Cambridge Neuropsychological Test Automated Battery, which assess spatial working memory, visuospatial associative memory, learning. Also a test of bimanual motor coordination and manual tracking were included. The subjects were challenged with 0.178-0.56 mg·kg(-1) mephedrone and 0.056-0.56 mg·kg(-1) d-methamphetamine, i.m. A pronounced improvement in visuospatial memory and learning was observed after the 0.32 mg·kg(-1) dose of each compound, this effect was confirmed with subsequent repetition of these conditions. Spatial working memory was not improved by either drug, and the progressive ratio, bimanual motor and rotating turntable tasks were all disrupted in a dose-dependent manner.

To summarize: mephedrone has a behavioral profile comparable to other amphetamine type stimulants but with some distinct differences.

Effects on cognition and behavior in humans

Herzig *et al.*, (2013) investigated the acute and chronic effects of mephedrone consumption on drug-sensitive cognitive measures. Volunteers from the general population (n=26) performed several tasks measuring verbal learning, verbal fluency and cognitive flexibility. Measuring was done before and after a potential drug-taking situation (pre-clubbing and post-clubbing at dance clubs, respectively). The participants also provided information on chronic and recent drug use, schizotypal (Oxford-Liverpool Inventory of Feelings and Experiences) and depressive symptoms (Beck Depression Inventory). Mephedrone users performed worse than non-users pre-clubbing and deteriorated from the pre-clubbing to the post-clubbing assessment. Post-clubbing depression scores predicted relative cognitive attenuations. And schizotypy was largely unrelated to cognitive functioning, apart from a negative relationship between cognitive disorganisation and verbal fluency. Results suggest that polydrug use and depressive symptoms in the general population negatively affect cognition.

Another study in humans by Freeman *et al.*, (2012) aimed to assess the acute cognitive and subjective effects of mephedrone use.

A mixed within- and between-subjects design compared 20 mephedrone users with 20 controls twice. The mephedrone users first while intoxicated (T1) and secondly drug free (T2); and the controls twice when drug free (T1 and T2). All were healthy adults recruited from the community and place of study was participants' own homes. Subjective effects, episodic and working memory, phonological and semantic fluency, psychomotor speed and executive control at were assessed at T1 and T2. Trait schizotypy, depression and changes in mephedrone use since the ban were indexed at T2 only. Compared with controls, mephedrone users had generally impaired prose recall (P = 0.037) and higher scores in schizotypy (P < 0.001) and depression (P = 0.01). Mephedrone acutely primed a marked 'wanting' for the drug (P < 0.001), induced stimulant-like effects, impaired working memory (P < 0.001) and enhanced

psychomotor speed ($P = 0.024$). Impulsivity in mephedrone users correlated with the number of hours in an average (nearly 8 hour) mephedrone session ($r = 0.6$). Mephedrone impairs working memory acutely, induces stimulant-like effects in users and is associated with binge use.

4.2. Routes of administration and dosage

Mephedrone is used by the oral route, nasal insufflation, intramuscular injection, intravenous injection and rectal insertion. And there are numerous reports of individuals using mixed routes during a single session (oral and nasal, oral and rectal) (EMCDDA, 2011).

The predominant routes are oral ingestion and nasal insufflation. According to the MixMag survey, 70 % of users use mephedrone by nasal insufflation and 30 % by oral ingestion (Dick and Torrance, 2010).

Swallowing took one of two forms: 'bombing' (wrapping a dose of powder in a paper wrap (Measham et al., 2010)) or drinking (mixing the powder into a beverage, and drinking it quickly). Mephedrone powder is usually sniffed or swallowed. Sniffing mainly took the forms of 'keying it': sticking a key into the bag of powder, piling up some powder on the thin end of the key, and then holding the key under a nostril and sniffing vigorously. Many users reported switching from sniffing to swallowing mephedrone, mainly because of its painful effects on the nasal membranes.

4.3. Pharmacokinetics

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

Mephedrone was administered to male Sprague-Dawley rats intravenously (10 mg/kg) and orally (30 and 60 mg/kg). Plasma concentrations and metabolites were characterized using 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 concentrations were achieved between 0.5 and 1 h and declined to undetectable levels at 9 h. The absolute bioavailability of mephedrone was about 10% and the percentage of mephedrone protein binding was $21.59 \pm 3.67\%$. They identified five phase I metabolites in rat blood after oral administration. The relationship between brain levels and free plasma concentration was 1.85 ± 0.08 . Mephedrone induced a dose-dependent increase in locomotor activity, which lasted up to 2 h. The pharmacokinetic-pharmacodynamic model successfully describes the relationship between mephedrone plasma concentrations and its psychostimulant effect.

Metabolites of mephedrone have been described earlier by Meyer et al. (2010). They administered a single 20 mg/kg dose of mephedrone by gastric intubation to rats and collected the urine over a 24-hour period after administration. Besides mephedrone, the following metabolites were detected: nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone.

In addition a urine sample submitted by a mephedrone user was analysed, and a further metabolite, 4-carboxy-dihydro mephedrone was also detected.

The following overlapping metabolic pathways were postulated:

- N-demethylation to the primary amine (metabolites nor-mephedrone, nor-dihydro mephedrone and nor-hydroxytolyl mephedrone);
- reduction of the keto moiety to the respective alcohol (metabolites nor-dihydro mephedrone and 4-carboxy-dihydro mephedrone);
- oxidation of the tolyl moiety to the corresponding alcohol (metabolites hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone).

It is thought that the hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone metabolites are partly excreted as glucuronides and sulphates.

Pedersen *et al.*, (2013) showed that cytochrome P450 2D6 (CYP2D6) was the main responsible enzyme for the in vitro Phase I metabolism of mephedrone, with some minor contribution from other NADPH-dependent enzymes.

In addition they did forensic casework on four traffic cases in which mephedrone was detected. They identified hydroxytolyl-mephedrone and nor-mephedrone, as well as 4-carboxy-dihydro-mephedrone. Also two new metabolites were identified, dihydro-mephedrone and 4-carboxy-mephedrone.

Other forensic casework has been performed by Cosbey *et al.* (2013). Analysis of blood samples for mephedrone was conducted by liquid chromatography-mass spectrometry. Mephedrone was detected in a total of 12 fatal cases. Most of these cases involved death by mechanical means; however in two cases, death was attributed directly to mephedrone intoxication (blood concentrations of 2.1 and 1.94 mg/L). In 32 impaired driving cases mephedrone was detected. Blood concentrations ranged up to 0.74 mg/L (mean 0.21, median 0.10).

Although not common, mephedrone may also be ingested by vaporization/inhalation. Therefor Kavanagh *et al.*, (2013) examined the pyrolysis products produced by heating mephedrone under simulated 'meth pipe' conditions. Thirteen pyrolysis products were identified. The major ones being iso-mephedrone, 4-methylpropiofenone, 4-methylphenylacetone, two pyrazine derivatives (formed by dimerization of mephedrone), N-methylated mephedrone (N,N,4-trimethylcathinone), two hydroxylated oxidation products and a diketone. Other minor products formed were identified as 4-methylacetophenone, two α -chloro ketones and N-methylated iso-mephedrone.

The results of this study clearly show that one should not only look for known metabolites when screening for the use of abused substances but also for other products that might have been formed during (co)administration.

Mephedrone is reported to be used in single doses that vary from 15 to 250 mg for oral ingestion and 5 to 125 mg for nasal insufflation, although due to short-lived effects the total doses used per session may be greater, possibly between 0.5–2 g. Onset of desired effects is typically seen within 15–45 minutes of oral ingestion. There are some reports of slower onset of action when mephedrone is taken orally on a full stomach. After nasal insufflation onset is reported by users to be within a few minutes and with peak desired effects within 30 minutes. Users report that the desired effects

last approximately 2–3 hours and therefore that they may consume multiple doses during a session to prolong the duration of the desired effects.

Reports from intravenous mephedrone users suggest that the high lasts approximately 10–15 minutes with an overall duration of desired effects of approximately 30 minutes (EMCDDA, 2011).

5. Toxicology

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

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 (James et al. 2011).

The following adverse events of mephedrone use have been mentioned:

Cardiovascular System:

Palpitations, tachycardia, arrhythmias;
Hypertension;
Hot flushes.

Central Nervous System, neurological symptoms:

Headaches, light-headedness, dizziness;
Tremors, convulsions;
Loss of concentration, and memory loss.

Central Nervous System, psychiatric symptoms:

Agitation, aggression;
Paranoia, hallucinations;
Insomnia, nightmares;
Anxiety, dysphoria, (post-use) depression;
Craving, addiction, dependence.

Central Nervous System, miscellaneous symptoms:

Increased or decrease in mean body temperature;
Dilated pupils, blurred vision.
Fatigue, loss of appetite.

Gastro-intestinal system:

Sore mouth/throat;
Abdominal pain;
Nausea, vomiting.

Musculoskeletal system:

Bruxism (teeth grinding);
Painful joints.

Respiratory system:

Chest pain, respiratory difficulties.

Skin:

Skin rash, sweating.

Discoloration of extremities/joints.

In addition, nasal insufflation of mephedrone is reported to be associated with significant nasal irritation and pain which has led to some users switching to oral use of mephedrone.

Serious adverse events

The pharmacological and toxicological profile of mephedrone is quite similar to that of other stimulant drugs of abuse like amphetamines, cathinones and cocaine.

But besides the expected adverse events also some other quite unexpected ones have been presented in publications.

To give an overview: reversible dilated cardiomyopathy (Sivagnanam et al., 2013), methaemoglobinaemia (Ahmed et al. 2010), pneumomediastinum (McCullough et al., 2013), acute kidney injury (Rhidian and Babu, 2013), urinary retention (Conway et al., 2013), subcutaneous emphysema (Maan and D'Souza 2012), posterior reversible encephalopathy syndrome (Omer and Doherty 2011).

Non-fatal intoxications

Wood *et al.* (2010) were the first to describe a series of seven analytically confirmed mephedrone-related acute intoxications. The presented cases had clinical signs of toxicity consistent with an acute sympathomimetic toxidrome (e.g. hypertension, tachycardia and agitation). These findings are similar to the pattern of toxicity seen with other sympathomimetic recreational drugs such as 3,4-Methylenedioxymethamphetamine (MDMA) and cocaine. Acute mephedrone-related toxicity was analytically confirmed in seven male patients; the mean \pm SD age was 24.6 ± 6.5 years (range 16-36 years). Agitation (4 patients) was the most common sign reported; other common symptoms included: palpitations (2 patients); chest pain (2 patients); self-limiting pre-hospital seizures (one patient) and headaches (one patient). The mean heart rate was 109.1 ± 21.8 (range 80-140) beats per minute. The mean systolic blood pressure was 153.0 ± 39.6 (range 110-210) mmHg.

Garrett and Sweeney (2010) describe a male patient with a clinical picture resembling a serotonin syndrome. The patient had tachycardia, diaphoresis, hypertonia, hyper-reflexia and clonus. Later on he became hyperthermic.

Fatal intoxications

The first death solely related to mephedrone was from Sweden (Gustavsson and Escher, 2009). This was an 18-year old female with a reported use of mephedrone and cannabis. She had an out of hospital cardio-respiratory arrest and was resuscitated in the emergency department. 36 hours later she was declared brain-dead. Toxicological screening of blood and urine revealed the presence of mephedrone only (unfortunately the mephedrone concentration was not reported), with no other drugs or alcohol detected.

Since that time a number of fatal intoxications with mephedrone have been published. For instance in the USA (Dickson *et al.*, 2010), The Netherlands (Lusthof *et al.*, 2011), Italy (Aromatario *et al.*, 2012), and Poland (Adamowicz *et al.*, 2013).

The most extensive series has been reported by Schifano *et al.*, (2012) from the UK. This series is based on information from the UK National Programme on Substance Abuse Deaths database. This database receives information from coroners on drug-related deaths among both addicts and nonaddicts in the United Kingdom, the Channel Islands, and the Isle of Man. The average annual response rate is 95%. The period of reporting is September 2009-October 2011.

An in-depth analysis of this series revealed the following.

In total 128 alleged mephedrone-associated fatalities have been reported. Mephedrone was identified at postmortem in 90 cases; 62 of which were analyzed.

Typical mephedrone victims were young (mean age, 28.8 years), male, and with a previous history of drug misuse.

Mephedrone alone was identified at postmortem on 8 occasions. In the other cases mephedrone has been found in combination with one or more other substances, for instance, alcohol (n=26), stimulants (n=22), hypnotics/tranquillizers (n=22) other new psychoactive substances (piperazines, other cathinones, n=26).

Circumstances of death were: acute drug toxicity (n=26), self-inflicting harm (n=18. Remarkable is the fact that in 11 cases the victims were found hanging), at-risk behavior, for instance driving under the influence, (n=6).

7. Dependence potential

Due to the resemblance of mephedrone with metamphetamine Motbey *et al.* (2013) decided to compare the characteristics of intravenous mephedrone self-administration in the rat. Intravenous self-administration is one of the established models to show dependence or abuse liability.

Methamphetamine was used as an active comparator. Male Sprague-Dawley rats were trained to nose poke for intravenous mephedrone or metamphetamine in daily 2 h sessions over a 10 d acquisition period. Dose-response functions were then established under fixed- and progressive-ratio (FR and PR) schedules over three subsequent weeks of testing. Results showed that mephedrone was readily and vigorously self-administered via the intravenous route. Under a FR1 schedule, peak responding for mephedrone was obtained at 0.1 mg/kg/infusion, versus 0.01 mg/kg/infusion for metamphetamine. Break points under a PR schedule peaked at 1 mg/kg/infusion mephedrone versus 0.3 mg/kg/infusion for methamphetamine. Final intakes of mephedrone were 31.3 mg/kg/d compared to 4 mg/kg/d for metamphetamine.

Two remarks should be made. Nose-poke based paradigms show higher levels of responding than lever press studies. And methamphetamine in this study showed weaker responses than usual. The low training dose might be the reason.

They concluded that mephedrone supported high levels of self-administration, matching or exceeding those previously reported with other drugs of abuse.

A similar kind of study was performed by Aarde *et al.* (2013), but they used the lever press model. Groups of male Wistar and Sprague-Dawley rats were prepared with intravenous catheters and trained to self-administer mephedrone in 1-hour sessions. Per-infusion doses of 0.5 and 1.0 mg/kg were consistently self-administered, resulting in greater than 80% discrimination for the drug-paired lever and mean intakes of about 2-3 mg/kg/hour. Dose-substitution studies after acquisition demonstrated that the number of responses and/or the total amount of drug self-administered varied as a function of dose. Their study confirmed the findings of Motbey *et al.*. In this traditional pre-clinical self-administration model mephedrone clearly shows evidence of stimulant-typical abuse liability.

Bajaj *et al.* (2010) presented a case of dependence and psychosis in a patient using mephedrone. The patient needed inpatient hospital care, was treated with olanzapine and recovered well.

Addiction/dependence symptoms were reported by 17.6 % of 205 mephedrone users in a Scottish survey of school and college/university students (Dargan *et al.*, 2010).

User reports suggest that some individuals with high/frequent use of mephedrone develop a 'craving' for it (Measham *et al.*, 2010); this could be due to the high associated with its use and its relatively short duration of action. A report from Slovenia suggests that many of the users consider craving to be the main problem associated with mephedrone use. Users in this survey compared their experience with cocaine, methamphetamine and speed and stated that they had not experienced similar craving with these drugs.

These reports of mephedrone 'dependence' suggest that it is associated with psychological rather than physical dependency similar to other stimulant drugs, such as MDMA and cocaine.

8. Abuse potential

Hadlock *et al.* (2011) studied the effects of repeated mephedrone injections (4× 10 or 25 mg/kg s.c. per injection, 2-h intervals, administered in a pattern used frequently to mimic psychostimulant "binge" treatment). This results in a rapid decrease in striatal dopamine and hippocampal serotonin transporter function. Mephedrone also inhibited both synaptosomal dopamine and serotonin uptake.

The results were similar to the results found after methylenedioxymethamphetamine, methamphetamine or methcathinone administration.

Like methylenedioxymethamphetamine, but unlike methamphetamine or methcathinone, repeated mephedrone administrations also caused persistent serotonergic, but not dopaminergic, deficits. However, mephedrone caused DA release from a striatal suspension approaching that of methamphetamine and was self-administered by rodents.

Intracranial self-stimulation (ICSS) measures the behavioral effects of neuroactive compounds on brain reward circuitry.

Robinson *et al.* (2012) investigated the ability of mephedrone and cocaine to alter responding for electrical stimulation of the medial forebrain bundle in C57BL/6J mice. Adult male mice (n=6) implanted with unipolar stimulating electrodes at the level of the lateral hypothalamus responded for varying frequencies of brain stimulation reward (BSR). The frequency that supported half maximal responding (EF50), the BSR threshold ($\theta(0)$), and the maximum response rate were determined before and after intraperitoneal administration of saline, mephedrone (1.0, 3.0, or 10.0 mg/kg), or cocaine (1.0, 3.0, or 10.0 mg/kg). Mephedrone dose-dependently decreased EF50 (max. effect=72.3% of baseline), $\theta(0)$ (max. effect=59.6% of baseline), and the maximum response rate (max. effect=67.0% of baseline) beginning 15 min after administration. Beginning immediately after administration, cocaine dose-dependently lowered EF50 (max. effect=66.4% of baseline) and $\theta(0)$ (max. effect=60.1% of baseline) but did not affect maximum response rate.

Bonano *et al.* (2014) examined the behavioral effects of (\pm)-methcathinone, (\pm)-3,4-methylenedioxyvalerone (MDPV), (\pm)-3,4-methylenedioxymethcathinone (methylone), and (\pm)-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. Methcathinone produced dose- and time-dependent facilitation of ICSS. 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.

Lisek *et al.* (2012) used motor activity and conditioned place preference (CPP) assays to investigate behavioral effects of mephedrone. Acute mephedrone (3, 5, 10, 30 mg/kg, ip) administration increased ambulatory activity in rats. Mephedrone (5 mg/kg, ip)-induced ambulation was inhibited by pretreatment with a dopamine D1 receptor antagonist (SCH 23390) (0.5, 1, 2 mg/kg, ip) and enhanced by pretreatment with a dopamine D2 receptor antagonist (sulpiride) (2 mg/kg, ip). Rats injected for 5 days with low dose mephedrone (0.5 mg/kg, ip) and then challenged with mephedrone (0.5 mg/kg, ip) following 10 days of abstinence displayed sensitization of ambulatory activity. In CPP experiments, mephedrone (30 mg/kg, ip) conditioning elicited a preference shift in both rats and mice.

Taken together the data show that mephedrone has a unique pharmacological profile with abuse liability. However, efficacies of compounds varied, with mephedrone displaying the lowest efficacy to facilitate ICSS.

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

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

11. Marketing authorizations (as a medicine)

Mephedrone has never been marketed as a medicinal product.

12. Industrial use

Mephedrone has no industrial use.

13. Non-medical use, abuse and dependence

The information in this paragraph is a compilation of the EMCDDA report on Mephedrone (2011) and some additional papers.

Mephedrone consumption has been identified in a range of sub-populations. In addition to psychonauts (UK), mephedrone use has been identified in clubbing and party milieu (France, UK, Netherlands, Slovenia), amongst school pupils (UK) and gay men (France).

Mephedrone users are reported to be primarily male and aged between their late teens and late-20s. The majority are recreational polydrug users, with alcohol, cannabis and often cocaine, amphetamine and ecstasy in their drug using repertoire.

A typical mephedrone session

Intranasal use is by far the most used route of administration with doses being administered every 30–60 minutes over the course of a session (typically 8–12 hours in length) which may last several days in the case of some users! Although the average consumption over a session is approximately 1 g, there are sub-groups of heavier users who report consuming far more (maximum reported session was 16 g).

On average, participants reported having been using for 6.1 months (SD = 3.1). All participants reported using with others (a mean of 10 (SD = 7.9) other users). 83 % administer the first dose of a session as a line of the drug, through the intranasal route (79.0%), 9.9% reporting bombing and 11.1 % put it in a drink. The first administered dose was estimated to be around 125 mg. Over the course of a mean typical session (lasting 13.9 hours (SD = 16.59)) an average of 1.09 g was consumed, though the range was huge (100–9000 mg). During a typical session quite a number of other psychoactive substances were used, like drinking alcohol (82 %), cannabis (36%), ketamine (35%), cocaine (26%), ecstasy (23%) GBL (2%) and amphetamine (1%).

Participants estimated that the total amount used in their heaviest session ranged from 100 mg–16 g (median = 1.5 g; mode = 1 g). The estimated duration of a maximum session varied widely between 1–192 hours with a median/mode of 12 hours. 47 % reported that they had used for more than two days in a row, a median of three days consecutive use was reported.

The reasons for continuing to use mephedrone included pleasure (wanting to repeat a desirable fun experience) and developing a habit (craving and dependence). Many participants stated that when they first tried mephedrone it was effective in fairly small doses, equivalent to about 50 to 75 mg. But with regular use, even within the first session, the amounts used soon escalated. All participants began as experimental occasional users of mephedrone, but most had quickly progressed to regular recreational use, with weekend use being the norm. Two persons reported that they had been using on a near daily basis for the past six weeks. Though most participants had become regular users of mephedrone, none explicitly indicated that they felt dependent on it or that they had become daily users. Even so, though withdrawal symptoms were not reported, craving and tolerance were clearly evident in the experiences of most participants. Craving is considered to be the main problem with mephedrone. Even the users with a lot of experience with other substances (cocaine, methamphetamine, speed, etc.) emphasised that they have never experienced such craving with any other substances and that craving was the main reason they used more mephedrone than they planned.

Of particular interest is the data collected on mephedrone related problems and dependence. The findings suggest that the drug has a high abuse liability with over 30 % of the sample reporting three or more DSM criteria of dependence and being classified as dependent. Tolerance, loss of control, a strong urge to use and using despite problems, predominate. The findings are consistent with the high abuse liability reported in the Mixmag survey (Winstock, 2010, Winstock et al., 2011).

Van Hout and Bingham (2012) describe the abuse potential of mephedrone when used by intravenous injection. Participants were aware of risks and safe injecting practises, but compulsive re-injecting with excessive binge use over long periods of time was common. Intense paranoia, violent behaviour and aggression and emergence of Parkinson type symptomatology were reported. Multi and serial drug injecting with heroin was used in efforts to manage the intense rush and avoid unpleasant comedown.

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 (methyline 40.1%, mephedrone 35.2%). The most frequent combination of RC with other illegal drugs was with cannabis (68.6%). There is a specific RC user profile with extensive knowledge and consumption of substances, using different strategies to reduce risks associated to its consumption.

Kelly et al. (2013) report on the results of a field-based survey of 1740 patrons at nightlife venues in New York City. Only 1.1% reported the use of mephedrone, while 8.2% reported use of synthetic cannabinoids. Gay and bisexual men reported higher prevalence of mephedrone use. Latinos reported higher prevalence of synthetic cannabinoid use. The findings suggest that the use of mephedrone among adults in US

nightlife scenes remains relatively low in comparison with European nightlife scenes, and is low relative to other drug use among young people within these scenes.

Legislative changes declined the use of mephedrone due to closure of headshops, increased street prices and concerns around contamination. But a more serious problem due to regulation of psychoactive substances is the emergence of new street stimulant drugs often with less information available on pharmacology and toxicology.

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

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

The information in this paragraph is a compilation of the EMCDDA report on Mephedrone (2011) and some additional papers.

Due to the absence of epidemiological data on prevalence, user self-reports place lifetime use of mephedrone at around 40 % amongst UK clubbers (33 % last month use), (20 % amongst Scottish students) and 40 % amongst the Northern Irish schoolchildren attending focus groups. French TREND reports describe use as restricted to a small, primarily Parisian milieu.

UK (focus group Middlesbrough)

In Middlesbrough a focus group was asked about how common mephedrone use was. The clear consensus was that ‘everyone is doing it’, presumably meaning most or all of the local recreational drug users and/or clubbers. Many participants reported switching from sniffing to swallowing mephedrone, mainly because of its painful effects on the nasal membranes.

In addition, some participants reported having friends and associates who had become daily users. The most common drugs used in the same session as mephedrone were alcohol and skunk-cannabis.

UK (survey Scotland)

In a survey of over 1000 school and college/university students in Scotland 20.3 % of those surveyed had used mephedrone on at least one occasion (Dargan et al., 2010). Of these, 23.4 % reported that they had used mephedrone on one occasion only; however, 4.4 % reported use on a daily basis (particularly in those aged under 21 years of age).

UK (online survey)

Winstock et al. (2011) report on an online survey. About 600 persons gave contact details. The current sample (>200 individuals) was drawn from members of this group, who were identified as ever having used mephedrone and who had provided their mobile telephone numbers.

A total of 100 participants completed the questionnaire. Their lifetime use of other stimulants was very high, with 96 % ever having used ecstasy and 92 % cocaine.

Participants were asked about the frequency and intensity of 28 typical stimulant and empathogen drug effects (both positive and negative and physical and psychological). Mephedrone's predominant effect profile is that of a typical stimulant drug with evidence of frequent sympathomimetic physical effects. The drug also appears to have a quite marked pro-social profile with relatively infrequent adverse psychological effects.

Participants were asked about how they felt during the next day or two after a session by indicating how frequently each of a number of typical stimulant withdrawal symptoms were experienced and their intensity.

Participants were also asked to rate each of the three drugs (mephedrone, cocaine and ecstasy) across a range of broad descriptors; the 'pleasurable high' of the drug, the 'negative effects of the drug when high', the 'strength of effect' and the 'urge to want more of the drug when using'. Mephedrone scored very high in most of the subjective effects.

The major findings are that mephedrone has an effect profile that is more similar to ecstasy than cocaine except for its shorter duration of action and its urge to use which is more similar to cocaine. 30% of the sample group potentially met criteria for DSM-IV dependence and there was evidence of a strong compulsion to use the drug.

France

In the second half of 2009 ethnographic reports of mephedrone came in from the Parisian gay milieu, where it was being used as an alternative to other psychotropics for its ecstasy-like effects. Information was collected from seven users presenting mephedrone powder for testing. Three users presented the powder as MDMA, two as amphetamine, one as 'MPK' and only one as mephedrone. All users were aged between 25 and 30 and all described the drug's effects as ecstasy-like or amphetamine-like. In terms of route of use, four users sniffed the drug and three swallowed. Quantities presented varied between 0.1 g and 0.25 g. The mephedrone was taken in combination with alcohol (7 cases), cannabis (7 cases), cocaine (3 cases) and heroin (1 case).

Netherlands

Information was gathered on the acute subjective effects of mephedrone from interviews with 70 regular drug consumers in the second half of 2009.

60 users indicated that they anticipated effects of ecstasy, the rest were already acquainted with mephedrone. The most frequently reported emotional effects were euphoria, improved mood and craving (often reported as 'redosing' after a short period) and the most frequently described somatic effects were increased energy and accelerated heartbeat.

Remarkable in all studies is that there is quite a high percentage of concomitant use of other psychoactive substances, including ethanol. That makes it difficult to assess the potential risks of mephedrone as such.

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

15. Licit production, consumption and international trade

There are no known uses of mephedrone as a research, industrial, agricultural or cosmetic compound, despite it being marketed as 'plant feeder', 'bath salts' or 'research chemical'.

Refer also 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

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Annex 1:**Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Mephedrone**

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 mephedrone; 4-methylmethcathinone (4-MMC). Of these, only 34 respondents (AMR 5, EMR 1, EUR 23, SEAR 1, WPR 4) had information on this substance.

LEGITIMATE USE

None reported that mephedrone 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 use stated for animal/veterinary care

HARMFUL USE

Twenty-one respondents confirmed that there was recreational/harmful use of mephedrone; common routes of administration were stated as oral/ inhaling/sniffing by 7, oral by 4, inhaling/sniffing by 4, injection/ inhaling/sniffing by 2, and oral/ injecting, inhaling/sniffing by 2. Thirteen respondents stated that this is obtained via trafficking, 3 via diversion plus trafficking, and 1 each via clandestine manufacturing and trafficking plus clandestine manufacturing. Seventeen respondents reported on the common formulations of mephedrone available with 8 reporting powder, 7 reporting powder/tablet and one each liquid and tablet forms. When asked if mephedrone was used by any special populations 2 respondents stated that it was used by the general population and in clubs, 3 only in clubs and 3 only in the general population. Two respondents report overdose deaths in 2012, one and 32 deaths respectively, the latter including deaths due to all cathinones. Two respondents report emergency room visits of one and two respectively for 2012. In addition, one provided emergency room visits data for 2012 and 2013 as 6 and 10 respectively. Nine respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by mephedrone. These included nasal irritation secondary to insufflation, pupil dilation, sweating and chills, hyperthermia, palpitations, tachycardia, hypertension, impaired memory, restlessness, insomnia, trismus and bruxism, light headedness, agitation, spasm, tremor, seizures, coma, blurred vision, hallucinations, psychosis, rhabdomyolysis, hyponatraemia and vomiting. Reports also suggest potential for dependence such as desire to redose. Reports also indicate that criminal groups are involved in the supply of mephedrone.

Additional information include 'a survey of college students in 2012 by the Monitoring the Future (MTF) showed that 0.2% of full-time college students used synthetic cathinone substances. The use of synthetic cathinone substances among 8th, 10th, and 12th grade students and young adults (non-college peers aged 19 to 28-years-old) was 0.8%, 0.6%, 1.3%, and 0.8%, respectively. According to a press release from the American Association of Poison Control Centers (AAPCC), there were 306 exposure calls related to synthetic cathinones in 2010, 6,137 calls in 2011, and 2,691 calls in 2012. According to the 2010 annual report of the American Association of Poison Control Centers, (AAPC) "bath salts" are an emerging drug

of concern, with the Center receiving a peak of approximately 40 calls per day between April and July 2011 (Bronstein et al. 2011). Another AAPC update reported receiving 6,138 calls related to “bath salts” in 2011 (AAPC 2012). It is unknown whether these calls were due to mephedrone specifically, although mephedrone has been positively identified in over-the-counter samples of “bath salts”. The majority of reports documenting behavioral effects and overdose with mephedrone or its analogues are case reports and media reports. These reports describe a wide variety of adverse effects typical of stimulant-like drugs (MMWR 2011) including hallucinations (Penders and Gestring 2011), paranoid psychosis (Antonowicz et al. 2011), delirium (Kasick et al. 2012), and death (Murray et al. 2012). Some of these case reports are based upon the consumption of “bath salts” so a direct link to mephedrone cannot be made. However, mephedrone has been confirmed in biological samples obtained from patients hospitalized after ingesting bath salts (Dickson et al. 2010;Lusthof et al. 2011;Maskell et al. 2011;Torrance and Cooper 2010;Wood et al. 2010a;Wood et al. 2010b).’

‘Kapitány-Fövény et al. (2012) carried out a survey among 135 mephedrone users in 2011. The questionnaire addressed the general characteristics of substance use, the circumstances of the first use and the current use of mephedrone. Typically the first use of mephedrone took place in recreational setting, at places of entertainment or in discos (56.3%), most typically jointly with one or more friends (91.9%). The substance was typically obtained from a close friend (48.9%) or acquaintance (34.1%), only a few respondents mentioned a person they did not know (8.9%) or the internet (5.2%) as their source. The route of administration was sniffing in the case of a significant proportion of the respondents 38 (85.2%) besides oral administration (34.8%). Injecting use was mentioned by 12.3% of the respondents, i.e. 17 persons, 11 of whom said that injecting use was their only route of administration. Other drugs used besides mephedrone were typically cannabis and amphetamines, opiate use was not typical. The most common answers relating to the cause of drug use included experiencing an altered state of consciousness (57.2%) and relaxation and recreation (41.2%). The most typical answers describing the effect of the substances mentioned pleasant mood (80.3%), light-heartedness (68.3%) and euphoria (68.2%). Two negative effects were mentioned, such as lack of appetite (58.6%) and troubled sleep, insomnia (50.7%). 75.4% of the respondents answered yes to the question whether mephedrone use caused dependence.’

CONTROL

Of those with information on this substance 32 reported that mephedrone was controlled under legislation that was intended to regulate its availability; 28 under “controlled substance act”, 1 under “medicines law” and 2 under “other” legislations. Only 5 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving mephedrone, two respondents reported clandestine manufacture and one the synthesis of the product itself. Five respondents reported processing into the consumer product, 16 reported trafficking, three reported diversion and 13 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	547 (12)	227 (14)
Total quantity seized (kg)	292.02 (12)	308.56 (13)
Total quantity seized (L)	4,051 (1)	2,855 (1)
Total quantity seized (tablets/pills)	8,755 (6)	716 (4)

Others seized	wraps, pieces, bags	wraps, pieces, bags
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IMPACT OF SCHEDULING

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