

Methiopropamine (MPA)
Critical Review Report
Agenda Item 4.8

Expert Committee on Drug Dependence
Thirty-eighth Meeting
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**World Health
Organization**

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Summary

Methiopropamine was first synthesized in 1942 but within the last 5 years has appeared on drug websites selling “research chemicals” or branded products, predominantly in powder form. Methiopropamine is a methamphetamine analogue in which the benzene ring has been replaced with a thiophene ring and is described to have similar effects to amphetamine and methamphetamine mediated through noradrenergic and dopaminergic neurotransmitter systems. Methiopropamine has no known or recorded therapeutic use, it is being used and abused for non-medical purposes. Effects following use include stimulation, euphoria, alertness and increase of focus and energy as well as talkativeness. Reported adverse effects (including intoxication) include chest pain/tightening, tachycardia, anxiety, panic attacks, perspiration, headache, nausea, difficulty in breathing, vomiting, difficulty urinating and sexual dysfunction. Auditory and visual hallucinations have also been described. Subsequent to the previous review of methiopropamine by the ECDD at its 36th Meeting, further instances of non-fatal and fatal intoxications have now been reported, few only involving methiopropamine but others where methiopropamine likely contributed to toxicity. Extrapolated animal studies have indicated both an abuse and dependence potential for methiopropamine but no human study data are available.

1. Substance identification**A. International Nonproprietary Name (INN)**

N-methyl-1-(thiophen-2-yl)propan-2-amine

B. Chemical Abstract Service (CAS) Registry Number

801156-47-8 free base
7464-94-0 hydrochloride salt

C. Other Chemical Names

MPA
Methiopropamine
N, α -dimethyl-2-thiopheneethanamine
N-methyl-1-(thiophen-2-yl)propan-2-amine
Methylthienylpropamine
2-thienomethamphetamine

D. Trade Names

“Slush Eric”, “Synthacaine” (*ad hoc* constituent of), MPA, “Syndrax”, “Blow”

E. Street Names

“Blow”, methedrene, MPA

F. Physical Appearance

The hydrochloride salt of methiopropamine is a crystalline powder at room temperature.

G. WHO Review History

Methiopropamine was previously critically reviewed by the Committee at its 36th meeting. Owing to the insufficiency of data regarding dependence, abuse and risks to public health, the Committee recommended that methiopropamine not be placed under international control but be kept under surveillance. Subsequent data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use warranting an updated critical review.

2. Chemistry

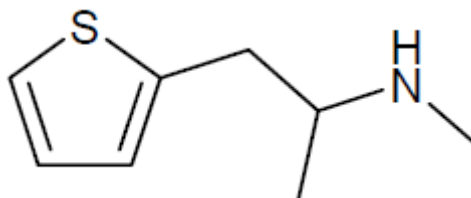
A. Chemical Name

IUPAC Name: 1-(thiophen-2-yl)-2-methylaminopropane

CA Index Name: Not applicable

B. Chemical Structure

Free base:

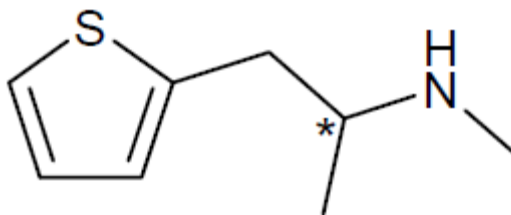


Molecular Formula: C₈H₁₃NS

Molecular Weight: 155.26 g/mol

C. Stereoisomers

Two enantiomers, the chiral centre is indicated below;



D. Methods and Ease of Illicit Manufacturing

Methiopropamine is a thiophene analogue of methamphetamine and was first described in 1942.¹ There is a four step synthesis of methiopropamine. It begins with (thiophen-2-yl)magnesium bromide, which is reacted with propylene oxide, yielding 1-(thiophen-2-yl)-2-hydroxypropane which is reacted with phosphorus tribromide, yielding 1-(thiophen-2-yl)-2-bromopropane which is finally reacted with methylamine, yielding 1-(thiophen-2-yl)-2-methylaminopropane.² An alternative route of synthesis has also been described starting with a solution of 1-(thien-2-yl)propan-2-amine (free base), di-*t*-butyl dicarbonate and triethylamine in dichloromethane.³

E. Chemical Properties

Melting point: 84.308 °C

Boiling point: 215.8 ± 15.0°C at 760 mm Hg

Solubility: Methiopropamine hydrochloride (salt) is soluble in organic solvents like ethanol (20 mg/mL), DMSO (10 mg/mL) and dimethyl formamide (20 mg/mL) and in aqueous, non-organic solvents like PBS (2 mg/mL).

F. Identification and Analysis

Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) (the latter with and without high resolution mass-spectrometry) have been used for identification of methiopropamine, including in biological fluid.⁴⁻⁹ IR spectroscopy, gas chromatography-mass spectrometry (GC-MS) and proton/carbon NMR spectroscopy have been used to identify methiopropamine.¹⁰ Furthermore, electrochemical identification of methiopropamine has been reported in “Synthacaine” product.¹¹ Capillary electrophoresis with sulfobutylether β -cyclodextrin serving as a chiral selector in an aqueous ammonium acetate solution containing acetonitrile was used to separate the enantiomers of methiopropamine.¹²

3. Ease of Convertibility Into Controlled Substances

Methiopropamine is not readily converted into other controlled substances.

4. General Pharmacology

Methiopropamine, a structural analogue of methamphetamine, functions primarily through the noradrenergic and dopaminergic systems, with inhibition of the respective transporters, thus increasing synaptic neurotransmitter levels, as determined by *in vitro* studies.¹³ Other studies have shown the effects of methiopropamine on the dopaminergic system to be similar to that of methamphetamine and that the reuptake of dopamine and noradrenaline is inhibited by 50% at low methiopropamine concentrations *in vitro*.¹⁴

A. Routes of administration and dosage

Methiopropamine is generally administered by insufflation, inhalation or orally. The dosage is ranging from 5–60 mg insufflated, 5–40 mg by inhalation and 10–50 mg when taken orally. The onset of effects occurs 5-10 minutes following administration. Rectal administration has also been reported in a few cases.¹⁵ Pyrolysis products of methiopropamine have been identified by researchers which have the potential to be psychoactive (N-methyl methiopropamine) while others are potentially toxic, such as 2-methylthiophene.³

B. Pharmacokinetics

The duration of effect of methiopropamine is suggested to be 2-4 hours following insufflation. However, effects may occur up to 24 hours following administration. Inhalation of vaporized methiopropamine displays a plateau in effect at 1-2 hours.¹⁶

Various animal, human, *in vitro* and *in silico* studies have been undertaken involving methiopropamine.^{4,17-18} Metabolism includes the cytochrome P450 enzyme CYP2C19 in the liver as well as CYP1A2, CYP2C19, CYP2D6 and CYP3A4. Whilst N-demethylation, hydroxylation at the side chain and at the thiophene ring followed by glucuronidation

and/or sulphation has been identified, the main metabolite detected in urine (human and rat) is the *N*-demethylated metabolite (*N*-desmethylnmethiopropamine, also referred to as nor-MPA). In *in vitro* studies, traces of methiopropamine hydroxy metabolites were also detected but were not found in human urine in all studies, however, Lee et al reported hydroxy-*N*-desmethylnmethiopropamine in a case of non-fatal intoxication along with nor-MPA.¹⁹

Pharmacokinetic studies in mice showed that methiopropamine was rapidly absorbed after i.p. injection and reached C_{max} in the blood at 5 minutes, with a reduction to 12% of C_{max} within 2 hours following administration. C_{max} in the brain was achieved after 10 minutes. Nor-MPA was present in much lower concentrations (factor of 10 lower) displaying a C_{max} in blood after 30 minutes and 45 minutes in the brain.¹⁴

C. Pharmacodynamics

In mice and in comparison to methamphetamine, methiopropamine exhibited a dose-dependent stimulation of locomotor activity in doses from 5-12.5 mg/kg (doses up to 20 mg/kg given) and gave a higher peak effect than the administration of methamphetamine. However, at low doses (below 5 mg/kg), the induced locomotor effect was more pronounced for methamphetamine.¹⁴

Whilst no pre-clinical or formal studies have been undertaken in humans, data from users and case reports (including clinically described intoxications) indicate that methiopropamine displays similar properties to methamphetamine including stimulation, alertness and increase of focus and energy as well as talkativeness. Adverse effects following administration that have been reported are tachycardia, anxiety, panic attacks, perspiration, headache, nausea, difficulty in breathing, vomiting, difficulty urinating and sexual dysfunction.^{16,19-21}

5. Toxicology

No acute or chronic pre-clinical studies were identified that have examined the toxicity of methiopropamine in humans or animals.

6. Adverse Reactions in Humans

Cases of Methiopropamine Intoxication in Humans

Non-fatal Cases

In Sweden during 2013, 21 cases of methiopropamine intoxication were reported. The substance was detected in 15 cases in urine and 5 cases in blood.²² It was present along with other new psychoactive substances (e.g. methoxphenidine and diphenidine) as identified by the STRIDA project.²³

In France, a 30-year-old man was admitted to the emergency department in a confused state with paranoid delusion, auditory and visual hallucinatory experiences as well as incoherent speech following the use of "Synthacaine" (a slang term derived from

"synthetic" and "cocaine"). Methiopropamine was detected and measured to be 14 ng/mL in a plasma specimen obtained 13 hours after hospital presentation.⁵

In the UK, a 27-year-old woman with no previous medical history presented to an emergency department with palpitations, chest tightness, anxiety, nausea, vomiting and visual hallucinations 21 hours after insufflation of "Hawaiian baby seeds" (thought to be *Argyreia nervosa* containing ergoline alkaloids such as lysergic acid amide) and 50 mg "Quicksilver" powder product from a London market stall.¹⁹ Specifically, after the use of the drugs, the patient had difficulty sleeping and had experienced intermittent palpitations and 'chest tightness'. Nine hours after use she developed nausea and vomited multiple times. During this time period, she had experienced a general feeling of anxiety and euphoria with visual hallucinations lasting until 6 hours prior to presentation. On arrival in the emergency department she was still experiencing nausea and dizziness, but her other symptoms had settled. She had a normal temperature (36.9 °C), heart rate (80 beats per minute) and blood pressure (109/77 mmHg). She was agitated but had a Glasgow Coma Score of 15/15; her pupils were dilated and reactive to light; the rest of her physical examination was unremarkable. The following morning her symptoms had settled and she was discharged with no sequelae 16 hours after presentation and 37 hours after the use of the drugs. Toxicological analysis of her urine collected at presentation to the hospital detected methiopropamine at a concentration of 400 ng/mL, along with two metabolites (*N*-desmethyl and hydroxy *N*-desmethylmethiopropamine). Morphine (100 ng/mL) and metabolites of the synthetic cannabinoids JWH-018 and JWH-019 and ergonovine were also detected in the urine (less than 10 ng/mL).

Elsewhere, non-analytically confirmed cases of adverse effects by self-reporting users included; chest pain, headache, visual/auditory hallucinations, insomnia, shaking/feverishness, increased heart rate (not medically confirmed) and vomiting.^{20,21}

Fatal Cases

The first fatalities involving methiopropamine occurred from January 2012 in the UK with another case occurring in September 2012 in the UK.²⁴⁻²⁶ The former cases are included in the table below, whilst the September case from Scotland detected methiopropamine along with oxycodone, temazepam and venlafaxine. Subsequently, between 2013 and 2016, methiopropamine was detected in 10 deaths (2013), 27 deaths (2014), 23 deaths (2015) and 2 deaths (2016).^{24,25} However, many of the deaths involved an alternative manner or cause of death. Specifically, methiopropamine was detected at a post-mortem blood concentration of 3.7 mg/L in an individual struck by a train and at a concentration of 0.31 mg/L in a deceased male who was found in a pond having jumped from a window. In the other cases, methiopropamine was detected at either low concentrations or in urine only and therefore did not significantly contribute to death. In the deaths detailed below, methiopropamine was thought to have contributed to death* (even in the presence of other drugs) in six cases or may have contributed to death but other drugs present may be more toxicologically significant.

Table. UK cases 2012-2016²⁴

Case	Year	MPA blood concentration (post-mortem)	Other relevant drugs	Comments
1*	2012	2.8	MXE 0.89 mg/L	“China White” packets
2*	2012	6.7	MDAI, lignocaine, caffeine, ethanol 59 mg/dL	“Blow” packet, white powder + snort pipe contained (MDAI, MPA, lignocaine, caffeine)
3	2013	0.43	6-APB 4.19 mg/L, lamotrigine 6.1 mg/L, phenytoin 8.7 mg/L, valproate 16.4 mg/L, butylone	Agitated. “Benzo Fury” packets. Epileptic.
4	2013	0.06 (ante-mortem)	5-APB 1.39 mg/L	Behaving bizarrely. High body temp. “Green Goblin” tablets.
5	2013	1.4	Methadone 1.03 mg/L, fluoxetine 2.91 mg/L	Found dead in the bath.
6	2014	0.5	PMA 1.8 mg/L	“Diablos” and/or “Dove” Ecstasy tablets
7*	2014	1.26	Olanzapine, lignocaine, ethylphenidate	Suddenly collapsed. May have taken “Gogaine”.
8	2014	9.81	Morphine (591 ng/mL)	None
9	2014	2.53	MDMA 0.74 mg/L, methamphetamine 3.28 mg/L, mephedrone, 5-MeO-DALT	Found dead at home.
10	2015	0.37	Buprenorphine 2.0 ng/mL, diclazepam	Missing person found in a field.
11*	2015	0.3	Zopiclone, citalopram, diazepam (all therapeutic)	Found dead.
12*	2015	0.6	Cocaine 84 ng/mL (BZE metabolite 869 ng/mL), levamisole	Collapsed at home
13	2015	1.8	Morphine (95 ng/mL)	Found dead at home.
14*	2016	1.14	3-Fluorophenmetrazine, diclazepam	Found dead in kitchen, white powder found.

In Sweden, one fatal case has been reported. The concentration of methiopropamine was determined to be 1,3µg/g (approximately equivalent to 1.3 mg/L) in femoral blood.²⁷

A death related solely to methiopropamine was reported in Australia involving a post-mortem blood methiopropamine concentration of 38 mg/L.²⁸

7. Dependence Potential

A. *Animal Studies*

In a study by Yoon et al, rats were pre-exposed to either saline or one of three different doses of methiopropamine (0.2, 1.0, or 5.0mg/kg, i.p.) with a total of four injections, respectively.²⁹ After a 2-week withdrawal period, when they were challenged with the same dose of methiopropamine, only the group that was pre-exposed to the high dose (5.0 mg/kg) showed sensitized locomotor activity. In the second experiment, all rats were pre-exposed to methiopropamine (5.0 mg/kg) only. The expression of methiopropamine-induced locomotor sensitization was inhibited by a pre-injection of a dopamine D₂ receptor antagonist, eticlopride (0.05 mg/kg, i.p.), though not by a dopamine D₁ receptor antagonist, SCH23390 (0.01 mg/kg, i.p.). The authors stated that the results suggested that repeated injection of methiopropamine in the rat provokes certain neuronal changes involving specific, likely D₂, dopamine receptor-mediated pathways that contribute to the expression of methiopropamine-induced locomotor sensitization.

B. *Human Studies*

No studies were identified that have examined the dependence potential of methiopropamine in humans.

8. Abuse Potential

A. *Animal Studies*

No studies (e.g. drug discrimination or self-administration) were identified that have examined the abuse potential of methiopropamine in animals. However, as described elsewhere, during pharmacodynamics studies in mice and in comparison to methamphetamine, methiopropamine exhibited a dose-dependent stimulation of locomotor activity in doses from 5-12.5 mg/kg and gave a higher peak effect than the administration of methamphetamine. This included a steep dose-response effect between 10 mg/kg and 12.5 mg/kg. However, at low doses (below 5 mg/kg), the induced locomotor effect was more pronounced for methamphetamine.¹⁴ Furthermore, the studies by Yoon et al, indicate a potential abuse liability mediated by the dopaminergic system.²⁹

B. *Human Studies*

No studies were identified that have examined the abuse potential of methiopropamine in humans.

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

No evidence has been found that methiopropamine has been therapeutically used.

10. Listing on the WHO Model List of Essential Medicines

Methiopropamine is not found on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

None known.

12. Industrial Use

No evidence has been found that methiopropamine has or is used in industry.

13. Non-Medical Use, Abuse and Dependence

As stated elsewhere, deaths and non-fatal intoxications have been reported in Europe and Australia, demonstrating the use and abuse of methiopropamine in the countries. Other evidence for use and abuse has been reported primarily in short-term, discrete epidemiological and toxicovigilance studies.

An internet snapshot study of UK, French and Canadian website searches in June 2013 found a total of 62 sites, most of which were found from English language searches. 45% of the suppliers seemed to originate from the UK. The prices of methiopropamine were comparable between suppliers (regardless of search engine or language). The cost of a unit of methiopropamine was inversely related to the purchased quantity, going from 19.49 ± 0.15 GBP per gram for a purchase amount of 500 mg to 3.54 ± 0.13 GBP per gram for a purchase amount of 1 kg.³⁰ Whilst internet advertised products may not subsequently contain the advertised product, analysis of drug material in the UK between July 2014 and July 2015 identified methiopropamine as one of the three most common new psychoactive substances found (the other common substances being ethylphenidate and 5F-AKB-48).³¹

A one year study of drug users (between July 2012 and June 2013) in Hungary showed that substances placed on the list of illicit drugs (mephedrone, 4-fluoro-amphetamine, MDPV, methylone and 4-MEC) showed a subsequent drop in frequency and were replaced by other stimulant drugs; pentedrone, 3-MMC and methiopropamine.³²

In the UK (London), methiopropamine was detected in samples of pooled urine from portable street urinals over a 5 month period of a 6 month testing period. This was compared to MDMA (all 6 months) and 4-methylethcathinone (3 months).¹⁸

A methodology of sewage analysis for epidemiology was applied on samples collected from sewage treatment plants in Belgium and Switzerland in which all investigated compounds (methoxetamine, butylone, ethylone, methylone, methiopropamine, PMMA and PMA), were detected except methiopropamine and PMA.³³

During a 3 year study (2012-2014) in Poland of new psychoactive substances in biological fluid, methiopropamine was only detected in a single case out of 112 cases.³⁴ This was compared to the most frequently detected, 3-methylmethcathinone (3-MMC), found in 50 cases.

Overall, methiopropamine use and abuse has currently been reported in: Australia, Canada, Estonia, Finland, France, Germany, Hungary, Netherlands, Norway, Poland, Russian Federation, Singapore, Sweden and the United Kingdom.

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

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

During a 12 week period in Norway, methiopropamine was detected in 10 (all males) DUID (driving under the influence of drugs) cases representing 0.8% of all cases during that period. Two of the cases were traffic accidents. Other drugs were also detected in all cases, therefore the exact contribution of methiopropamine was unclear.⁸

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

15. Licit Production, Consumption and International Trade

Not applicable.

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

16. Illicit Manufacture and Traffic and Related Information

Reports of seizures of methiopropamine have been noticed in North America and Europe, especially in Canada and the UK. The amount is typically in milligram to gram amounts in powder form. The distribution and trafficking mainly occurs through the Internet. No specific reports on the licit and illicit production are available.

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

17. Current International Controls and Their Impact

Methiopropamine is not controlled under the United Nations conventions.

18. Current and Past National Controls

Methiopropamine is a controlled substance in the US state of Florida but in the United States in general, methiopropamine is not controlled under the Controlled Substances Act (CSA). However, may be considered as a controlled substance analogue of methamphetamine.

Methiopropamine is a controlled substance in Belarus, China, Denmark, Estonia, Germany, Hungary, Portugal, Slovenia, Sweden and Turkey. It is under a temporary class drug order in the United Kingdom.

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

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

References

1. F.F. Blicke and J.H. Burkhalter. *J Am Chem Soc.* 1942, 64:477-480.
2. D. Angelov, J. O'Brien, P. Kavanagh. The syntheses of 1-(2-thienyl)-2-(methylamino) propane (methiopropamine) and its 3-thienyl isomer for use as reference standards. *Drug Test Anal.* 2013, 5(3): 145-149.
3. Bouso ED, Gardner EA, O'Brien JE, Talbot B, Kavanagh PV. Characterization of the pyrolysis products of methiopropamine. *Drug Test Anal.* 2014 Jul-Aug;6(7-8):676-83.
4. Welter J, Meyer MR, Wolf EU, Weinmann W, Kavanagh P, Maurer HH. 2-methiopropamine, a thiophene analogue of methamphetamine: studies on its metabolism and detectability in the rat and human using GC-MS and LC-(HR)-MS techniques. *Anal Bioanal Chem.* 2013;405(10):3125-35.
5. Daveluy A, Castaing N, Cherifi H, Richeva C, Humbert L, Faure I, Labadie M, Allorge D, Haramburu F, Molimard M, Titier K. Acute methiopropamine intoxication after "Synthacaine" consumption. *J Anal Toxicol.* 2016 Jul 29:1-3.
6. Acton WJ, Lanza M, Agarwal B, Jürschik S, Sulzer P, Breiev K, Jordan A, Hartungen E, Hanel G, Märk L, Mayhew CA, Märk TD. Headspace analysis of new psychoactive substances using a Selective Reagent Ionisation-Time of Flight-Mass Spectrometer. *Int J Mass Spectrom.* 2014; 360:28-38.
7. Lanza M, Acton WJ, Sulzer P, Breiev K, Jürschik S, Jordan A, Hartungen E, Hanel G, Märk L, Märk TD, Mayhew CA. Selective reagent ionisation-time of flight-mass spectrometry: a rapid technology for the novel analysis of blends of new psychoactive substances. *J Mass Spectrom.* 2015 Feb;50(2):427-31.
8. Tuv SS, Bergh MS, Vindenes V, Karinen R. Methiopropamine in blood samples from drivers suspected of being under the influence of drugs. *Traffic Inj Prev.* 2016;17(1):1-4.
9. Holler JM, Vorce SP, Knittel JL, Malik-Wolf B, Levine B, Bosy TZ. Evaluation of designer amphetamine interference in GC-MS amine confirmation procedures. *J Anal Toxicol.* 2014 Jun;38(5):295-303.
10. J.F. Casale, P.A. Hays. Methiopropamine: an analytical profile. *Microgram Journal.* 2011, 8 (2): 53-57.
11. Cumba LR, Kolliopoulos AV, Smith JP, Thompson PD, Evans PR, Sutcliffe OB, do Carmo DR, Banks CE. Forensic electrochemistry: indirect electrochemical sensing of the components of the new psychoactive substance "Synthacaine". *Analyst.* 2015 Aug 21;140(16):5536-45.
12. Taschwer M, Hofer MG, Schmid MG. Enantioseparation of benzofurys and other novel psychoactive compounds by CE and sulfobutylether β -cyclodextrin as chiral selector added to the BGE. *Electrophoresis.* 2014 Oct;35(19):2793-9.
13. L. Iversen, S. Gibbons, R. Treble, V. Setola, X.P. Huang, B.L. Roth. Neurochemical profiles of some novel psychoactive substances. *Eur J Pharmacol.* 2013, 30;700(1-3):147-51.

14. Tuv SS, Vindenes V, Skov-Skov Bergh M, Nerem E, Karinen R, Huestis M, Lise Bogen I. Pharmacokinetic and pharmacodynamics effects of methiopropamine in mice. Presented at 54th Annual meeting of The International Association of Forensic Toxicologists (TIAFT), Brisbane, Australia, 2016.
15. Erowid: https://www.erowid.org/chemicals/methiopropamine/methiopropamine_dose.shtml (accessed August 2016)
16. Erowid: https://www.erowid.org/chemicals/methiopropamine/methiopropamine_effects.shtml (accessed August 2016)
17. E. Tyrkkö, A. Pelander, R.A. Ketola, I. Ojanperä. In silico and in vitro metabolism studies support identification of designer drugs in human urine by liquid chromatography/quadrupole-time-of-flight mass spectrometry. *Anal Bioanal Chem.* 2013, 405(21):6697-709.
18. J.R. Archer, P.I. Dargan, H.M. Lee, S. Hudson, D.M. Wood. Trend analysis of anonymised pooled urine from portable street urinals in central London identifies variation in the use of novel psychoactive substances. *Clin Toxicol (Phila).* 2014 Mar;52(3):160-5.
19. Lee HM, Wood DM, Hudson S, Archer JR, Dargan PI. Acute toxicity associated with analytically confirmed recreational use of methiopropamine (1-(thiophen-2-yl)-2-methylaminopropane). *J Med Toxicol.* 2014 Sep;10(3):299-302.
20. Erowid experiences: https://www.erowid.org/experiences/subs/exp_Methiopropamine.shtml (accessed August 2016)
21. Bluelight forum: [http://www.bluelight.org/vb/threads/544266-The-Methiopropamine-N-methyl-1-\(thiophen-2-yl\)propan-2-amine-\(MPA\)-Megathread](http://www.bluelight.org/vb/threads/544266-The-Methiopropamine-N-methyl-1-(thiophen-2-yl)propan-2-amine-(MPA)-Megathread) (accessed August 2016)
22. Cases collected from the Public Health Agency of Sweden, 2014
23. Helander A, Beck O, Bäckberg M. Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. *Clin Toxicol (Phila).* 2015 Jun;53(5):446-53.
24. Elliott S. Casework data from Alere Forensics (formerly ROAR Forensics, UK), 2016.
25. Elliott S, Evans J. A 3-year review of new psychoactive substances in casework. *Forensic Sci Int.* 2014 Oct;243:55-60.
26. European Early Warning System alert from European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal (27th September 2012).
27. Kronstrand R (Linköping, Sweden), personal communication, 2016
28. Anne S, Tse R, Cala AD. A Fatal Case of Isolated Methiopropamine (1-(Thiophen-2-yl)-2-Methylaminopropane) Toxicity: A Case Report. *Am J Forensic Med Pathol.* 2015 Sep;36(3):205-6

29. Yoon HS, Cai WT, Lee YH, Park KT, Lee YS, Kim JH. The expression of methiopropamine-induced locomotor sensitization requires dopamine D2, but not D1, receptor activation in the rat. *Behav Brain Res.* 2016 Sep 15;311:403-7.
30. Vermette-Marcotte AE, Dargan P, Archer JR, Gosselin S, Wood DM. An Internet snapshot study to compare the international availability of the novel psychoactive substance methiopropamine. *Clin Toxicol (Phila).* 2014 Aug;52(7):678-81.
31. Ford LT, Berg JD. Analysis of legal high materials by UPLC-MS/TOF as part of a toxicology vigilance system. What are the most popular novel psychoactive substances in the UK? *Ann Clin Biochem.* 2016 May 10.
32. Institóris L, Árok Z, Seprenyi K, Varga T, Sára-Klausz G, Keller É, Tóth RA, Sala L, Kereszty É, Róna K. Frequency and structure of stimulant designer drug consumption among suspected drug users in Budapest and South-East Hungary in 2012-2013. *Forensic Sci Int.* 2015 Mar;248:181-6.
33. Kinyua J, Covaci A, Maho W, McCall AK, Neels H, van Nuijs AL. Sewage-based epidemiology in monitoring the use of new psychoactive substances: Validation and application of an analytical method using LC-MS/MS. *Drug Test Anal.* 2015 Sep;7(9):812-8.
34. Adamowicz P, Gieroń J, Gil D, Lechowicz W, Skulska A, Tokarczyk B. The prevalence of new psychoactive substances in biological material - a three-year review of casework in Poland. *Drug Test Anal.* 2016 Jan;8(1):63-70.

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of Methiopropamine

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

A total of 41 Member States (4 AFR, 2 EMR, 22 EUR, 7 PAH, 1 SEAR and 5 WPR) answered the questionnaire for Methiopropamine (MPA). Of these, 22 respondents (17 EUR, 3 PAH and 2 WPR) had information on this substance.

LEGITIMATE USE

There were 20 countries that reported no approved medical products containing MPA for human or veterinarian indications.

MPA is not currently being used in any medical or scientific research (excluding use as an analytical reference standard) in 15 countries, or for any industrial purpose in 16 countries.

MPA was not reported to be used for any cultural, religious or ceremonial purposes in 18 countries.

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

There were 16 countries that reported MPA as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are oral (11 countries), injection (4 countries), inhalation (3 countries), sniffing (9 countries), smoking (3 country) and rectal (2 countries). Also reported by one country was bombing (powder wrapped in cigarette paper). The main route of administration for MPA was reported as oral (5 countries) followed by sniffing (3 countries) and smoking (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (14 countries), followed by tablets (9 countries), liquid or solution for oral administration/use (2 country) and injectable (1 country) formulations. There were also 3 countries which reported plant material/herbal mixture as a formulation.

There were 11 countries which reported that the source of MPA for non-medical/non-scientific use was smuggling.

One country specified former or current injectors of heroin as a subpopulation known to misuse MPA. Another country specified the party scene as another subpopulation known to misuse MPA.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (1 country), substantial (4 countries) or serious (3 countries). For the countries that indicated a substantial or serious level of negative health-impact, they specified that it was due to the association of MPA with adverse events (including transmission of

communicable diseases through injection drug use) and fatalities. It was commented that MPA has amphetamine-like side effects and is a harmful substance used by problematic drug users.

Three countries reported emergency room/department visits related to the non-medical use of MPA. A combined total of 2 cases in 2013 and 11 cases (unknown no further information or time frame) were reported.

The adverse effects which presented for MPA at the emergency room/department included anxiety, blurred vision, seizures, chest pain, consciousness disorders, nausea, vomiting, palpitation, insomnia, euphoria, dizziness, agitation and visual hallucinations.

In regards to the mortality rate, data was provided by 4 countries. The rate where only MPA was involved, included 2 cases in 2015. The rate which included involvement of other substances was reported to be 1 case in 2012, 2 cases in 2013, 4 cases in 2014 and 9 cases in 2015. Finally the rate, where it was unknown if other substances were involved was 1 case in 2014 and 1 case in 2015. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 18 countries reported that MPA was under national control. The legislation the control is based upon included Medicines Act (3 countries), Controlled Substances Act (10 countries), Criminal Law Act (1 country), Analog Act (1 country) and other specific legislation (3 stated that it was specific legislation for new psychoactive substances). In two countries the control is a temporary measure. There were no challenges to implementing controls for MPA reported.

The scope of the controls includes production (15 countries), manufacturing (17 countries), exporting (16 countries), importing (18 countries), distribution (16 countries), use (12 countries) and possession (15 countries).

Reported illicit activities involving MPA include manufacture of the substance by trafficking (9 countries), smuggling (1 country), internet sales from abroad (9 countries), internet sales from unknown locations (5 countries) and finally sales to people who use this substance (4 countries).

There were 14 countries which completed the section on the number of seizures. The combined number of seizures was 344 (2014), 565 (2015) and 25 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If MPA was placed under international control, 21 countries responded that they would have the capacity to enforce the control at the national level. There were 21 countries which responded that they would have the forensic laboratory capacity to analyse the substance.