Ethylone

Critical Review Report

Agenda Item 4.5

Expert Committee on Drug Dependence

Thirty-eighth Meeting

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Contents

Acknowledgements

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Summary

Ethylone is (*RS*)-1-(1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one (aka, 3,4-methylenedioxy-N-ethylcathinone). It has a chiral center with two stereoisomers. Ethylone has no authorizations as a medicinal product/medication. Ethylone is a slight chemical modification of methylone (3,4-methylenedioxymethcathinone) that is in Schedule II of the Convention on Psychotropic Substances of 1971, although it would likely be inefficient to intentionally synthesize ethylone or otherwise obtain ethylone to convert it to methylone. Other than in unpublished reports of the discriminative stimulus effects of ethylone in rats, reports of ethylone's evaluation in controlled, systematic preclinical and clinical abuse-related procedures are not available. However, it could be interpreted that it has demonstrated similar abuse and ill effects as substances in Schedule II of the Convention on Psychotropic Substances of 1971, and that there is evidence that the substance is being abused, and is likely to continue to be abused, so as to constitute a public health and social problem.

Some of these preclinical effects include:

1) Ethylone binds to the NET, DAT and SERT transporters with Ki's (mean ±SD) of 9.89±0.9, 1.43±0.4 and 9.04±0.6 µM, respectively.
2) Ethylone has relatively nonselective monoamine uptake inhibition with IC_{50}'s (95% CI) at the NET, DAT and SERT transporters of 2.54 (2.0-3.2), 5.68 (4.9-6.5), and 4.46 (3.8-5.2) µM, respectively.
3) This binding and uptake inhibition profile has caused some researchers to characterize ethylone as a "cocaine-MDMA-mixed cathinone" type drug.
4) Ethylone substitutes fully (ED_{50}=4.16 mg/kg) for the discriminative stimulus effects produced by 1 mg/kg of (+)-methamphetamine and of 10 mg/kg cocaine (ED_{50}= 3.37 mg/kg) in rats.

Some of these clinical effects (often observed when accompanied by other drugs) include:

1. Adverse effects including impaired driving, slurred speech, bloodshot watery eyes, dilated pupils, involuntary muscle movements and elevated pulse and blood pressure.
2. Association with several deaths (>8). The proximal cause of some of these deaths has been through acts of violence.

Evidence of its sale and distribution:

1. By 2014, ethylone had become the most commonly confiscated synthetic cathinone in the US. In the first six months of 2015 there had already been 4,894 identifications of ethylone in the United States NFLIS system. Initial seizures in Canada of ethylone occurred in 2012, and as of 2015 the Canada Border Services Agency has seized over 100 different shipments containing it.
2. There have several reported confiscations in Europe including from the Netherlands, Sweden, Romania, Finland, France and Italy.
3. Additionally, sales or confiscations of ethylone have been reported in Australasia and in the Far East including from New Zealand, Japan and Thailand, and from South America.
4. Ethylone is aggressively marketed on the Internet, being sold in products marketed as bath salts, plant food and cleaning products.
5. Several countries including Canada, Germany, the United Kingdom, New Zealand, Japan, Singapore and Switzerland have imposed regulatory controls over ethylone.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

1112937-64-0
1454266-19-3 (ethylone HCl polymorph B)
Other Chemical Names

1. Ethylone
2. 2-Ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-one
3. 1112937-64-0
4. bk-MDEA
5. SCHEMBL2641160
6. CTK6F2113
7. MJEMIOXXNCZZFK-UHFFFAOYSA-N
8. 3,4-Methylenedioxy-N-ethylcathinone
9. AKOS022543141
10. HE295685
11. 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)-1-propanone
12. 1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(ethylamino)propan-1-on
13. bk-Methylenedioxyethylamphetamine

C. Trade Names

None as a medicinal product.

D. Street Names

(N.B., street names are not always consistently used for only one substance): M1, MDEC, bk-MDEA

E. Physical Appearance

Reference standard (Cayman Chemical, Ann Arbor, MI, U.S.A.) is a crystalline solid. Color: White powder.[(1)] Some street samples have been lightly orange tan in color. Taste: A user reported, "The taste is reminiscent of lemon juice and salt, and it burns your mouth like crazy."[(2)]

F. WHO Review History

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

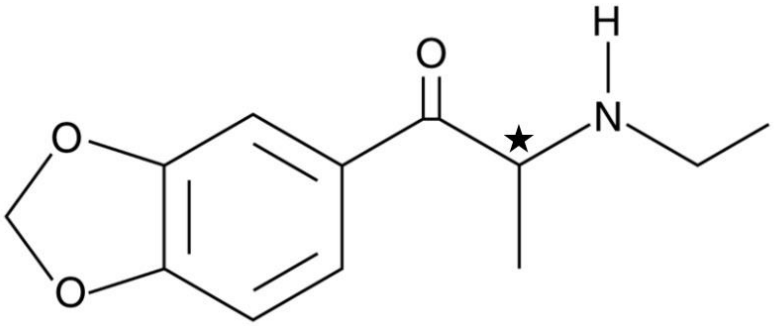
A. Chemical Name

IUPAC Name:
(*RS*)-1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)propan-1-one
CA Index Name:
1-Propanone, 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-

B. Chemical Structure

Free base:

"Star" indicates chiral center.



Molecular Formula: $C_{12}H_{15}NO_3$
Molecular Weight: 221.2524 g/mol

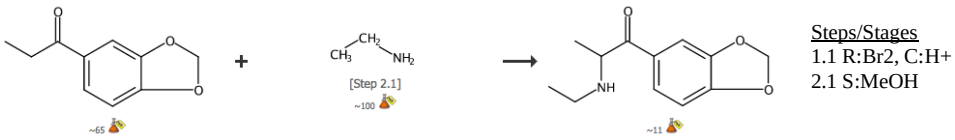
C. Stereoisomers

Ethylone has a chiral center and methods to resolve its isomers have been reported.[3-7] Seizures in at least one country, Canada, have been racemic.[8]
The hydrochloride salt of ethylone can exist in two conformations (polymorphs) at the C-C bond linking the side chain to the aromatic ring.[9] Polymorphs can differ in solubility, stability and biological activity. The ethylone polymorphs are identical by mass spectrometry and nuclear magnetic resonance (NMR), but differ when analyzed by Fourier transform infrared spectroscopy FT-IR, FT-Raman, and powder X-ray diffraction, and solid-state NMR spectroscopy.[8, 9]

D. Methods and Ease of Illicit Manufacturing

Ethylone can be prepared by the acid-catalyzed bromination of 3,4-methylenedioxypropriophenone followed by the reaction of the intermediate, 3,4-methylenedioxy-(2-bromopropiophenone), with ethylamine.[10] These precursor substances are readily available and not under international control.[11]

Potential synthetic route: (adapted from SciFinder 2016 based upon Russell and Bogun 2011.[10, 12]



Synthesis of ethylone taken based upon Russell and Bogun 2011.[10, 12]

E. Chemical Properties

Melting point:
(1) *Flash point:* 172.8±27.9 °C[12]

Boiling point:
(1) 362.2± 42.0 °C[12]

Solubility:
(1) Slightly soluble (2.9g/L) in unbuffered water pH 9.93 Temp: 25°C
(2) Very soluble (1000g/L) at pH 4 Temp: 25°C[12]

F. Identification and Analysis

Detailed human urine preparation and analysis of ethylone and its metabolites using gas chromatography–mass spectrometry, liquid chromatography–mass spectrometry, and liquid chromatography–tandem mass spectrometry has been reported.[13] In addition, a liquid chromatography − tandem mass spectrometry (LC–MS/MS) method for the analysis of ethylone in dried urine, plasma and oral fluid samples using volumetric absorptive microsampling (10 µl; VAMSTM®) for collecting dried biological samples has been reported and validated.[14] Recently (August 2016) technology was reported in which a simple and rapid LC–MS/MS screening method for the simultaneous detection of 5 amphetamines and 64 NPS including ethylone in blood extracts in a single run was reported.[15] Accuracy for detecting ethylone ranged from 19.1% at 1 ng/mL; 6.5% at 50 ng/mL; and 2.4% at 100 ng/mL. Overall, intra-day and inter-day precisions ranged from 2.5 to 17.2% and from 2.1 to 16.7%, respectively. This method presumably is very fast, easy to perform and cheap as it only requires the deproteinization of 200 µL of blood sample with acetonitrile.[15] Reference standards are available.

3. Ease of Convertibility Into Controlled Substances

Ethylone is a slight chemical modification of methylone (3,4-methylenedioxymethcathinone)[16] that is in Schedule II of the Convention on Psychotropic Substances of 1971. It would likely be inefficient to intentionally synthesize ethylone to convert it to methylone because the same initial synthesis is required for both with the exception that ethylamine is used instead of methylamine for the synthesis of ethylone and methylone, respectively.[10, 12]

In terms of expert opinion, there is likely no controlled substance that might be made from ethylone except ethylamphetamine, and few would bother when the starting materials are likely less expensive than the cost of ethylone.[17] Ethylone can be converted to methylone,

but it would require several steps and it's inconceivable why someone would do this. The synthesis of ethylone and methylone are exactly the same except for the last step.[17]

4. General Pharmacology

A. Routes of administration and dosage

Users report using oral, rectal, insufflation (sometimes reported as undesirable), sublingual (sometimes reported as undesirable), and intravenous routes of administration.[18, 19]

B. Pharmacokinetics

The 3,4-methylenedioxy ring-substituted cathinones such as ethylone are generally metabolized by demethylation, and also by similar Phase 1 reactions as those of other cathinones, e.g. N-dealkylation, O-methylation and reduction of the β-keto moiety.[20-22] Analyzing the urines from two subjects having consumed ethylone, Zaitsu and colleagues found using GC/MS and LC/MS, that N-dealkylation, demethylation followed by O-methylation, and β-ketone reduction resulted in bk-MDA, βk-MDEA-M1, βk-MDEA-M2, and β-OH-MDEA as the principle metabolites (βk-MDEA-M1 and -M2 involve '4-OH-'3-MeO and the 3'-OH-'4-MeO metabolites on the benzene ring).[13, 22] In this study by Zaitsu, metabolites of ethylone in abusers' urine were identified using the synthesized metabolites 2-amino-1-(3,4-methylenedioxyphenyl)propan-1-one (bk-MDA), 2-ethylamino-1-(4-hydroxy-3-methoxyphenyl)propan- 1-one (bk-4,3-HMEA), 2-ethylamino-1-(3-hydroxy-4-methoxy phenyl)propan-1-one (bk-3,4-HMEA), and 2-ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-ol (beta-hydroxy-MDEA) and, as has been commented by Meyer and Maurer, the authors had not checked, "...for other metabolites than the synthesized ones. In consequence, such study design impedes the elucidation of uncommon pathways in designer drug metabolism."[23]

Systematic time course studies in human subjects could not be identified. Some idea of the time course of effects, as well as the subjective experience with ethylone, can be obtained from the following user report (with qualification that it is an unmonitored user report):[24]

Re: Ethylone (bk-MDEA)
Test subject & chemical information
Gender: Male
Weight: 140 lbs
Height: 5' 6"
Compound: Ethylone
Dosage: 200 milligrams
Route of administration: Oral Consumption
Stomach Contents: Moderately full
Prior drug experience: A variety of research chemicals; cannabinoids, beta-Ketones, phenethylamines, tryptamines, and dissociatives.
Substance Description: Off white, almost yellow, clumpy powder.
Setting: My personal research area, listening to music, relaxing, positive state of mind.

Experience

T+0:00 - 200 milligrams of Ethylone (bk-MDEA) is consumed via oral administration. My most recent meal was consumed approximately 3 hours prior.

T+0:45 - My body feels lighter, a bit of muscle tension in my neck though not related to the compound, a heightening of senses definitely makes the sensation more noticeable. Some mild euphoria washes over, definitely some noticeable physical stimulation is present. Heart rate is at 88 bpm.

T+1:15 - My stomach is a bit upset, my body feels as if lighting is moving through it, and colors appear to be slightly enhanced. I feel quite euphoric, mildly empathogenic, and considerably stimulated. Definitely an increased musical appreciation and my pupils are quite dilated. Heart rate remains at 88 bpm.

T+1:45 - I feel warm, the stimulation has resided a bit, as well as the euphoria, my vision is considerably more sensitive, things appear brighter, colors appear more vivid, music is still very pleasant to listen too. Heart rate is at 84 bpm.

T+2:15 - I continue to grow warmer, to the point of sweating, the euphoria has much faded, though a bit of the stimulation remains, my interest for music has diminished and overall my feelings toward this compound aren't too good. The effects feel quite sloppy, not like that of typical serotonin releasing agent such as bk-MDMA or 4-FA. Heart rate remains at 88 bpm.

T+2:30 - 10 milligrams of pentedrone is administered via insufflation, the stimulation increases, the sloppy effects of the ethylone begin to clean up a bit. Heart rate remains at 88 bpm.

T+3:00 - The effects of the ethylone have pretty much diminished, possibly some residual simulation remains.

C. Pharmacodynamics

Simmler and colleagues evaluated the affinity of ethylone, other cathinones, several amphetamines, as well as cocaine to inhibit DA, NA and 5-HT transport into transporter-transfected HEK 293 cells, to elicit DA and 5-HT efflux from monoamine-preloaded cells, and to bind to monoamine receptors.[25] Results indicated that ethylone bound to the NET, DAT and SERT transporters with Ki's (mean ±SD) of 9.89±0.9, 1.43±0.4 and 9.04±0.6 µM, respectively, and more potently than methylone of >25, 2.73±0.2, and >30 µM, respectively. Ethylone had negligible (>10 µM) affinity at several of the receptors tested including $5HT_{1A}$, $5HT_{2A}$, $5\text{-}HT_{2C}$, α_{2A}, D_1, D_3, H_1, TA_{1rat}, and TA_{1mouse}, and had weak (>6µM) affinity at the α_{2A} receptor. Ethylone had relatively nonselective monoamine uptake inhibition with IC_{50}'s (95% CI) at the NET, DAT and SERT transporters of 2.54 (2.0-3.2), 5.68 (4.9-6.5), and 4.46 (3.8-5.2) µM, respectively. The rank order of potency for DAT inhibition among the tested drugs was MDPV and pyrovalerone >> naphyrone, cocaine, methamphetamine, amphetamine and methcathinone > butylone, mephedrone, methylone, ethylone, flephedrone and MDEA > cathinone, MDMA and MBDB. The rank order of potency for SERT inhibition was naphyrone, MDEA and MDMA > MBDB, cocaine, ethylone, mephedrone and butylone all of the others. Ethylone had a DAT/SERT selectivity ratio of 0.8 (0.6-1.1). Ethylone ineffectively stimulated the release of dopamine through the DAT (EC_{50} > 100 µM) and impotently stimulated the release of serotonin

through the SERT (EC_{50} =9.9 (2.4-40 µM). Recent, unpublished data obtained from the U.S. Drug Enforcement Agency[26] indicates ethylone binds (Ki, nM) to the DAT (5000), SERT (23,700), and NET (18,800), inhibits bioamine uptake (IC_{50}, nM) at the DAT (1720), SERT (464), and NET (1,420), and stimulates bioamine release ($EC_{50,}$ nM) of dopamine (>10,000), serotonin (1,480), and norepinephrine (>10,000).[26]

Overall, given these *in vitro* binding and *in vitro* functional activity results, Simmler and colleagues characterized ethylone as a "cocaine- MDMA-mixed cathinone" type drug that included mephedrone, methylone, ethylone, butylone and naphyrone, because they acted as relatively nonselective monoamine uptake inhibitors similar to cocaine and, with the exception of naphyrone, also as an MDMA-like 5-HT releaser.[25] This classification was in contrast to two other classes of drugs, (1) methamphetamine-like cathinones (including cathinone, methcathinone and flephedrone, which acted as preferential catecholamine inhibitors and DA releasers, similar to amphetamine and methamphetamine); and (2) pyrovalerone–cathinones (including pyrovalerone and MDPV, which acted as very potent and selective catecholamine uptake blockers but not substrate releasers).

In a recent (July, 2016) unpublished study, six male Sprague-Dawley rats were trained to discriminate 1 mg/kg i.p. (+)-methamphetamine from vehicle, and following training were tested for substitution with a range of ethylone doses administered intraperitoneally.[27] Ethylone substituted fully (ED_{50}=4.16 mg/kg) for the discriminative stimulus effects produced by 1 mg/kg of (+)-methamphetamine.[27] In a subsequent study (August, 2016), this research group observed that ethylone also substituted fully (ED_{50}= 3.37 mg/kg) for the discriminative stimulus effects produced by 10 mg/kg cocaine in rats.[28] The discriminative stimulus effects of a drug in laboratory animals are thought predictive of its subjective effects in humans, and the observation that ethylone substitutes completely for (+)-methamphetamine's and cocaine's discriminative stimuli suggests its effects would overlap with the subjective and corresponding abuse liability effects of these drugs.

Additional, systematically controlled pharmacodynamic reports with ethylone in laboratory animals or human subjects could not be identified. Some pharmacological effects are suggested by ethylone user reports. Uralets in his 2013 monograph on ethylone[29] described the following: "Internet drug forums report stimulating effects similar to methylone, but less potent with slower onset. It is usually taken by oral ingestion in divided doses, totaling 50-400 mg over a period of 2-4 hours. Excitation, increase in energy, feeling of mental happiness starts at about one hour after the first dose. Coming down begins after about 4-5 hours, depending on re-dosing. Desire to re-dose was very common and persistent. All users report unpleasant hangover effects after the experience has gone, feeling tired or "burned out" even at low doses. During the crash, sleeping and eating is difficult or impossible, which lasts for at least 10-12 hours. The users often ingest high doses of benzodiazepines to counteract negative effects."[29]

5. Toxicology

Controlled, systematic preclinical or clinical toxicological studies could not be found. Sample safety sheets from legitimate providers of ethylone (e.g., Cayman Chemical and AK Scientific) indicated data were not available in pertinent safety categories.

6. Adverse Reactions in Humans

A driver was arrested for impaired driving in the state of Washington and was observed with slurred speech, bloodshot watery eyes, dilated pupils, involuntary muscle movements and an elevated pulse and blood pressure.[30] During a psychophysical test, the subject was observed to have a fast internal clock when performing the Romberg balance test, estimating the passage of 30 s in 24 s. Body temperature was normal. Blood of the impaired driver was identified with α-pyrrolidinovalerophenone (α-PVP), methylone and ethylone (see Section #14 for more details).[30]

Several deaths have been reported in which ethylone was detected as present. A case report by McIntyre and colleagues 2015 was the first in the U.S. to report postmortem ethylone concentrations.[31] A healthy, athletic 30-year-old man reportedly ingested pills and used illicit drugs with another person. They both fell asleep and the following afternoon the other person found him dead. There were hypodermic needles (appeared used) and a metal spoon with dark tarry substance at the death scene, and two recent puncture sites (right elbow and left foot) were found on his body. There was no known family history of cardiovascular disease or evidence of natural disease or trauma. Postmortem analysis identified borderline methamphetamine in blood (ELISA screen). GC-SIM-MS quantitation confirmed ethylone concentrations in the peripheral blood (0.39 mg/L), central blood (0.38 mg/L), liver (1.4 mg/kg), vitreous (0.58 mg/L), urine (20 mg/L) and gastric contents (12 mg). Other compounds detected and confirmed in peripheral blood were morphine (0.05 mg/L), alprazolam (<0.05 mg/L), delta 9-THC (<1 ng/mL), delta 9-carboxy-THC (3.6 ng/mL) and naproxen (<5 mg/L). A urine screen (GC–MS) also confirmed 6-monoacetylmorphine, codeine and sildenafil. "Based on the circumstances, autopsy findings, histology and toxicology results, the cause of death was certified being due to mixed ethylone, heroin and alprazolam intoxication."[31]

Lee and colleagues examined nine postmortem cases that were submitted to the Forensic Toxicology Laboratory at the University of Florida from April to November 2014 for toxicological testing.[32] The decedents were young males, 18-32 years old. Six of the nine died from gunshot wounds or from blunt trauma, one from hanging, one from intoxication with alprazolam, cocaine and heroin, and one was undetermined. Seven of the cases had measurable concentrations of ethylone in blood, ranging from 38 to 2,572 ng/mL; ethylone was detected in the blood sample of one case with a concentration below the assay limit of quantification (25 ng/mL), and one case did not have detectable ethylone in blood. Besides ethylone, all but one case were also positive for 11-nor-9-carboxy-Δ9-tetrahydrocannabinol; seven cases had other drugs quantified in blood, including ethanol, alprazolam, benzoylecgonine, diphenhydramine, morphine and tramadol.[32]

7. Dependence Potential

A. Animal Studies

Controlled, laboratory animal studies regarding the potential physical dependence effects of ethylone have not been reported. No relevant studies could be identified after minimally searching on "(ethylone OR bk-MDEA) AND (rat OR mouse OR monkey) AND (discrimination OR self administration OR withdrawal OR dependence OR reinforce*) in Web of Science, PubMed or Scopus databases as the "topic" or in "title+abstract" or in "title+abstract+keywords", respectively, as late as 21 Aug 2016.

B. Human Studies

Controlled, human studies regarding the potential physical dependence effects of ethylone have not been reported. No relevant controlled human subject studies could be found after minimally searching on "((ethylone OR bk-MDEA) AND (withdrawal OR dependence))" in Web of Science, PubMed or Scopus databases as the "topic" or in "title+abstract" or in "title+abstract+keywords", respectively, as late as 21 Aug 2016.

8. Abuse Potential

A. Animal Studies

No relevant studies could be identified after minimally searching on "(ethylone OR bk-MDEA) AND (rat OR mouse OR monkey) AND (discrimination OR self administration OR withdrawal OR dependence OR reinforce*) in Web of Science, PubMed or Scopus databases as the "topic" or in "title+abstract" or in "title+abstract+keywords", respectively, as late as 21 Aug 2016.

B. Human Studies

Controlled, laboratory studies using human subjects addressing the abuse potential of ethylone could not be identified after minimally searching on "(ethylone OR bk-MDEA) AND (abuse) in Web of Science, PubMed or Scopus databases as the "topic" or in "title+abstract" or in "title+abstract+keywords", respectively, as late as 21 Aug 2016. Several studies, however, reported instances of intoxication with ethylone or detection of ethylone in biosamples from humans making it reasonable to infer that ethylone has a more than negligible abuse potential and those studies are reviewed in Section #13.

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

Ethylone was originally patented for its potential antidepressant and antiparkinsonian properties by Jacob and Shulgin within a series of N-substituted-2-amino-3',4'-methylene-dioxypropiophenones in 1995[33], but no currently approved medical applications for it could be identified (see Section #11 for further details).

10. Listing on the WHO Model List of Essential Medicines

Ethylone is neither listed on the 19th List for Adults, nor on the 5th List for children in the WHO Model List of Essential Medicines.[34, 35] .

11. Marketing Authorizations (as a Medicinal Product)

Ethylone was originally patented for its potential antidepressant and antiparkinsonian properties by Jacob and Shulgin within a series of N-substituted-2-amino-3',4'-methylene-dioxypropiophenones in 1995.[33] Despite this patent, searching on the terms "ethylone", the CAS Registry number "1112937-64-0", or the IUPAC Name "1-(1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one" in the European Medicines Agency database, the U.S. FDA database (Drugs@FDA), The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) database of the Australian Government Department of

Health, nor the Pharmaceuticals and Medical Devices Agency of Japan yielded any results which suggested a lack of any major marketing authorization (search conducted 17 Aug 2016).

12. Industrial Use

A legitimate industrial use of ethylone could not be identified.

13. Non-Medical Use, Abuse and Dependence

Also see Section #16 for reports of ethylone seizures and identification in biosamples for additional evidence of non-medical use, abuse and dependence.

When a drug is recreationally used, it is often administered concurrently with other drugs. Ethylone has been detected concurrently with known abused drugs in human biosamples. For example, ethylone was detected with diphenidine (1-(1,2-diphenylethyl)piperidine, a dissociative anesthetic, in a 27 year old male who had been recently introduced in the STRIDA project.[36] The possibility of co-presence with other drugs should be kept in mind when evaluating reports of ethylone in biosamples below.

The National Forensic Laboratory Information System of the United States (NFLIS) had not received ethylone-positive cases until the second half of 2011. From then to the first half of 2013, 105 ethylone-positive reports were submitted from Federal, state and local laboratories throughout the USA.[37] Uralets and colleagues analyzed 34,561 random urine samples collected in 2011–2013 from various clients in the USA that had been submitted to the Redwood Toxicology Laboratory (Santa Rosa, CA, USA) for designer stimulant screening.[38] After liquid/liquid extraction and trifluoroacetylation, samples were screened by gas chromatography–mass spectrometry (GC–MS) for drugs and metabolites excreted free in urine and 16 (0.05%) were positive for ethylone.[38]

Ethylone has been identified in several seizures or sampled products in the United States. The U.S. National Forensic Laboratory Information System (NFLIS) identifies confiscated drugs throughout the U.S. and among the 25 most commonly confiscated drugs in 2014, three were synthetic cannabinoids (with over 22,000 reports), and three were synthetic cathinones (a.k.a.: "bath salts;" 5,425 reports (17th highest) involving ethylone, 4,768 involving methylone, and 3,905 involving α-pyrrolidinopentiophenone [alpha-PVP; "Flakka"]). Mephedrone (4-methylmethcathinone [4-MMC]) was once the most commonly confiscated synthetic cathinone (in 2010), but in 2012, methylone became the most commonly confiscated synthetic cathinone, and in 2014, ethylone became the most commonly confiscated synthetic cathinone.[37, 39, 40] In the first six months of 2015 there had already been 4,894 identifications of ethylone in the NFLIS system advancing ethylone's placement to 12th of the most commonly confiscated drugs.[41]

Data on confiscations of ethylone outside of North America appear limited but increasing. Several reports from Europe including from the Netherlands[42], Sweden[36], Romania[43], Finland[44], France[45] and Italy[46, 47] have identified seized ethylone or its presence in biosamples. Additionally, reports from New Zealand[10], Colombia[48], Japan[49], and recently from Thailand[50] have indicated the use or sale of ethylone on the black market.

Also refer to 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

See Section #6 for reports of ethylone-associated deaths and driving intoxications.

Blood analysis of an impaired driver in Washington State (U.S.A.) identified 63 ng/mL α-PVP, 6.1 ng/mL methylone and positive for ethylone.[30] The driver, a 34-year-old male, was stopped by a law enforcement officer for improper lane travel and stopping in the wrong place. He was reported to have stopped 10 feet before a stop sign for no apparent reason. He then drove forward and stopped again. The driver entered the oncoming lane of travel upon turning onto the intersecting highway before quickly moving into the correct lane. The arresting officer observed the vehicle cross the center line three times in the span of 1.5 miles before initiating a traffic stop. The driver was observed to appear disoriented and confused. The drug recognition expert (DRE) officer observed slurred speech, bloodshot watery eyes, dilated pupils, involuntary muscle movements and an elevated pulse and blood pressure.[30]

There have been several (~10) known deaths in which ethylone has been found in postmortem biosamples[31, 32] Details of these deaths are provided in Section #6.

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

15. Licit Production, Consumption and International Trade

Details of the amount of licit international production and trade of ethylone could not be found. SciFinder identifies 11 commercial sources purporting to be able to supply a range of ethylone amounts, from mg levels to "bulk".[12]

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

16. Illicit Manufacture and Traffic and Related Information

Wood and colleagues commented that, "As with previously popular synthetic cathinones, the abuse of ethylone has seen a recent increase due to regulatory efforts on previous generations of cathinones that are now banned."[16] Ethylone has been detected in products marketed as bath salts, plant food and cleaning products.[16, 49] Initial seizures in Canada of ethylone occurred in 2012, and as of 2015, the Canada Border Services Agency has seized over 100 different shipments containing it. Seizures have only been by arrival by air and post. All shipments had originated from China as high purity crystals except for one shipment from Spain that had been a mix of ethylone with methylone and other drugs.[8] These shipments of ethylone into Canada had various declarations or labeling (e.g., "Ocean Snow Ultra", "Iron Oxide Black", "Zeolite", "Geolite", "Acrylic Paint", "Sodium

Isethionate", "Food Materials", "Facial Mask Powder", "Salt Rock", "Phenolic Resin", and "Gelatin") and were of different sizes ranging from several grams to 10 kg, with an average mass of 1 kg.[8]

Ethylone appears readily available. Searching on "ethylone for sale" using the Google search engine yielded over 92,000 hits (August 23, 2016). A superficial sampling of these hits indicated sale for recreational use including one web site promoting, "For those who are seeking a confident time-tested stimulant Ethylone should be the answer." (http://buyresearchchemicalsusa.biz/products/ethylone.html). As one example, Schneir and colleagues obtained 35 samples of "bath salts" purchased at retail stores in six California cities and over the Internet (U.S. sites only), between August 11, 2011 and December 15, 2011.[51] The majority (32/35, 91%) of "bath salts" had one (n=15) or multiple cathinones n=17 present. A total of 14 different cathinones were found. MDPV was the most commonly identified cathinone (n=19), followed by MDPBP (n=10), methylone (n=7), pentedrone (n=6), flephedrone (n=4), ethcathinone (n=4), ethylone (n=4), PVP (n=3), mephedrone (n=3), MDPPP (n=2), buphedrone (n=1), butylone (n=1), pyrovalerone (n=1), and PBP (n=1).[51] One of the branded products purchased was "Ivory Wave Ultra". In one instance, "Ivory Wave Ultra" contained 155 mg of ethylone along with ethcathinone, PVP, pentedrone and MDPBP; in another instance it just contained MDPV.[51]

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

17. Current International Controls and Their Impact

Ethylone is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

CA: Schedule I
DE: Anlage I (Controlled)
UK: Class B
New Zealand: Analogue legislation of the Misuse of Drugs Act 1975
Japan: regulated as ''designated substances (Shitei-Yakubutsu)'' in 2007 under the Revised Japanese Pharmaceutical Affairs Law
Switzerland: Controlled under 2011 regulation enacted by the Swiss Agency for Therapeutic Products
Singapore: Listed in Fifth Schedule of Misuse of Drugs Act

Also refer to 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. Lowe DM, Corbett PT, Murray-Rust P, Glen RC. Chemical name to structure: OPSIN, an open source solution. J Chem Inf Model. 2011;51(3):739-53. doi: 10.1021/ci100384d. PubMed PMID: 21384929.
2. cyberius. bk-MDMA delivery methods: Bluelight.org; 2014 [cited 2016 10/12/16]. Available from: http://www.bluelight.org/vb/threads/713033-bk-MDMA-delivery-methods?highlight=ethylone.
3. Aturki Z, Schmid MG, Chankvetadze B, Fanali S. Enantiomeric separation of new cathinone derivatives designer drugs by capillary electrochromatography using a chiral stationary phase, based on amylose tris(5-chloro-2-methylphenylcarbamate). Electrophoresis. 2014;35(21-22):3242-9. doi: 10.1002/elps.201400085.
4. Merola G, Fu H, Tagliaro F, Macchia T, McCord BR. Chiral separation of 12 cathinone analogs by cyclodextrin-assisted capillary electrophoresis with UV and mass spectrometry detection. Electrophoresis. 2014;35(21-22):3231-41. doi: 10.1002/elps.201400077.
5. Mohr S, Taschwer M, Schmid MG. Chiral separation of cathinone derivatives used as recreational drugs by hplc-uv using a chiralpak as-h column as stationary phase. Chirality. 2012;24(6):486-92. doi: 10.1002/chir.22048.
6. Mohr S, Weiss JA, Spreitz J, Schmid MG. Chiral separation of new cathinone- and amphetamine-related designer drugs by gas chromatography-mass spectrometry using trifluoroacetyl-L-prolyl chloride as chiral derivatization reagent. J Chromatogr A. 2012;1269:352-9. doi: 10.1016/j.chroma.2012.09.079.
7. Geryk R, Kalikova K, Schmid MG, Tesarova E. Enantioselective separation of biologically active basic compounds in ultra-performance supercritical fluid chromatography. Anal Chim Acta. 2016;932:98-105. doi: 10.1016/j.aca.2016.04.044.
8. Maheux CR, Alarcon IQ, Copeland CR, Cameron TS, Linden A, Grossert JS. Identification of polymorphism in ethylone hydrochloride: Synthesis and characterization. Drug testing and analysis. 2015. doi: 10.1002/dta.1859.
9. Cameron TS, Grossert JS, Maheux CR, Alarcon IQ, Copeland CR, Linden A. Inversion twinning in a second polymorph of the hydrochloride salt of the recreational drug ethylone. Acta Crystallographica Section C: Structural Chemistry. 2015;71:266-70. doi: 10.1107/S2053229615004295.
10. Russell MJ, Bogun B. New "party pill" components in New Zealand: The synthesis and analysis of some β-ketone analogues of 3,4-methylenedioxymethamphetamine (MDMA) including βk-DMBDB (β-ketone-N,N-dimethyl-1-(1,3-benzodioxol-5-yl)-2-butanamine). Forensic Science International. 2011;210(1-3):174-81. doi: 10.1016/j.forsciint.2011.03.005.
11. European Monitoring Centre for Drugs and Drug Addiction. Synthetic cathinones drug profile [Accessed August 24, 2016]. Available from: http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cathinones.
12. 1112937-64-0 [Internet]. Chemical Abstracts Service. 2016 [cited August 10, 2016].
13. Zaitsu K, Katagi M, Tatsuno M, Sato T, Tsuchihashi H, Suzuki K. Recently abused β-keto derivatives of 3,4-methylenedioxyphenylalkylamines: a review of their metabolisms and toxicological analysis. Forensic Toxicology. 2011;29(2):73-84. doi: 10.1007/s11419-011-0111-8.
14. Mercolini L, Protti M, Catapano MC, Rudge J, Sberna AE. LC-MS/MS and volumetric absorptive microsampling for quantitative bioanalysis of cathinone analogues in dried urine, plasma and oral fluid samples. J Pharm Biomed Anal. 2016;123:186-94. doi: 10.1016/j.jpba.2016.02.015.

15. Vaiano F, Busardo FP, Palumbo D, Kyriakou C, Fioravanti A, Catalani V, Mari F, Bertol E. A novel screening method for 64 new psychoactive substances and 5 amphetamines in blood by LC-MS/MS and application to real cases. J Pharm Biomed Anal. 2016;129:441-9. doi: 10.1016/j.jpba.2016.07.009. PubMed PMID: 27490334.
16. Wood MR, Lalancette RA, Bernal I. Crystallographic investigations of select cathinones: Emerging illicit street drugs known as 'bath salts'. Acta Crystallographica Section C: Structural Chemistry. 2015;71:32-8. doi: 10.1107/S2053229614025637.
17. Glennon RA. Ethylone, Personal communication to P. M. Beardsley. Virginia Commonwealth University; 2016.
18. Various users. bk-MDMA delivery methods: Bluelight.org; 2014 [cited 2016 10/12/16]. Available from: http://www.bluelight.org/vb/threads/713033-bk-MDMA-delivery-methods?highlight=ethylone.
19. nonumbas. molly injectors be warned: GRINDFACTOR.COM; 2015 [cited 2016 August 25, 2016]. Available from: http://www.grindfactor.com/Forum/showthread.php?1002-molly-injectors-be-warned&highlight=ethylone.
20. Kamata HT, Shima N, Zaitsu K, Kamata T, Miki A, Nishikawa M, Katagi M, Tsuchihashi H. Metabolism of the recently encountered designer drug, methylone, in humans and rats. Xenobiotica. 2008;36(8):709-23. doi: 10.1080/00498250600780191.
21. Zaitsu K, Katagi M, Kamata HT, Miki A, Tsuchihashi H. Discrimination and identification of regioisomeric β-keto analogues of 3,4-methylenedioxyamphetamines by gas chromatography-mass spectrometry. Forensic Toxicology. 2008;26(2):45-51. doi: 10.1007/s11419-008-0050-1.
22. Zaitsu K, Katagi M, Kamata HT, Kamata T, Shima N, Miki A, Tsuchihashi H, Mori Y. Determination of the metabolites of the new designer drugs bk-MBDB and bk-MDEA in human urine. Forensic Science International. 2009;188(1-3):131-9. doi: 10.1016/j.forsciint.2009.04.001.
23. Meyer MR, Maurer HH. Metabolism of designer drugs of abuse: An updated review. Current Drug Metabolism. 2010;11(5):468-82. doi: 10.2174/138920010791526042.
24. syntheticdave. Re: Ethylone (mk-MDEA) drugs-forum.com: drugs-forum.com; 2013 [cited 2016 August 25, 2016]. Available from: https://drugs-forum.com/forum/showthread.php?t=40125.
25. Simmler LD, Buser TA, Donzelli M, Schramm Y, Dieu LH, Huwyler J, Chaboz S, Hoener MC, Liechti ME. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol. 2013;168(2):458-70. doi: 10.1111/j.1476-5381.2012.02145.x.
26. Janowsky A. 33,800, Ethylone, binding and functional activity at biogenic amine transporters. Department of Veterans Affairs Medical Center, Portland, OR, Research Service (R&D-22); December 2015.
27. Forster MJ, Gatch MB, Dolan SB. Ethylone (33,800): Test of substitution for the discriminative stimulus effects of (+)-methamphetamine. Fort Worth, TX: University of North Texas Health Science Center at Fort Worth and National Institute on Drug Abuse, Center for Neuroscience Discovery; July 28, 2016.
28. Forster MJ, Gatch MB. Ethylone (33,800): Test of substitution for the discriminative stimulus effects of cocaine. Fort Worth, TX: University of North Texas Health Science Center at Fort Worth and National Institute on Drug Abuse, Center for Neuroscience Discovery; August 2, 2016.
29. Uralets V. Ethylone. Mesa, AZ: 2013.
30. Knoy JL, Peterson BL, Couper FJ. Suspected impaired driving case involving α-pyrrolidinovalerophenone, methylone and ethylone. Journal of Analytical Toxicology. 2014;38(8):615-7. doi: 10.1093/jat/bku073.

31. McIntyre IM, Hamm CE, Sherrard JL, Gary RD, Burton CG, Mena O. Acute 3,4-methylenedioxy-N-ethylcathinone (ethylone) intoxication and related fatality: A case report with postmortem concentrations. Journal of Analytical Toxicology. 2015;39(3):225-8. doi: 10.1093/jat/bku146.
32. Lee D, Chronister CW, Hoyer J, Goldberger BA. Ethylone-Related Deaths: Toxicological Findings. J Anal Toxicol. 2015;39(7):567-71. doi: 10.1093/jat/bkv053. PubMed PMID: 26025164.
33. Jacob P, III, Shulgin AT, inventors; Neurobiological Technologies, Inc., USA . assignee. Preparation of novel N-substituted-2-amino-3',4'-methylenedioxypropiophenones as anti-depressant and anti-Parkinsonism agents patent WO9639133A1. 1996.
34. World Health Organization. WHO Model List of Essential Medicines for Children: 5th List (April 2015) (Last amended August 2015). 2015. p. 1-42.
35. World Health Organization. WHO Model List of Essential Medicines:19th List (April 2015) (Amended August 2015). World Health Organization; 2015. p. 1-55.
36. Helander A, Beck O, Baeckberg M. Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. Clinical Toxicology. 2015;53(5):446-53. doi: 10.3109/15563650.2015.1033630.
37. U.S. Drug Enforcement Administration, Office of Diversion Control,. National Forensic Laboratory Information System Special Report: Synthetic Cannabinoids and Synthetic Cathinones Reported in NFLIS, 2010–2013. Springfield, VA: U.S. Drug Enforcement Administration, 2014.
38. Uralets V, Rana S, Morgan S, Ross W. Testing for designer stimulants: Metabolic profiles of 16 synthetic cathinones excreted free in human urine. J Anal Toxicol. 2014;38(5):233-41. doi: 10.1093/jat/bku021.
39. U.S. Drug Enforcement Administration, Office of Diversion Control,. National Forensic Laboratory Information System: Annual Report 2014. 2015.
40. Palamar JJ, Acosta P, Sherman S, Ompad DC, Cleland CM. Self-reported use of novel psychoactive substances among attendees of electronic dance music venues. Am J Drug Alcohol Abuse. 2016:1-9. doi: 10.1080/00952990.2016.1181179. PubMed PMID: 27315522.
41. U.S. Drug Enforcement Administration, Office of Diversion Control,. National Forensic Laboratory Information System: Midyear Report 2015. 2016.
42. Hondebrink L, Nugteren-van Lonkhuyzen JJ, Van Der Gouwe D, Brunt TM. Monitoring new psychoactive substances (NPS) in The Netherlands: Data from the drug market and the Poisons Information Centre. Drug and Alcohol Dependence. 2015;147:109-15. doi: 10.1016/j.drugalcdep.2014.11.033.
43. Licsandru A. An overview of the NPS situation in Romania. Directorate for Countering the Organized Criminality Central Laboratory for Drug Analysis and Profiling. Sarajevo 2015.
44. Sundstroem M, Pelander A, Simojoki K, Ojanperae I. Patterns of drug abuse among drug users with regular and irregular attendance for treatment as detected by comprehensive UHPLC-HR-TOF-MS. Drug Test Anal. 2016;8(1):39-46. doi: 10.1002/dta.1818.
45. Table PPP-9. Composition of illicit drug tablets, 2011 [Internet]. European Monitoring Centre for Drugs and Drug Addiction. 2011 [cited August 23, 2016]. Available from: http://www.emcdda.europa.eu/html.cfm/indexEN.html.
46. Odoardi S, Romolo FS, Strano-Rossi S. A snapshot on NPS in Italy: Distribution of drugs in seized materials analysed in an Italian forensic laboratory in the period 2013-2015. Forensic Sci Int. 2016;265:116-20. doi: 10.1016/j.forsciint.2016.01.037. PubMed PMID: 26874736.
47. Strano Rossi S, Odoardi S, Gregori A, Peluso G, Ripani L, Ortar G, Serpelloni G, Romolo FS. An analytical approach to the forensic identification of different classes of new psychoactive

substances (NPSs) in seized materials. Rapid Commun Mass Spectrom. 2014;28(17):1904-16. doi: 10.1002/rcm.6969.
48. Inter-American Drug Abuse Control Commission (CICAD). Early warning system (EWS) observatory on drugs Colombia challenges. Organization of American States Fifty-Seventh Regular Session. Washington, D.C.2015.
49. Uchiyama N, Kikura-Hanajiri R, Kawahara N, Goda Y. Analysis of designer drugs detected in the products purchased in fiscal year 2006. Yakugaku Zasshi Journal of the Pharmaceutical Society of Japan. 2008;128(10):1499-505. doi: 10.1248/yakushi.128.1499.
50. United Nations Office on Drugs and Crime (UNODC). The challenge of synthetic drugs in east and south-east asia and oceania: Trends and patterns of amphetamine-type stimulants and new psychoactive substances. A report from the Global SMART Programme, May 2015. Vienna, Austria: 2015.
51. Schneir A, Ly BT, Casagrande K, Darracq M, Offerman SR, Thornton S, Smollin C, Vohra R, Rangun C, Tomaszewski C, Gerona RR. Comprehensive analysis of "bath salts" purchased from California stores and the internet. Clin Toxicol (Phila). 2014;52(7):651-8. doi: 10.3109/15563650.2014.933231. PubMed PMID: 25089721.

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

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 (3 AFR, 1 EMR, 23 EUR, 7 PAH, 1 SEAR and 6 WPR) answered the questionnaire for ethylone. Of these, 28 respondents (19 EUR, 5 PAH and 4 WPR) had information on this substance.

LEGITIMATE USE

There were 24 countries that reported no approved medical products containing ethylone for human or veterinarian indications. There was also no reported industrial use in 21 countries.

Ethylone is currently being used in medical or scientific research in one country for metabolism and abuse potential research. Importation is the origin/source of ethylone when used for legitimate non-medical/non-scientific use.

Ethylone was not reported to be used for any cultural, religious or ceremonial purposes in 22 countries.

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

There were 19 countries that reported ethylone as being misused for its psychoactive properties (as a recreational drug). Common routes of administration are oral (13 countries), injection (2 countries), inhalation (2 countries), sniffing (10 countries), smoking (2 countries). The main route of administration for ethylone was reported as oral (7 countries), sniffing (1 country) and smoking (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (16 countries), followed by tablets (7 countries), liquid or solution for oral administration/use (1 country). There was also one report of plant material impregnated with the ethylone being used as a formulation. Two countries also reported ethylone being found as crystals, another country commented that it is infrequently found in very small amounts in ecstasy tablets.

There were 13 countries which reported that the source of ethylone for non-medical/non-scientific use was via smuggling from other countries.

One country identified the party scene as a specific subpopulation known to misuse ethylone.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (2 countries), substantial (4 countries) or serious (4 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 ethylone with fatalities. It was also commented that ethylone exceeds the potency of cocaine, and its side effects resemble those of MDMA.

One country reported 5 emergency room/department visits related to the use of ethylone related to the non-medical use.

The adverse effects which presented for ethylone at the emergency room/department included difficulty in breathing, high pulse, tactility loss in face and hands and chest pain.

In regards to the mortality rate, data was provided by 3 countries. The combined total rate which included involvement of other substances was reported to be 1 case in 2014 and 1 case in 2015. Finally the rate, where it was unknown if other substances were involved was 1 case 2015. One country stated that there had been 11 fatalities between 2013 and 2015, however, other substances were also involved. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 22 countries reported that ethylone was under national control. The legislation the control is based upon included Medicines Act (2 countries), Controlled Substances Act (16 countries), Criminal Law Act (1 country) and other specific legislation (3 countries stated it was specific legislation for new psychoactive substances). In two countries the control is a temporary provision. There were no challenges to implementing controls for ethylone reported.

The scope of the controls includes production (17 countries), manufacturing (18 countries), exporting (17 countries), importing (20 countries), distribution (20 countries), use (14 countries) and possession (18 countries).

Reported illicit activities involving ethylone include manufacture of the substance by chemical synthesis (1 country), trafficking (11 countries), smuggling (1 country), diversion (1 country), domestic internet sales (1 country), internet sales from abroad (8 countries), internet sales from unknown locations (3 countries) and finally sales to people who use this substance (5 countries).

There were 16 countries which completed the section on the number of seizures. The combined number of seizures was 5480 (2014), 8985 (2015) and 802 (2016 to date).

If ethylone was placed under international control, 26 countries responded that they would have the capacity to enforce the control at the national level. There were 25 countries which responded that they would have the forensic laboratory capacity to analyse the substance.