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Subject:	Risk assessment report of a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) In accordance with Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances

Following the Council's request to conduct a Risk Assessment on 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.

European Monitoring Centre
for Drugs and Drug Addiction

Technical report on
1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45)

Prepared by: Dr István Ujváry, Budapest, Hungary

EMCDDA contract: CC.14.SAT.006

Date: 15 September 2014

Annex 1 to the risk assessment report of a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45)

This Technical Report was prepared under EMCDDA contract. Given the time frame stipulated in the Council Decision, it has not been formally edited by the EMCDDA. As a result, while the scientific data presented has been verified to the extent possible, minor changes may be introduced at a later date when the report is officially published. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The risk assessment report on 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45), to which this report is annexed was produced by the Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

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Summary

MT-45 is an *N,N'*-disubstituted piperazine having a cyclohexane ring attached to one of the nitrogen atoms of the piperazine ring and a 1,2-diphenylethyl moiety attached to the other nitrogen atom. MT-45 was invented by the Japanese company Dainippon Pharmaceutical Co., Ltd. in the early 1970s. The analgesic properties of MT-45 were studied in preclinical trials in the 1970s and the 1980s, but the drug was not developed into a medicine. MT-45 has no current known legitimate industrial, agrochemical, cosmetic, human or veterinary medical use.

MT-45 has appeared recently on the illicit drug market typically as a white powder. It is offered on the Internet. It was first detected ([1]) in a seizure by customs in Sweden in October 2013 with formal notification to the European Union Early warning system in December 2013. MT-45 has also been detected in Germany and Belgium. Most of the seizures have been reported by Sweden; the largest seizure (250 g) was reported by Germany.

According to experience reports posted on the Internet MT-45 appears to have been available since 2012. It is advertised for sale on its own as a 'research chemical' or a 'legal opioid' in amounts ranging from gram to kilogram quantities.

Due to the lack of co-ordinated national or European population surveys related to MT-45, there is no information on the prevalence of use of MT-45.

From information available from self-reports posted on Internet forums, many of the users of MT-45 appear to be only experimenting with this new substance. Routes of administration are oral, nasal, intravenous or intramuscular injection; inhalation of the vapours of the free amine has also been mentioned. Typical single oral or nasal doses range from 30 to 75 mg.

The pharmacology, with special emphasis on analgesic effects, of racemic MT-45 as well as the individual (*S*) and (*R*) enantiomers has been studied in several animal models. Studies with opioid receptor preparations have also been carried out. Racemic MT-45 and its *(S)* isomer appear to be morphine-like opioid analgesics with the dextrorotatory *(S)* isomer being more potent than morphine in most rodent assays regardless of the route of administration. One receptor study has revealed that (*S*)-MT-45 is an opioid receptor agonist with selectivity towards the δ and κ opioid peptide (DOP and KOP, respectively) receptor types, with affinities comparable to or higher than those of morphine. It appears that the high analgesic activity of the racemic mixture is due to synergistic interactions of the individual stereoisomers. It is also conceivable that some of the metabolites contribute to analgesic activity *in vivo* of MT-45, though the metabolism of MT-45 is not known.

([1]) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or other specimens (tissues, hair, etc.).

The levorotatory (*R*) isomer of MT-45 has been shown to induce learning and memory impairment in mice that is associated with its antagonism at sigma receptors.

There are no clinical studies on the subjective effects of MT-45 in humans. According to self-reports available on Internet forums, the effects of MT-45 resemble those of opioids.

Information on the dependence liability of MT-45 is limited. Studies involving rodent models indicate that MT-45 can substitute for morphine; withdrawal symptoms could also be induced.

The acute toxicity of MT-45 upon oral and intravenous administration to rodents is higher than that of morphine. Typical opioid type adverse effects, including respiratory depression and constipation, were noted in rodent studies.

Eighteen non-fatal intoxications were reported from one Member State, Sweden; twelve of these were analytically confirmed. In life-threatening intoxications the opioid receptor antagonist naloxone was valuable in reversing overdose symptoms.

Twenty-eight deaths associated with analytically confirmed MT-45 have been reported. All occurred in Sweden between November 2013 and July 2014. In all but four of these cases forensic analysis detected other psychoactive substances, including alcohol, prescription medicines and/or new psychoactive substances. In eight cases, MT-45 intoxication was declared to be the cause of death. In one case, MT-45 was detected in an accidental fatality.

In conclusion, MT-45, first described in the scientific literature in 1975, is a recently emerged synthetic opioid analgesic with a novel chemical structure. The powder products currently sold are presumed to be racemic mixtures of the hydrochloride salts of (*S*) and (*R*) stereoisomers of MT-45. The pharmacological properties of MT-45, including dependence liability and toxicity, are similar to morphine. Currently, the substance appears to have a limited use in EU Member States, Norway and Turkey. Between October 2013 and July 2014, MT-45 was seized in two Member States, Sweden and Germany; it was also detected in a single sample in Belgium. Fatal and non-fatal intoxications, occurring within a period of six months, have been reported from a single EU member state, Sweden. Between November 2013 and April 2014, MT-45 has been detected in number of non-fatal poisonings; in the life-threatening cases the opioid receptor antagonist naloxone proved to be a useful antidote. There have been altogether 28 deaths where MT-45 was detected in biological fluids and in four of these cases MT-45 was the sole drug present. Furthermore MT-45 was declared to be the cause of the death in eight of the fatalities.

Section A. Physical, chemical, pharmaceutical and pharmacological information

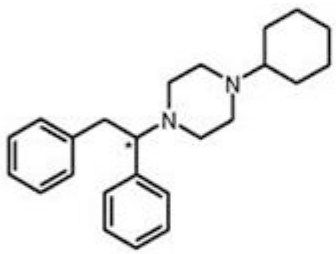
A1. Physical, chemical and pharmaceutical information

A1.1. Physical and chemical description (including methods of synthesis, precursors, impurities if known — type and level)

Chemical description and names

MT-45 is an *N,N'*-disubstituted piperazine compound, having a cyclohexane ring attached to one of the nitrogen atoms of the piperazine ring and a 1,2-diphenylethyl moiety attached to the other nitrogen atom (Figure 1).

Figure 1. The molecular structure, formula and weight of MT-45. Asterisk indicates chiral centre.



Molecular formula: $C_{24}H_{32}N_2$

Molecular weights: 348.52 (base); 421.45 (2 x HCl salt)

MT-45 is a structurally unique synthetic analgesic developed by the Japanese company Dainippon Pharmaceutical Co., Ltd., in the early 1970s while searching for analogues of the tricyclic tranquilizer-antipsychotic perathiepine ([2]) and of the structurally related analgesic lefetamine ([3]) (Umemoto et al., 1972; Natsuka et al., 1975; Nishimura et al., 1976; see also Hori and Fujimura, 1975). The pharmacological properties of MT-45 were studied by industrial and academic laboratories in the 1970s and 1980s in animals and *in vitro*; it would appear that it has not been studied in humans. These experiments revealed that the pharmacology, including analgesic activity, of MT-45 is complex and may involve not only opioid receptors but also non-opioid targets, which have not been fully characterised (Section A2). The development of the compound was apparently abandoned for unknown reason.

The systematic (International Union of Pure and Applied Chemistry, IUPAC) name of MT-45:

1-cyclohexyl-4-(1,2-diphenylethyl)piperazine

([2]) 1-(10,11-Dihydrodibenzo[*b,f*]thiepin-10-yl)-4-methylpiperazine

([3]) Lefetamine, that is (1*R*)-*N,N*-dimethyl-1,2-diphenylethanamine, is controlled under the UN 1971 Convention on Psychotropic Substances as a Schedule IV substance. It is also called (−)-SPA.

Other names, acronyms or synonyms reported: MT-45 ([4]); I-C6 ([5]); IC-6; CDEP; NSC299236 ([6]).

One Member State (Belgium) reported that the street name 'wow' has been used in reference to a combination of MT-45 with a synthetic cathinone analogue methylone ([7]).

MT-45 is a chiral molecule with one asymmetry centre thus two enantiomers exist. The pure isomers may be obtained by resolution of the racemic mixture obtained by synthesis. The optical rotation ($[\alpha]^{22}_{D}$ values) determined for the dihydrochloride salts of (*R*)-(–) and (*S*)-(+) isomers are –56.0 (*c* 1.0, methanol) and +56.3 (*c* 2.0, methanol), respectively (Natsuka et al., 1975). There is no information on the isomeric composition of the samples seized in the EU reflecting, in part, the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Of note in this respect is that no optical rotation was observed for MT-45 isolated from a collected sample of a colourless 'liquid aroma' drug product purchased in Japan in early 2013 indicating that the product contained the racemic mixture (Uchiyama et al., 2014).

The Chemical Abstract Service Registry Numbers (CAS RNs) for MT-45 ([8]):

52694-55-0	racemic free base
57314-55-3	dihydrochloride (2 x HCl) salt
57377-70-5	(*R*)-isomer
57426-38-7	(*R*)-isomer dihydrochloride salt
52694-52-7	(*S*)-isomer
52694-54-9	(*S*)-isomer dihydrochloride salt

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) ([9]) was searched using the CAS registry numbers listed above and also 41537-67-1. The search returned no results.

Identification and analytical profile

Analysis of MT-45 using gas chromatography (GC) or liquid chromatography (LC) coupled with

([4]) It has not been possible to ascertain the origin of the commonly used name MT-45.

([5]) In this acronym used in the scientific and patent literature the Roman numeral 'I' refers to structural 'Group I' studied while 'C6' indicates the 'six-membered cyclohexane' ring.

([6]) The "NSC number" is a Cancer Chemotherapy National Service Center assigned number from the National Cancer Institute of the United States of America.

([7]) 2-Methylamino-1-[3,4-methylenedioxyphenyl]propan-1-one or 1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-2-one

([8]) The CAS RNs were obtained by an exact but not stereodefined structural search in the *SciFinder®* database (CAS, American Chemical Society). Many suppliers and Internet databases, including *PubChem*, *ChemSpider* and *Wikipedia*, give a CAS RN of '41537-67-1' for MT-45 but this identifier is no longer used by CAS for registration purposes.

([9]) http://echa.europa.eu/information-on-chemicals

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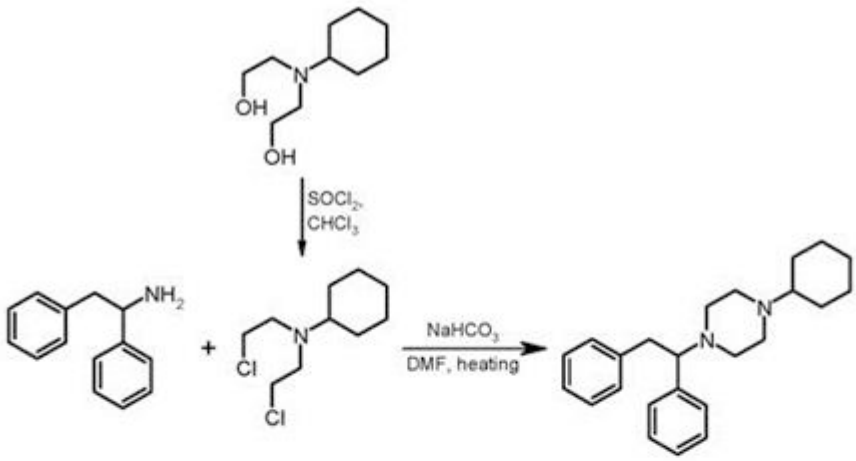
Methods and chemical precursors used for the manufacture of MT-45

There is no information regarding the manufacturing sites, the precursors or the synthetic methods used for MT-45 detected within the European Union. Furthermore, suppliers that advertise MT-45 might not necessarily be the manufacturers of the chemical.

The patent and scientific literature describes two methods for the synthesis of MT-45 and closely related analogues (Natsuka et al., 1975; Nishimura et al., 1978). One of the routes is depicted in Figure 2: the key precursor is the commercially available racemic 1,2-diphenylethylamine, which is readily converted to MT-45 by ring-forming alkylation with *N*,*N*-bis(2-chloroethyl)cyclohexanamine ([13]), which is prepared from the diethanolamine derivative of cyclohexane (Wilson and Tishler, 1951). Alternatively, MT-45 can be prepared by alkylating cyclohexylamine with *N*,*N*-bis(2-chloroethyl)-1,2-diphenylethanamine ([14]) obtained by a multi-step process involving Grignard reaction (Goodson and Christopher, 1950). Note that these syntheses afford a 1:1 mixture of the (*S*) and (*R*) enantiomers each possessing distinct biological activities (Section A2). The pure enantiomers used in pharmacological studies were obtained by optical resolution of the racemic mixture (Natsuka et al., 1975).

Figure 2. The synthesis of MT-45 according to Natsuka et al. (1975).



The syntheses of MT-45 mentioned above use readily available starting materials and require conventional laboratory equipment. No special chemical expertise is needed for the production of the substance. However, familiarity with special precautions that should be taken during handling the 'nitrogen mustard' intermediate products is a requirement.

([13]) The blister-producing bis(2-chloroethyl)amine derivatives (nitrogen mustards) should be considered to be dangerous (cytotoxic) substances due to their bioalkylating properties.

([14]) See previous footnote on the toxicity of nitrogen mustards.

Other synthetic methods are also feasible and have, in fact, been used for the synthesis of related 1,2-diphenylethylamines (see, for example, Yamakawa, 1960). One of such routes relies on the reaction of a benzyl Grignard reagent and an α-piperazino-benzonitrile, which can be obtained from benzaldehyde, an alkali metal cyanide and the appropriate piperazine (Strecker synthesis) ([15]). A similar, cyanide-free synthetic procedure that uses benzaldehyde, a benzyl Grignard reagent and an appropriately substituted piperazine as precursors may also be applicable (Fray et al., 2006).

Typical impurities encountered in seized samples

There is currently no information available on impurities arising from the synthesis of MT-45 in the seized and collected samples obtained from the drug market (Section C). For seizures reported to the EMCDDA and Europol, the ingredient content has usually not been quantified.

Of the 28 seizures made in Sweden, one powder contained a synthetic cathinone (α-PBP ([16])), while another one contained an arylethylamine stimulant (6-APDB ([17])). A white powdery sample detected in Belgium contained MT-45 and methylone. A 'light brown, chunky substance' seized in Germany contained MT-45, heroin base, caffeine, paracetamol and sorbitol. In two plant materials seized in Sweden, MT-45 was detected in the presence of the synthetic cannabinoid receptor agonist AB-FUBINACA ([18]) in one case and APINACA (AKB-48) ([19]) in the second case. For details on seized and collected samples, see Section C.

During forensic analysis of a range of products purchased in Japan between January and March 2013, MT-45 was found along with other new psychoactive substances in an herbal mixture, in a 'fragrance powder' and in two 'liquid aroma' formulations (Uchiyama et al., 2014).

A1.2. Physical/pharmaceutical form

A structured search conducted by the EMCDDA of Internet suppliers and retailers selling MT-45 (Section 3.4.2) found that, where specified, the substance is offered as the dihydrochloride salt form; in most cases the form offered was not specified. Self-reported experiences on user websites mention the use of the dihydrochloride salt (Bluelight, 2014a; Flashback, 2014; Shroomery, 2014).

Information provided from seizures and a collected sample reported by the Member States has usually noted the presence of MT-45 in powder form. Whether the MT-45 was the free amine or a salt has not been reported. Since no systematic analysis has been done, it is not known

([15]) This type of a reaction has general applicability for the synthesis of phencyclidine and related drugs. Alkali cyanides, however, are highly poisonous substances and their manufacture, trade and use require special permit.

([16]) 1-Phenyl-2-(pyrrolidin-1-yl)butan-1-one

([17]) 6-(2-Aminopropyl)-2,3-dihydrobenzofuran or 1-(2,3-dihydro-1-benzofuran-6-yl)propan-2-amine

([18]) *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide

([19]) *N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide or 1-pentyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1*H*-indazole-3-carboxamide

that the substance traded under the name 'MT-45' is the free amine or its (di)hydrochloride salt. In one instance it was detected in a seized sample of brown heroin base. MT-45 has also been detected in samples of plant material in the presence of synthetic cannabinoid substances. In two non-fatal intoxications reported by Sweden the physical form used by the patients included a tablet in one case and a capsule in the other.

A detailed description of MT-45 seizures and collected samples that have been encountered can be found in Table 4 (Section C).

A1.3. Route of administration and dosage

Information provided by the Member States and obtained from user websites suggests that the route of administration for MT-45 include nasal insufflation ('snorting'), oral intake (tablets, capsules or 'bombing'), smoking, as well as intravenous and intramuscular injection, and rectal administration (see also Section D1.2 and Tables 6 and 7). Self-reported doses in non-fatal intoxications relating to MT-45 use were 100 mg for oral and 60 mg for nasal intake (Helander et al., 2014). Information from several user websites indicates that a range of doses may be used: single oral doses typically ranged from 25 mg to 75 mg with re-dosing reported; doses for nasal insufflation included 15–30 mg (this route of administration was noted by several users to cause painful irritation). One user reported inhaling the vapours of MT-45 base made from 50 mg of the salt; the same user reported rectal administration of '80 mg of MT-45 salt as the solution' (Bluelight, 2014a). Single acute oral doses as high as '215 mg' and repeated dosages totalling 500 mg over the course of 12 hours have also been reported by other users. For further details, see Section D1.2 (see also Bluelight, 2014a; Flashback, 2014; Shroomery, 2014).

In non-fatal intoxications associated with MT-45 use other psychoactive substances have also been detected in biological samples (Helander et al., 2014; for details, see Section D1.2.2). In several of the deaths reported by Sweden forensic analysis of biological samples detected MT-45 in conjunction with other new psychoactive substances, medicines and/or controlled drugs (details provided in Section D1.2.3 and Table 8). Information from user websites also suggests that MT-45 may be used on its own as well as in combination with other drugs (Bluelight, 2014a).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacokinetics

There are no data available from animal studies in the literature on the pharmacokinetics of MT-45. Likewise, there are no data on the metabolic fate of MT-45 in humans.

It is of note that a recent study on the metabolism in the rat of structurally related 1,2-diphenylethylamines identified aromatic ring hydroxylation as one of the initial metabolic steps (Wink et al., 2014). Similar phenolic derivatives could be formed from MT-45 as well, and such compounds have been prepared and shown to be bioactive (Natsuka et al., 1978; Nakamura et al., 1980; Nozaki et al., 1989; Kobayashi, 1991) and may contribute to the overall pharmaco-

toxicological profile of MT-45 *in vivo*. (see also subsection on *Pharmacodynamics* below).

In the absence of studies examining the pharmacokinetics of MT-45 in humans, user reports available on the Internet are the only source of information relating to the time course of the effects of MT-45. According to these self-reports, the psychoactive effects of MT-45 become apparent at about 15 min after nasal intake of 30 mg, or at about 60 min after oral intake of single doses in the range of 45–70 mg; at these dosages the effects of MT-45 subside after 2 hours; by re-dosing, which is frequently reported, the effects may be extended for over 8 hours (Bluelight, 2014a). For examples of user reports, see Section D1.2.1.

Pharmacodynamics

The unusual pharmacological properties of compounds containing the 1,2-diphenylethylamine core have been studied since 1940 (see, for example, Dodds et al., 1945). The structurally simple lefetamine, also known as (–)-SPA, is an obsolete – and internationally controlled – analgesic with some stimulant properties investigated in Japan in the early 1960s and with limited medical use in Italy (*Santenol*) (see Janiri et al., 1989), also contains this structural core. From a historical point of view, the development of MT-45 was based on structural analogies to the experimental antipsychotic perathiepine and the analgesic-stimulant lefetamine. Interestingly, four substances related to MT-45 have recently emerged in the EU as 'new psychoactive substances': diphenidine ([20]), methoxphenidine ([21]), NEDPA ([22]) and NPDPA ([23]) also contain the 1,2-diphenylethylamine moiety. The pharmacology of the former two is, however, different: their anesthetic and 'dissociative' effects are similar to ketamine and are due to their noncompetitive antagonism at the NMDA (*N*-methyl-D-aspartate) receptor complex (Berger et al., 2009; Wallach et al., 2014).

During a research programme starting in the early 1970s and spanning two decades, scientists at Dainippon Pharmaceutical Company prepared and investigated over 100 *N*-(1,2-diphenylethyl)piperazine derivatives (Umemoto et al, 1972; Natsuka et al., 1975, 1978, 1987, 1999). Among the first series of compounds, MT-45 stood out as a promising analgesic agent comparable to morphine (Natsuka et al., 1975).

The analgesic activity of racemic MT-45 as well as the individual *(S)*- and (*R*)-MT-45 stereoisomers were compared to morphine and lefetamine and used methods according to the standards of the day with rodents as experimental animals. Specifically, thermal pain was induced by heat light radiation onto the tail of the animal (D'Amour-Smith or tail-flick method), mechanical pain was induced by pressing the tail of the animal (modified Haffner test), chemical pain was induced by administering phenylquinone or acetic acid intraperitoneally to the animal (writhing method), while electrical pain was induced by applying electrical stimuli by

([20]) 1-(1,2-diphenylethyl)piperidine

([21]) 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine

([22]) *N*-ethyl-1,2-diphenylethylamine

([23]) *N*-isopropyl-1,2-diphenylethylamine

subcutaneous electrodes inserted in the base of the tail of the animal. The analgesic activity of the compounds is expressed as weight-based ED_{50} values ([24]) calculated from dose-response curves (for details, see Nakamura and Shimizu, 1976). The results are summarised in Table 1.

Table 1. Analgesic activity (ED_{50} values in mg/kg) of morphine hydrochloride and MT-45 and its stereoisomers, all as dihydrochlorides, and lefetamine hydrochloride upon subcutaneous (s.c.) or oral administration (male animals; n = 18–54) (Natsuka et al., 1975; Nakamura and Shimizu, 1976; Imai, 1982) ([25]). Key: a: phenylquinone-induced pain (Natsuka et al., 1975; Nakamura and Shimizu, 1976); b: acetic acid-induced pain (Kobayashi, 1991).

Drug		Mice				Rats	
		Thermal	Mechanical	Electrical	Chemical	Thermal	Mechanical
morphine	s.c.	2.39	2.41	1.22	0.58[a]	3.79	1.17
	s.c.				0.47[b]		
	oral	29.4	15.4	7.70	4.20[a]	41.0	32.0
rac. MT-45	s.c.	3.09	2.15	1.54	2.24[a]	6.62	0.73
	s.c.				0.64[b]		
	oral	20.9	11.9	30.8	12.5[a]	29.5	36.4
(*S*)-MT-45	s.c.	1.92	1.09	0.91	1.97[a]	5.39	0.73
	s.c.				0.40[b]		
	oral	20.9	5.51	14.8	10.6[a]	no data	26.0
(*R*)-MT-45	s.c.	50.7	27.4	38.3	36.0[a]	≥75	45.0
	s.c.				1.0[b]		
	oral	no data	no data	41.0	73.3[a]	no data	no data
lefetamine	s.c.	46.6	19.4	17.9	3.86[a]	36.9	42.0
	s.c.				6.0[b]		
	oral	>240	68.6	>100	52.3[a]	>240	>240

As can be seen in Table 1, the analgesic activity of racemic MT-45 was comparable to morphine against all noxious stimuli except, perhaps, against chemically induced pain. Comparing the ED_{50} values shown in Table 1, it is also evident that the analgesic activity of MT-45 resides in the dextrorotatory (*S*) isomer. For example, the respective subcutaneous ED_{50} values of (*S*)- and (*R*)-MT-45 are 1.92 and 50.7 mg/kg in the mouse thermal pain test.

([24]) ED_{50}, or median effective dose, is the dose causing 50% of the maximum or an arbitrary but well defined effect for the measured biological effect of interest.

([25]) Thermal pain was induced by heat light radiation onto the tail of the animal (D'Amour-Smith or tail-flick method), mechanical pain was induced by pressing the tail of the animal (modified Haffner test), chemical pain was induced by administering phenylquinone or acetic acid intraperitoneally to the animal (writhing method), while electrical pain was induced by applying electrical stimuli by subcutaneous electrodes inserted in the base of the tail of the animal.

Because of its higher molecular mass ([26]), racemic MT-45 is somewhat more active than morphine on a molar basis in some of the assays.

It is notable that upon subcutaneous injection the analgesic activity of the (*S*) enantiomer of MT-45, even on weight-based terms, is higher than that of morphine in most animal tests. Upon oral administration, however, morphine appears to be more active in some of the assays shown in Table 1.

Lefetamine was less active than MT-45 as an analgesic in all tests in both rodent species.

The relationship between the analgesic activity in the mouse and the opioid receptor binding *in vitro* using rat brain homogenate preparations was studied for MT-45 and its individual enantiomers; morphine and lefetamine were used as comparative standards (Fujimura et al., 1978; Imai, 1982; Nozaki et al., 1983; see also Nozaki et al., 1989). To evaluate the effect of the substances on peripheral opioid receptors, inhibition of electrically induced contractions of the longitudinal muscle of guinea-pig isolated ileum ([27]) was also determined. Receptor affinities of the test compounds were characterised by estimating the binding inhibition (IC_{50} values ([28])) of the specific radioligand to the receptor preparation. The radioligands used were: [^{3}H]naloxone (preference to MOP receptors), [^{3}H]dihydromorphine (preference to MOP receptors), DADLE ([^{3}H](D-Ala^2,D-Leu^5]enkephalin; DOP receptor specific), and EKC ([^{3}H]ethyl-ketocyclazocine; KOP receptor specific). The results are shown in Tables 2 and 3 ([29]).

A comparison of the *in vivo* analgesic activity data shown in Table 2 indicates that the racemate and the (*S*)-isomer of MT-45 are more potent than morphine. The (*R*)-isomer is less active than morphine though its analgesic effect is comparable to that of lefetamine. In the isolated guinea pig ileum assay *in situ*, the (*S*)-isomer of MT-45 displayed high activity although it was still 2.6-fold less active than morphine in inhibiting electrically induced contractions in this experimental setup. Similar to morphine, MT-45 and both its isomers displayed strong antinociception when injected directly into the brain (i.e., by the intracerebroventricular route), thus a central mode of analgesic action is evident.

Table 2. Analgesic activity in mice and inhibition of electrically induced contraction of guinea pig ileum preparation by MT-45 and its stereoisomers, all as dihydrochlorides, morphine hydrochloride and lefetamine hydrochloride (Fujimura et al., 1978; Imai, 1982; Nozaki et al, 1983). Abbreviations: s.c.: subcutaneous injection; i.c.v.: intracerebroventricular injection.

([26]) Because of its higher molecular weight, MT-45 (348.54 for the free base and 421.45 for the dihydrochloride salt) is more active than morphine (285.34 for the free base and 321.80 for the hydrochloride salt) in some assays when using molar ED_{50} values instead of the weight-based values given in Table 1. For example, the respective molar ED_{50} values for subcutaneously administered morphine and racemic MT-45 are 7.4 and 7.3 µmol/kg thermal (tail-flick) test, 7.5 and 5.1 µmol/kg in the mechanical (Haffner) test, and 1.8 and 5.3 µmol/kg in the chemical (writhing) test in the mouse.

([27]) The guinea-pig ileum is now known to possess multiple opioid receptor types, namely MOP and KOP receptors with little or no DOP receptors.

([28]) IC_{50} is the concentration of the test compound required to displace 50% of the radiolabelled ligand from the receptor.

([29]) Since discrepancies in some of the receptor affinity values on morphine-competition assays in publications from this group have been noted, relevant data were taken from the most recent publication (Nozaki et al., 1983).

Drug	Analgesic activity, ED_{50}		Guinea pig ileum contraction, IC_{50}
	s.c. mg/kg	i.c.v. µg/kg	nM
morphine	5.9	0.40	4.8
rac. MT-45	1.7	0.12	15.3
(*S*)-MT-45	4.4	0.35	12.7
(*R*)-MT-45	30.0	2.00	107
lefetamine	19.0	3.20	138

Table 3. Affinities of morphine hydrochloride, MT-45 and its stereoisomers, all as dihydrochlorides, and lefetamine hydrochloride to binding sites of various tritiated ligands in rat brain homogenates (Fujimura et al., 1978; Imai, 1982; Nozaki et al, 1983). Abbreviations: DHM: [$^3H_2$]dihydromorphine; NLX: [^{3}H]naloxone; DADLE: [^{3}H](D-Ala^2,D-Leu^5]enkephalin; EKC: [^{3}H]ethylketocyclazocine.

Drug	IC_{50}, nM			
	DHM	NLX	DADLE	EKC
morphine	4.6	5.5	78.6	242
rac. MT-45	644	743	156	176
(*S*)-MT-45	736	143	70.6	78.0
(*R*)-MT-45	1610	1210	614	791
lefetamine	3082	3685	1110	4022

Data on competitive binding to purified receptor preparations reveal some receptor type selectivity (Table 3). The (*S*) isomer and the racemate of MT-45 are poor inhibitors of the binding of the tritiated dihydromorphine and naloxone probes indicating low affinity to MOP receptors. However, (*S*)-MT-45 efficiently competes with the DOP-selective tritiated enkephalin analogue probe DADLE and even more efficient in inhibiting the binding of the KOP-selective [^{3}H]ethylketocyclazine ligand with an IC_{50} value three-fold lower than that of morphine. Accordingly, this isomer is a preferential DOP and KOP receptor ligand. According to data shown in Table 3, the receptor selectivity of (*R*)-MT-45 is lower than that of its enantiomer, though a relatively high affinity to MOP receptors is retained.

In a separate study using different receptor preparations and [^{3}H]diprenorphine as radioligand, the IC_{50} values for the MOP receptor were 0.17 µM and 11 µM for morphine and MT-45, respectively, while for the KOP receptor the IC_{50} values were 0.42 µM and 16 µM for morphine and MT-45, respectively (Kobayashi, 1991).

Receptor binding experiments conducted in the presence or absence of Na^+ shed light on the functional nature of receptor interaction and indicated that, similar to morphine, racemic MT-45 and (*S*)-MT-45 are opioid receptor agonists: the 'sodium index' ([30]) for morphine, racemic MT-45, (*S*)-MT-45, (*R*)-MT-45 and naloxone was 26, 5, 6, 1 and 1, respectively (Fujimura et al, 1978; Imai, 1982).

Molecular modelling studies attempted to interpret the structural and conformational requirements responsible for the unique analgesic activity and receptor selectivity of the enantiomers of MT-45 and some of its analogues, lefetamine and morphine (Nozaki et al, 1989; Kobayashi, 1991).

The above experimental results indicate that MT-45 is an opioid receptor agonist and its morphine-like properties *in vitro* reside in the (*S*) enantiomer. The mode of analgesic action of the individual enantiomers and the racemic mixture, however, appears to be complex ([31]). It is notable that the (*S*)-isomer shows binding preference to DOP and KOP receptors. Interactions at an allosteric site that could contribute to the analgesic activity of the racemic mixture of MT-45 have also been suggested ([32]). Since the metabolism of MT-45 has not been studied, the potential contribution of metabolites, such as ring-hydroxylated derivatives, to the analgesic activity – or to the toxicity – of the substance is not known. (The analgesic activity and receptor binding of related synthetic phenols, which in theory could be formed *in vivo* by ring-hydroxylation of MT-45, has been studied; see Section A2 *Pharmacokinetics* above and paragraph below).

Among the 1-substituted-4-(1,2-diphenylethyl)piperazine derivatives disclosed in a series of publications by Dainippon Pharmaceutical company, several compounds had equal or higher analgesic activity than MT-45. For example, replacement of the cyclohexane ring of MT-45 by larger (e.g., cycloheptane or cyclooctane) rings affords substances with strong analgesic activity. Notable are also certain phenol and methoxy derivatives ([33,34]) (Nishimura et al., 1978; Natsuka et al., 1987; Kobayashi, 1991; Natsuka et al., 1999). Some analogues containing a substituted-phenyl group in place of the cyclohexyl group of MT-45 are 20 to 100 times more potent analgesics than morphine in animal assays (Natsuka et al., 1987). A further potent analogue is AD-1211 ([35]) which produces analgesia through a central mechanism but lacks

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([30]) The ability of Na^+ to decrease the potency of opioid receptor agonists to opioid receptors with negligible effect on the potency of antagonist can be used to differentiate agonists from antagonists in simple binding experiments. Thus, for opioid receptor agonists the 'sodium index', that is the ratio of IC_{50} values determined in the presence and in the absence of Na^+, is larger than 1 (for a recent review on this allosteric phenomenon, see Katritch et al., 2014).

([31]) Several lines of evidence indicate that co-administration of MOP and DOP receptor agonists can result in synergistic analgesic effects (Ananthan, 2006), while KOP receptor activation antagonises the analgesic activity of MOP receptor agonists (Pan, 1998).

([32]) It could be of relevance that a study by Matsuno et al. (1998) revealed that the (*R*)-MT-45 interacts with sigma receptors, which are known to modulate opioid analgesia.

([33]) 3-[2-(4-Cyclohexylpiperazin-1-yl)-2-phenylethyl]phenol and 1-cyclohexyl-4-[2-(3-methoxyphenyl)-1-phenylethyl]-piperazine, respectively.

([34]) The *para*-hydroxy analogue, that is '4-[2-(4-cyclohexylpiperazin-1-yl)-2-phenylethyl]phenol', which is less active than MT-45 (Natsuka et al., 1978), has been advertised on the Internet: http://www.lookchem.com/cas-633/63384-27-0.html; http://www.molbase.com/en/cas-63384-27-0.html (August 2014).

([35]) 3-[2-[4-(3-methylbut-2-en-1-yl)piperazin-1-yl]-2-phenylethyl]phenol

respiration inhibition (Nakamura et al., 1985).

Respiratory depression, which is one of the most prominent adverse effects of MOP receptor agonists, of racemic MT-45, of its pure enantiomers and of morphine was examined in rabbits upon intravenous administration (Nakamura and Shimizu, 1976). At the 1 mg/kg dose, racemic MT-45 and (*S*)-MT-45 depressed respiration by 59% and 57%, respectively; the (*R*) enantiomer failed to cause any respiratory depression even at 5 mg/kg. In comparison, a dose of 3 mg/kg morphine depressed respiration by 63%. These results suggest that for racemic MT-45 the acute toxicity risk due to respiratory depression is at least as high as for morphine ([36]).

The effects of racemic MT-45, its pure enantiomers and morphine on gastrointestinal motility were compared using the charcoal meal test in mice (Nakamura and Shimizu, 1976). At 3 mg/kg and 10 mg/kg subcutaneous doses, both racemic MT-45 and (*S*)-MT-45 reduced gut propulsion dose-dependently but their potency was somewhat weaker than that of morphine at the same dosages. The (*R*) isomer of MT-45 was about tenfold less potent than the (*S*) isomer.

The effect on pupil size of subcutaneously administered MT-45 and its isomers was studied in mice and rabbits (Nakamura and Shimizu, 1976). In the mouse, the mydriatic activity of racemic MT-45 was higher than that of morphine at the equal 10 mg/kg dose; at the 3 mg/kg dose the synthetic drug was somewhat less effective than morphine in increasing pupil diameter. However, the (*S*) isomer of MT-45 and morphine appeared to be equally active at the 3 mg/kg dose. The (*R*) isomer had negligible effect of pupil size even at the 30 mg/kg dose. In the rabbit, miotic response was observed for morphine at 10 mg/kg but none of the MT-45 preparations had any effect on pupil size at this dose.

In the mouse, the Straub-tail indexes ([37]) for racemic MT-45, its (*S*) isomer and morphine were estimated to be 7.34, 30 and 33.1, respectively, suggesting the involvement of the opioid system in the pharmacology of the synthetic piperazine derivatives (Nishimura et al.,1976; see also: Natsuka et al., 1987).

The local anesthetic activity of MT-45 and both of its isomers was investigated using the corneal reflex method in guinea pigs with morphine and procaine as comparative standards (Nakamura and Shimizu, 1976). The local anesthetic activity of (*R*)-MT-45 was the highest of the test compounds with a mean effective concentration of 0.03%. For racemic MT-45, (*S*)-MT-45, morphine and procaine the mean effective concentration values were 0.092, 0.16, 2.0 and 0.27 %, respectively. (Note that it is (*S*)-MT-45 that is mostly responsible for the analgesic activity of the drug, although it is assumed that the (*R*) enantiomer also contributes to the overall biological activity of the racemic mixture; see Tables 1 and 2).

([36]) The toxic symptoms, including respiratory depression, observed in non-fatal human overdose cases related to MT-45 use could successfully be treated with naloxone administration (Helander et al., 2014; see also Section D1.2).

([37]) The 'Straub-tail index' is defined as the ratio of the intravenous LD_{50} value and the Straub tail ED_{50} value, where the Straub tail ED_{50} is defined as the dose, injected intravenously through the tail vein of the animal, producing Straub-reaction (rigid tail held upright and tending to curling over the back of the animal in an S-shaped curve) in 50% of the treated animals. The Straub-index was once used to assess dependence liability of drugs, including narcotics.

The effect of MT-45, its isomers and morphine on body temperature after subcutaneous injection of 3 or 10 mg/kg doses were studied by recording changes in rectal temperature of separately kept Wistar rats (Nakamura and Shimizu, 1976). While (*R*)-MT-45 had negligible effects at these doses, 10 mg/kg of racemic MT-45 transiently increased the rectal temperature by 1.02 °C though this hyperthermia was much milder than that of morphine at the same dose; the effect of (*S*)-MT-45 on body temperature was comparable to that of the racemic drug.

While morphine at 10 mg/kg subcutaneous administration caused a remarkable change (~136% increase) in plasma glucose level in rabbits compared to untreated animals, the hyperglycemic activity MT-45 was much weaker (~40% increase) at this dose (Nakamura and Shimizu, 1976).

Matsuno et al. (1998) examined the involvement of sigma receptors ([38]) in the psychopharmacological activity of MT-45. It was found that intraperitoneally administered (*R*)-MT-45 ([39]) produced significant memory impairment in the mouse passive avoidance learning performance test. This memory impairment could be alleviated by subcutaneous administration of sigma receptor agonists, such as (+)-*N*-allylnormetazocine, suggesting that the observed memory impairment is due to the antagonist effect of (*R*)-MT-45 at sigma receptors and thus unrelated to opioid receptors (see Pan, 1998). A receptor binding study, using guinea pig brain membrane preparation and [^{3}H]pentazocine as radioligand, revealed that (*R*)-MT-45 possessed high affinities for both σ_1 and σ_2 receptor subtypes with IC_{50} values of 1.4 nM and 1.8 nM, respectively.

In an *in vivo* screening programme conducted at the National Cancer Institute (USA), MT-45, codenamed NSC299236, was found inactive in two P388 leukemia mouse models at 25 or 50 mg/kg intraperitoneally injected doses (NCBI, 2014).

No studies were identified that have examined the pharmacology of MT-45 or its close analogues in humans. For the acute physiological and psychological effects noted in users of MT-45, see Section D1.2.

A3. Psychological and behavioural effects

As described in Section A2, animal studies only characterised the narcotic-analgesic effects of MT-45. There is scarce information on the behavioural effects of MT-45 in animals (for dependence liability studies, see Section B1; for different toxic symptoms observed for the enantiomers administered at non-lethal doses, see Section D1.1).

There are no published formal studies assessing the psychological and/or behavioural effects

([38]) Initially, sigma receptors were proposed to be as a subtype of opioid receptor but they are no longer considered to be opioid receptors. Nevertheless, sigma receptors can influence opioid actions, including analgesia. The σ_1 and σ_2 sigma receptor subtypes have been well characterised. Receptor subtype σ_1 could be a potential target for the treatment of a host of neuropsychiatric disorders, such as schizophrenia, depression, and cognitive disorders, as well as brain ischemia and drug dependence.

([39]) The substance was codenamed 'CDEP' by the authors of this study.

of MT-45 in humans. Limited information available on user websites indicates that the effects of MT-45 resemble those of opioids. (For effects described in selected users' self-reports, see Section D1.2.1)

A4. Legitimate uses of the product

No information was provided by any Member State, Turkey and Norway indicating industrial, agrochemical, cosmetic, veterinary or human medical use. The legitimate use of MT-45 is currently restricted to scientific research, if any, and as an analytical reference standard.

There is no information that MT-45 is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products this information cannot be verified. There is no marketing authorisation (existing, ongoing or suspended) for MT-45 in the European Union or in the Member States (EMCDDA–Europol, 2014).

Literature searches have indicated that the 1-(1,2-diphenylethyl)piperazine core structure present in MT-45 is a unique and rarely used template in medicinal chemistry ([40]).

As mentioned in Section A2, several 1,2-diphenylethylamine derivatives structurally related to MT-45 have been investigated but none of them was marketed as a medicine.

Close analogues of 1-(1,2-diphenylethyl)piperazines, such as the corresponding cathinone-like aminoketones (also called 'desyl-piperazines' or, formally, 1,2-diphenyl-2-(piperazin-1-yl)-ethanones) and ephedrine-like aminoalcohols (formally 1,2-diphenyl-2-(piperazin-1-yl)ethanols) have been described (Gruenman and Hoffer, 1967; Shimokawa et al., 1979; Li et al., 2006).

Section B. Dependence and abuse potential

B1. Animal *in vivo* and *in vitro* data

The dependence liability of racemic MT-45 and (*S*)-MT-45 was assessed in rodents (Nishimura et al.,1976; see also: Natsuka et al., 1987). Nalorphine-treatment of mice that had received repeated doses of the test substances precipitated jumping behaviour and other withdrawal signs similar to those noted for morphine in the same assay. Furthermore, MT-45 substituted for morphine in morphine-dependent rats. To assess dependence liability, Nishimura et al. (1976) determined the Straub-index in the mouse (see Section A2 for discussion) for racemic MT-45, (*S*)-MT-45 and morphine as 7.34, 30 and 33.1, respectively. Note, however, that the Straub-tail response is now known to be an inadequate method for dependence assessment. Nevertheless, these data indicate that (*S*)-MT-45 has morphine-like pharmacological properties.

([40]) A literature search in SciFinder® (CAS, American Chemical Society) using the molecular structure of MT-45 retrieved a patent (Haggerty et al., 2012) listing MT-45, by its systematic name, among hundreds of potential adjuvants with possible use in cancer therapy. Furthermore, the search retrieved not only publications on the queried substance but also two irrelevant inorganic chemistry publications that apparently use 'IC6' as an acronym for some other chemical.

No animal self-administration studies appear to have been published. Tolerance, cross-tolerance or sensitisation studies are also lacking.

B2. Human data

No studies were identified that have examined the dependence and/or abuse potential of MT-45 in humans. There are no user reports or published cases in the scientific or grey literature describing the potential for dependence or abuse potential for MT-45. Additionally, there have been no formal studies investigating the dependence and/or abuse potential of MT-45 in humans.

We are not aware of any reports from local, regional or national drug treatment agencies relating to MT-45 dependence.

Some self-reported user experiences ('trip reports') on user websites suggest tolerance and describe withdrawal-like symptoms as "minor but still unpleasant", "hot and cold, dry retching" and "my pupils were huge" (Bluelight, 2014a).

Section C. Prevalence of use

Information from seizures, collected and biological samples

MT-45 was first detected in a seizure by customs in Sweden on 15 October 2013 with formal notification to the EU Early Warning System on 5 December 2013. Subsequently, an additional two European countries, that is Belgium and Germany reported the detection of MT-45 to the EU Early Warning System ([41])either in one or more seizures, collected samples or intoxication cases. The details of the seizures, indicating year, number, amount and seizing authority, by these member states are listed in Table 4. MT-45 has mostly been encountered in white or off-white powder form. In three of the powder samples another 'new psychoactive substance' was also detected. MT-45 was also found in two herbal smoking mixtures along with a synthetic cannabinoid. No detection of MT-45 has been reported by the other Member States, Turkey and Norway.

Table 4. Details of seizures and collected samples of MT-45 reported to the EMCDDA and Europol

Country	Amount and details of the seizure / collected sample
Belgium	

([41]) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or other specimens (tissues, hair, etc.).

Country	Amount and details of the seizure / collected sample
2014	Detected in a powder sample obtained from a user who purchased it from an Internet shop and had it tested by a 'pill testing' service. The sample also contained methylone.
Germany	
2013	One seizure by the police of a "light brown chunky substance" (11.3 g) containing MT-45, heroin base, caffeine, paracetamol, and sorbitol.
2014	One seizure by the police of white powder (250.49 g) containing MT-45 of 95% purity.
Sweden	
2013	One seizure of white powder (49.9 g) by customs, four seizures (0.51, 1.3, 2.12 and 4.08 g; all white powders) by police.
2014	Twenty-nine seizures (ranging from 0.1 g to 9 g) as white powders; one of these samples contained 6-APDB another one alpha-PBP, both synthetic stimulant. Two further seizures (0.55 and 0.99 g) of herbal material contained MT-45 along with a synthetic cannabinoid (AB-FUBINACA or AKB48). With the exception of one seizure that was made by customs all seizures were made by the police.

The drug has also been encountered in Japan (Uchiyama et al., 2014) and in the USA ([42]).

Availability from Internet retailers

According to Internet searches for 'MT-45' conducted several times from early-2014 to August 2014, the family of "piperazine-opioids" was discussed as early as October 2006 with a short list of scientific publications on MT-45 (Bluelight, 2014b). A Wikipedia entry was created in March 2011 (Wikipedia, 2014). Experience reports followed from 2012 (Bluelight, 2014a; Flashback, 2014; Shroomery, 2014).

According to 'Google Trends' ([43]), the first peak of the Google-defined relative search frequency for 'MT-45' emerged in September 2012.

According to Swedish chat forums on psychoactive substances, MT-45 became used in Sweden in May 2013 (Helander et al., 2014).

For the purpose of the EMCDDA-Europol Joint Report on MT-45, a structured search of the Internet was conducted in June 2014 for Internet suppliers (that typically appear to be manufacturers and/or wholesalers) and retailers selling MT-45 ([44]) (Google, 2014). Twelve sites that appear to be based either within the EU, Canada, China and India were identified.

([42]) 'HSI seizes websites selling potentially deadly illegal narcotics' news release dated April 11, 2014. Available at http://www.ice.gov/news/releases/1404/140411buffalo.htm

([43]) http://www.google.com/trends

([44]) Using the standardised EMCDDA methodology for monitoring Internet sales of new psychoactive substances. Briefly, google.co.uk was searched using the term 'buy "MT-45"' and the first 100 search results were reviewed. Further details on the methodology are available from the EMCDDA on request.

Five of the sites only provided quantities and prices for MT-45 on application. The remaining seven sites listed quantities and prices. Briefly: the minimum quantity offered was 1 g (n=2 sites) with a mean price of EUR 33.25 (EUR 22.16–44.34); the maximum quantity offered was 5000 g (n=1 site) with a price of EUR 12,900. Most of the seven sites offered quantities ranging from 10 g to 1000 g. The mean price for 10 g (n=5 sites) was EUR 178.11 (EUR 129–311.01); the mean price for 100 g (n=5 sites) was EUR 778.37 (EUR 498.00–1,107.90); the mean price for 1000 g (n=5 sites) was EUR 3,041.02 (EUR 2,363.52–3,914.58). On these sites MT-45 was typically sold as a 'research chemical'. Repeating the search in August 2014 gave similar results. For example, 10 g, 100 g or 1 kg of MT-45 were offered for USD 180.00, 700.00 or USD 3200.00, respectively ([45]); another supplier offered 1 kg of MT-45 for USD 6716.00 ([46]).

An Internet snapshot survey undertaken in English during June 2014 identified 17 sites selling MT-45 (16 were common to both the "google.co.uk" and "google.com"; 1 identified on "google.com" only). The country of origin was identifiable from the Internet site as follows: China – 8; Canada– 2; Germany – 1; India – 1 and Sweden 1; it was not possible to identify the country of origin for 4 Internet sites. Nine Internet sites had no information directly available on cost and this was only available to registered users and/or on request. Of the eight Internet sites where information was available on cost, six were selling in dollars (assumed to be US dollars, although not explicitly stated), one in Euros and one in Swedish Krona. MT-45 was for sale in amounts ranging from 500mg to 5kg. The mean price of MT-45 decreased with increasing purchase amounts from USD57.6 ± 19.37 per gram for a 1g purchase to USD 3.36 ± 1.83 per gram for a 1kg purchase (personal communication to the EMCDDA from David Wood).

In three of the non-fatal intoxications reported by Sweden the source of the MT-45 was reported to be the Internet. In the remaining seven cases, the source was unknown (see Table 6 in Section D1.2).

Prevalence of use

There are currently no coordinated national or European surveys on the prevalence of use of MT-45 in the general population or in targeted populations. Further, neither the European school survey project on alcohol and other drugs (ESPAD) nor other school/college/university surveys have investigated or reported on MT-45 use.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

([45]) http://www.jsresearchchems.com/views.asp?hw_id=155

([46]) http://www.molbase.com/en/cas-41537-67-1.html

The acute toxicity of MT-45 to rodents was extensively studied by the company developing it. The toxicity data are shown in Table 5 and are expressed as LD_{50} values, that is the dosage causing death in 50% of the exposed animals. Mortality was monitored for seven days after the administration of a single dose of the drug. In summary, by the oral and subcutaneous route, the (*S*) isomer was more toxic than racemic MT-45 though no such difference could be observed by the intravenous route. It is also evident that MT-45 preparations, regardless of stereochemical composition, are more toxic to rodents than morphine. On weight basis in the mouse, for example, racemic MT-45 was over fourfold more toxic than morphine by the oral route; by the intravenous route the toxicity difference was larger: MT-45 was about elevenfold more toxic than morphine. During the toxicity study, it was also noted that animals receiving toxic doses of racemic MT-45 and its analgesically more active (*S*) isomer died with symptoms of laboured breathing (dyspnoea), severe sedation and muscle rigidity. Interestingly, in lower, sub-lethal doses the racemic mixture and the (*S*) isomer of MT-45 caused excitation, while the (*R*) isomer caused sedation. This remarkable observation *in vivo* indicates different modes of action for the two stereoisomers that is also reflected by *in vitro* studies (Section A2).

Table 5. Acute toxicity data (LD_{50} values in mg/kg) of morphine hydrochloride, MT-45 and its stereoisomers, all as dihydrochlorides, and lefetamine hydrochloride upon subcutaneous (s.c.), intravenous (i.v.) or oral administration (male animals; n = 20–50) (Nakamura and Shimizu, 1976; Nishimura et al., 1976).

Drug	Mice			Rats		
	oral	s.c.	i.v.	oral	s.c.	i.v.
morphine	1402	560	204	335	not tested	not tested ([47])
rac. MT-45	329	743	17.8	150	136	7.8
(*S*)-MT-45	274	320	18.5	not tested	not tested	8.0
(*R*)-MT-45	250	not tested	17.9	288	97.7	12.9
lefetamine	176	104	32.6	~300	148	not tested

Apart from respiratory depression (see above), there is insufficient information available to determine the clinical features in animals of acute toxicity associated with MT-45.

No data are available on the chronic toxicity of MT-45.

The RTECS Number for the dihydrochloride of MT-45 is TL3486500 ([48]).

([47]) For comparison, LD_{50} values of morphine (rat, i.v.) ranges between 64 to 223 mg/kg depending upon which salt of the drug and which strain of rat are used (Strandberg et al., 2006; Niemegeers et al., 1976. Finnegan et al., 1948).

([48]) 'RTECS' stands for 'Registry of Toxic Effects of Chemical Substances', which is a compendium of toxicity data extracted from the scientific literature. The database was originally developed by The US National Institute of Occupational Safety

D1.2. Human data

No clinical studies were identified that have systematically examined the toxicity or adverse effects of MT-45 in humans. The sub-sections that follow summarise selected, though typical, user reports as well as reports from Sweden on 18 non fatal-intoxications requiring emergency treatment following MT-45 use ([49]). The clinical findings reported by Sweden on 28 deaths are also presented.

D1.2.1. User reports

There are few user reports discussing the subjective effects of MT-45. The section below is mainly based on discussions originating from Internet drug forums and related websites (hereafter 'user websites') and includes self-reports. As such it is important to note that it is not possible to confirm the identity, the purity, the dose/amount, etc., of the specific substance(s) used. Analyses of new psychoactive substances or products containing them that are sold on the drug market have shown that the composition can differ between that claimed by the retailer, as well as vary over geographical areas and time. Furthermore, the users' physical characteristics and health status are rarely reported. In addition, the information on user websites should be regarded as illustrative only and not taken as representative of users of MT-45 in general. Consequently, these reports need to be interpreted with caution.

Some users reported feeling high, a 'decent buzz' followed by sedation; and some of them add qualifying comments, such as 'feels good like an opi but lacking euphoria or that good deep opi feeling' or 'nice calm opiate undertones'. Typical opioid effects such as itching were noted by several users and nausea appears to be a common feature. Several users reported that they experienced analgesia whilst taking MT-45. One user reported commencing MT-45 use 'as I was going into heroin withdrawal last week', suggesting self-medication with MT-45 to ease opiate withdrawal symptoms. This was echoed by another user who noted 'maybe good to avoid w/d but not much recreation in my opinion'. Three users suggested the effects of MT-45 were similar to those of methadone, one to the synthetic opioid AH-7921, and one to codeine, another one to oxycodone. No serious adverse events were mentioned in these reports (Bluelight, 2014a; Chems'R'us, 2014; Shroomery, 2014). Representative quotations follow.

Bluelight:

The first user report appeared in September 2012 at this user website (Bluelight, 2014). One user who had before experimented with inhaling the vaporised base of MT-45 "tried 80 mg of MT-45 salt solution rectally. I expected this to be a full dose and was surprised to find 'maybe threshold' effects over the following hour. This was supplemented by 30 mg converted to base

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and Health (http://www.cdc.gov/niosh/rtecs/RTECSaccess.html) but it is now maintained by Accelrys-BIOVIA of Dassault Systèmes.

([49]) During data collection for the risk assessment, the Swedish National Focal Point reported a total of 20 non-fatal intoxications associated with MT-45 use for the period from November 2013 up to August 2014 (see Table 6). Subsequently, Helander et al. (2014) reported the details of clinical findings of nine non-fatal intoxications all of which had been included in the report from the Swedish National Focal Point.

and vaped, which gave full effects". Another user compared the effect of a total of 75 mg with redosing (10 mg + 15 mg + 15 mg + 35 mg doses at one hour intervals) on one occasion to the effects of same amount taken in a single dose on an empty stomach. In the former case, the effects were described as "subtle night but was quite decent, was itchy and pretty warm. Definite opiate." In the latter case, two hours after the bolus intake "I was way too high, profusely sweating and vomited. Felt reminiscent of Kratom and Codeine/Promethazine". An 'opioid-tolerant' user compared the effect of 100 mg of MT-45 to 10-15 mg of methadone. This user "took 30 mg on one night and was hung over the next day feeling akin to how I feel the day after MDMA, something no opiate has done to me before". A self-medicating user described "35mg very pure MT-45 Dihydrochloride taken in a capsule alongside with 250mg of Chelated Magnesium and copious amount of bud [most likely Budweiser beer].... All my back pain and arthritis pain disappeared". A report described the "high very pleasant" after snorting about 20 mg of MT-45; "pupil constriction, dulled sensation to pain and a mild amount of euphoria" were noticed. Another user wishing to relieve the symptoms of heroin withdrawal needed altogether about 240 mg of MT-45, taken orally over the course 2.5 hours, to feel the calming effect of the substance; for a lasting relief, additional amounts "whenever I felt the need ... around 300-400 mg over 6 hours" were ingested. The same report concluded: "for getting high - no so great.... For (minor) withdrawals – Amazing considering its availability and legality (grey area). Took away almost all symptoms". The effects of a mixed intoxication with MT-45, cannabis and ketamine were also communicated by one opioid naïve user as follows: "I weighed 45mg of mt45, capped it and swallowed on an empty stomach and normal habitual cannabis consumption"; after 30 min "I notice myself scratching my head..."; after 1.5 hours "seems equivalent to taking 10mg hydrocodone, with maybe some tramadol like agonist/antagonist feelings"; after 2 hours, being "bored with opiate lazies... I shovel myself up 75 mg of racemic ketamine hcl for an IM injection...lower than normal khole because I am alone, and I expect it to be potentiated by the mt45"; about 15 minutes after injecting ketamine, "Bliss...My mind is completely free to wander. I feel like I am floating in the clouds. .. I may have found my sweet spot for dosage. Right on the edge of K-Hole"; 3.5 hours after MT-45 intake "I seamlessly doze off to sleep".

Flashback:

The first report on this Swedish-language user website on MT-45 experience appeared in December 2013 and described a total of 200 mg of MT-45 administered first nasally (10 mg) and sublingually (5mg) (Flashback, 2014). Apart from the bad taste and smell, the first noticeable effect was the numbing of the mouth and the throat. Nasal redosing of 20 mg and 40 mg at 60 minutes and 110 minutes, respectively, after the first dose, resulted in strongly constricted pupils, relaxed but not euphoric feeling. Additional oral doses (2 x 60 mg as 'bombing') and one sublingual dose (35 mg) followed 3 and 3.5 hours after the first dose.

Chems'R'us:

Discussions of MT-45 started on this website in the 'legal opioids' category early 2013 (Chems'R'us, 2014). One experience report described that by rubbing over the gums ('dabbing') a few milligrams of powdery MT-45, the effects "within 5 mins...kicked in. Very

trippy, no warm opiate sensation"; 30 minutes later "sweaty palms and feet, little anxiety" were noted. Another user commented later that a mixture of AH-7921 and MT-45 in a 1:1 ratio was as euphoric and addictive as oxycodone.

Shroomery:

An experience report was posted in May 2014 on the effects of a "76mg capsule of MT-45 Dihydrochloride" taken on an empty stomach by a person with "zero opiate tolerance" (Shroomery, 2014). One hour after drug ingestion and a subsequent meal the effect described were "general sense of well-being, slightly stimulated," getting warm and sweaty palms and some itching" and these effects peaked half an hour later with some anxiety. At about 2 hours post-ingestion the user felt "woozy and dizzy", was sweating and had to vomit. The effects started to fade 4 hours after drug intake with only "after effects" being felt 8 hours after ingestion. It was concluded: "The effects lasted VERY long. I would say similar to methadone? This is a great chemical. With no human research besides us guinea pigs, you have to wonder what receptors this stuff binds to and what it is actually doing."

D.1.2.2. MT-45 associated acute toxicity

Between November 2013 and July 2014, the Swedish National Focal Point reported 46 serious adverse events ([50]) associated with MT-45. Of the 46 cases, 18 were non-fatal intoxications (12 have been analytically confirmed) and 28 were deaths. In one of these deaths MT-45 was detected in biological samples and the cause of death was reported as 'injury'.

Belgium notified that a user had reported to a pill testing organization on sedation due to the consumption of a powdery substance that, upon analytical examination, turned out to be a mixture of MT-45 and methylone.

No non-fatal intoxications or deaths were reported by other EU Member States, Turkey and Norway.

Non-fatal cases reported by Sweden:

There have been 12 cases where MT-45 was analytically confirmed in non-fatal intoxications associated with MT-45 as reported by the Swedish Poison Information Centre or National Laboratory of Forensic Chemistry ([51]). The cases occurred during 2013 (4 cases) and 2014 (8 cases). All these cases were males aged between 17 and 37 years. The forensic and clinical

([50]) Serious adverse event means any adverse event associated with the consumption of a new psychoactive substance in a human that: results in death; is life-threatening; requires hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect; or is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also be considered serious. Examples of such events are intensive treatment in an emergency room; convulsions that do not result in hospitalisation; or development of substance dependency or substance abuse. This definition was adapted from the guidelines of ICH (1994).

([51]) Simultaneously, details for two of these cases were also provided by the Swedish National Board of Forensic Medicine, Department of Forensic Genetics and Forensic Toxicology.

results for these cases are summarised in Table 6.

A recent scientific publication by Helander et al. (2014) describes the details of analytical and clinical findings for nine of these 12 non-fatal intoxications. Key data are summarised in Table 7. Note that all these cases are also listed in Table 6.

Based on the reports on non-fatal intoxications, the clinical features of MT-45 overdose are opioid-like adverse symptoms typically including:

- somnolence or unconsciousness
- tachycardia
- shortness of breath (apnoea) or decreased respiratory rate
- cyanosis
- miosis.

In four of the nine cases described by Helander et al. (2014), various neurological disturbances, such as paraesthesia in hands and feet, difficulties in grip and coordinating hand movements, balance disturbances, and/or blurred and double vision were also noted. Furthermore, bilateral hearing loss developed in three cases as a result of MT-45 exposure; in two of the cases the hearing impairment was transient but in one case the unusual ototoxicity ([52]) persisted for two weeks after discharge as documented at a follow-up audiology testing.

It is of importance that in serious overdose cases the judicious administration of the opioid receptor antagonist naloxone (total injected dose range: 0.1–2.0 mg) proved to be successful (Table 7).

In addition to the above non-fatal intoxications, Sweden also reported six other cases were MT-45 was mentioned but not confirmed analytically: in one of them (male, aged 24 years) the clinical symptoms (constricted pupils, somnolence, seizures and high body temperature) could have been due to the synthetic opioid AH-7921, which was detected in biological fluids. In another case (male, aged 24) no bioactive substance was reported or detected; treatment of the symptoms (unconsciousness and low blood oxygen saturation) consisted of naloxone administration and flumazenil as antidotes.

([52]) Opioid-induced hearing loss has been described but its etiology is unclear (Saifan et al, 2013; see also Helander et al., 2014).

Table 6. Non-fatal intoxications reported by Sweden where MT-45 was analytically confirmed in biological samples (or quantified in femoral blood using LC/MS/MS). Intoxications occurred from November 2013 (Cases 1–4) through April 2014 (Cases 5–10). Cases 11 and 12 also occurred in 2014 but no information on their specific dates is available. All cases were male, aged between 17 and 37.

Case	Toxicology results for MT-45	Results for other substances detected	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, sources of MT-45)	Details of serious adverse event - Clinical symptoms, treatment - Why the event was considered serious?
1	detected	none	oral; 100 mg	-	- Hypertension, tachycardia, muscular symptoms - Non-life threatening event, but required treatment in hospital
2	detected	dextromethorphan, methiopropamine (*), THC	not known	-	- Constricted pupils, cyanosis, unconsciousness, tachycardia. Naloxone was administered - Life threatening event, requiring treatment in hospital
3	detected	pyrazolam (*), THC	injected (intravenous and intramuscular) and snorted; 3 g during a week	α-PBP (1 g) (*); MT-45 was obtained from the Internet	- Somnolence, hypotension, tachycardia, low oxygen saturation. Naloxone was administered - Life threatening event, requiring treatment in hospital

Case	Toxicology results for MT-45	Results for other substances detected	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, sources of MT-45)	Details of serious adverse event - Clinical symptoms, treatment - Why the event was considered serious?
4	detected	3-MeO-PCP	snorted	'Maybe some stimulating drugs'; MT-45 was obtained from the Internet	- Somnolence, apnoea, hearing loss. Naloxone was administered - Life threatening event requiring treatment in hospital
5	330 µg/g in blood	none	not known	-	- Somnolence, decreased respiratory rate, tachycardia, hearing loss, muscular symptoms. Naloxone was administered - Life threatening event requiring treatment in hospital
6	0.06 µg/g in blood	flubromazepam (*), THC	not known	-	- Somnolence, tachycardia - Described both as life threatening and non-life threatening event by two different reporting agencies; required treatment in hospital
7	detected	none	oral, rectal	-	- Somnolence, decreased respiratory rate, tachycardia. - Life threatening event, requiring treatment in hospital. Outcome not known

Case	Toxicology results for MT-45	Results for other substances detected	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, sources of MT-45)	Details of serious adverse event - Clinical symptoms, treatment - Why the event was considered serious?
8	detected	none	not known	-	- Unconsciousness, hypoxia, vomiting, hearing loss - Life threatening event, requiring treatment in hospital
9	detected	3-MMC/4-MMC (5), flubromazepam (3), pyrazolam (5)	oral (powder)	-	- Unconsciousness, decreased respiratory rate, hypokalaemia. Naloxone was given; - Life threatening event, requiring treatment in hospital
10	detected	α-PPP (1), N-ethyl-buphedrone (2), α-PBP (1), 3-MeO-PCP, methio-propamine (4)	oral (tablet)	flubromazepam (3)	- Somnolence - Life threatening event, requiring treatment in hospital
11	detected	4-hydroxy-midazolam	not known	-	- Unconsciousness, cyanosis - Life threatening event, requiring treatment in hospital
12	detected	DPT (1), des-methyldiazepam	not known	APB (1)	- Anxiety, tachycardia, hallucinations - Non-life threatening event but required treatment in hospital

(4) 'Methiopropamine' is a name for a thiophene-containing analogue of methamphetamine first reported as 'new psychoactive substance' to EMCDDA in January 2011.

(5) 'Pyrazolam' is a name for a benzodiazepine derivative first reported as 'new psychoactive substance' to EMCDDA in August 2012.

(6) 'α-PBP' is an acronym of a cathinone derivative first reported as 'new psychoactive substance' to EMCDDA in December 2011.

(7) 'Flubromazepam' is a name for a benzodiazepine derivative first reported as 'new psychoactive substance' to EMCDDA in March 2013.

(8) '3-MMC' and '4-MMC' are the abbreviations of the respective regioisomers of 3- or 4-methylmetcathinone first reported as 'new psychoactive substances' to EMCDDA in September 2012 and March 2008, respectively. The actual isomer present in the biological specimen was not identified in this case.

(9) 'N-Ethylbuphedrone' is a name of a cathinone derivative first reported as 'new psychoactive substance' to EMCDDA in January 2009.

(10) 'α-PPP' is an acronym of a cathinone derivative first reported as 'new psychoactive substance' to EMCDDA in January 2009.

(11) 'DPT' is an acronym for *N,N*-dipropyltryptamine first was reported as 'new psychoactive substance' to EMCDDA in November 2004.

(12) 'APB' probably stands for an isomer of aminopropylbenzofurans, the first of such substances was reported to EMCDDA in December 2010.

Table 7. Main laboratory and clinical findings for non-fatal intoxications reported by Helander et al. (2014) where MT-45 was analytically confirmed in biological samples (urine or blood using LC/MS/MS). Intoxications occurred between November 2013 and February 2014. All cases were male, aged between 17 and 32.

Case	Reported or suspected substances (a)	Reported dose and route of MT-45 intake	MT-45 in blood (ng/ml)	MT-45 in urine (ng/mmol creatinine)	Other substances detected in urine (a)	Main clinical symptoms (a); naloxone treatment (c), if any
1	MT-45	100 mg; oral	6	5.4	none	Conscious (RLS 1), paraesthesia in the extremities; -
2	MT-45, alcohol	no information	102	43	THC-COOH (b), dextromethorphan, methiopropamine	Deep unconsciousness (RLS 8), respiratory depression, cyanosis, miosis; 2 x 1.0 mg naloxone
3	MT-45, cannabis, benzofurans, pyrazolam, flubromazepam, α-PVP (a),	3 g during a week (in 60 mg doses); intravenous injection, snorted	19	0	THC-COOH (b), pyrazolam	Depressed level of consciousness (RLS 3), prolonged low oxygen saturation, vision impairment; 1 x 0.1 mg naloxone
4	MT-45, methiopropamine, phencyclidine (PCP)	unknown;dose snorted	39	200	3-MeO-PCP	Deep unconsciousness (RLS 5), apnoea (requiring intubation and assisted ventilation), cyanosis, miosis, hearing impairment; 1 x 0.4 mg naloxone

Case	Reported or suspected substances ([a])	Reported dose and route of MT-45 intake	MT-45 in blood (ng/ml)	MT-45 in urine (ng/mmol creatinine)	Other substances detected in urine ([a])	Main clinical symptoms ([b]); naloxone treatment ([c]), if any
5	MT-45	no information	157	221	none	Deep unconsciousness (RLS 8), respiratory depression, hand weakness, hearing impairment; 3 x 0.2 + 2 x 0.1 mg naloxone
6	MT-45, oxycodone	no information	47	1.7	THC-COOH ([d]), flubromazepam	Depressed level of consciousness (RLS 2); -
7	MT-45 ([f])	unknown; dose taken orally and rectally	65	35	none	Depressed level of consciousness (RLS 2), prolonged low oxygen saturation, Unspecified dose of naloxone was given
8	MT-45	unknown; dose administered orally or by intravenous injection	45	0.6	none	Deep unconsciousness (RLS 8), apnoea, miosis, left ventricular dysfunction, prolonged low oxygen saturation and respiratory depression, several neurological disturbances incl. hearing loss; 1 x 0.4 mg naloxone
9	MT-45	100 mg, oral	56	132	3-MMC, pyrazolam	Deep unconsciousness (RLS 8), prolonged respiratory depression; 3 x 0.4 mg naloxone

(*) For explanation of names and abbreviations, see Table 6.

(*) Used almost exclusively in Sweden, the Reaction Level Scale (RLS85) is an eight grade coma scale for direct bedside assessment of consciousness or overall reaction level to external stimuli. It ranges from RLS 1 (alert, no delay in response) through RLS 3 (very drowsy or confused, responsive to strong stimulation) to RLS 8 (unconscious, no response to pain stimuli) (Kornbluth and Bhardwaj, 2011).

(*) Naloxone was administered in single or multiple doses as intravenous and/or intramuscular injection.

(*) 'THC-COOH' refers to the major urinary metabolite of THC indicating cannabis use.

(*) 'α-PVP' is an acronym for a cathinone derivative first reported as 'new psychoactive substance' to EMCDDA in April 2011

(*) This patient provided a zip-locked unlabelled plastic bag containing an off-white powder. Analyses by LC-MS/MS and NMR identified it as MT-45 of high purity.

D1.2.3. MT-45 associated deaths

Since November 2013, when the first death associated with MT-45 use was reported by Sweden, a total of 28 deaths where MT-45 was detected have been reported from one Member State, Sweden (EMCDDA-Europol, 2014). All but one of the death cases were males aged between 19 and 59 years old; the one female was 23 years old. Forensic information on these deaths, which occurred within a nine-month period between November 2013 and July 2014 and typically in a home environment, are summarised below and tabulated in Table 8.

In all the death cases reported by the Swedish National Board of Forensic Medicine (Department of Forensic Genetics and Forensic Toxicology, Linköping) MT-45 was analytically confirmed. In four of these cases MT-45 was the sole detected drug in post-mortem femoral blood at concentrations ranging from 0.2µg/g to 1.9 µg/g ([53]). In one additional case where MT-45 was the sole detected drug in post-mortem femoral blood (0.15 µg/g) death was due to an accident ('injury'). In the remaining 24 cases at least one other psychoactive substance was detected. These included: THC (one case); ethanol (four cases); stimulants (six cases); benzodiazepines and/or their metabolites (thirteen cases); other opioids (ten cases); as well as other medicines and, in some cases, their metabolites: alimemazine (also known as trimeprazine) or levomepromazine (also known as methotrimeprazine), bupropion, citalopram, duloxetine, fluoxetine, gabapentin, lamotrigine, metoclopramide, mirtazapine, olanzapine, promethazine, propranolol, quetiapine, sertraline, venlafaxine and/or zopiclone (one or more of these in 14 cases). In the polydrug-intoxications, the concentration of MT-45 in post-mortem femoral blood ranged from 0.006 to 1.7 µg/g. (For further details, see Table 8.)

For twenty-two cases the cause of death was provided as follows: 'MT-45 intoxication' (eight cases); 'mixed intoxication' (six cases); 'mixed intoxication' specifying 'opioids' (one case), 'opiates and illicit drugs' (one case) and 'tramadol and MT-45' (one case); 'ethanol and drugs' intoxication (one case); 'alimemazine, MT-45 and diclazepam' intoxication (one case); and 'pneumonia + intoxication' (two cases). As mentioned in the previous paragraph, one death was due to a fatal accident. For six cases the cause of death has not been declared (as of September 2014).

([53]) For comparison, in fatal heroin or morphine poisoning cases the reported blood concentrations range from 0.04 to 3.0 mg/L (Musshoff et al., 2004; Moffatt et al., 2011; Häkkinen et al., 2012).

Table 8. Deaths reported by Sweden where MT-45 was analytically confirmed in biological samples (quantified in femoral blood using LC/MS/MS). Deaths occurred between November 2013 and July 2014. Twenty seven of the cases were male, aged between 19 and 59; the remaining case was a female aged 23.

	Toxicology results for MT-45 µg/g	Results for other substances µg/g (*)	name of drug	Circumstances	Cause of death
1	1.9	no other substance detected		found dead at home	MT-45 intoxication
2	0.82	0.51	quetiapine	found dead at home	MT-45 intoxication
3	0.46	27 1.3 0.43 + +	gabapentin methiopropamine (°) flubromazepam (°) pyrazolam (°) ethylphenidate (°)	found dead at home	mixed intoxication
4	0.008	0.06 5.5 0.02 0.0006	alprazolam gabapentin morphine THC	not known	pneumonia and intoxication
5	0.38	0.16 0.1 0.3 +	flubromazepam (°) sertraline desmethylsertraline pyrazolam (°)	found dead at home	pneumonia and intoxication
6	0.35	0.03 0.02 0.6	mirtazapine desmethylmirtazapine APDB (°)	found dead at home	mixed intoxication

	Toxicology results for MT-45 µg/g	Results for other substances µg/g (*)	name of drug	Circumstances	Cause of death
7	0.93	0.57 0.51	fluoxetine norfluoxetine	found dead at home	MT-45 intoxication
8	1.0	0.02 0.12	oxycodone flubromazepam (°)	found outside, cardiac arrest, died in hospital	MT-45 intoxication
9	0.51	0.1 0.3 0.6 0.79	flubromazepam (°) sertraline desmethylsertraline tramadol	found dead at home	mixed intoxication
10	0.39	2.3 1.0 0.08 +	gabapentin lamotrigine amphetamine ethanol	found unconscious, died in hospital	mixed intoxication
11	0.27	4 0.03 + +	gabapentin codeine methiopropamine (b) 2-aminoindane	found dead at home	MT-45 intoxication
12	0.16	0.09 +	flubromazepam (°) diclazepam (b)	died at a friend's house	mixed intoxication
13	0.19	0.6 0.0053 0.3 0.24 0.05 0.01 0.04	alimemazine (*) fentanyl fluoxetine norfluoxetine bupropion alprazolam nordiazepam	found dead at home	mixed intoxication (opioids)

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	Toxicology results for MT-45 µg/g	Results for other substances µg/g (*) name of drug	Circumstances	Cause of death
14	0.09	0.61 codeine 0.06 morphine 0.03 hydrocodone 0.03 diazepam 0.10 nordiazepam 0.08 olanzapine 0.05 desmethylolanzapine + ethanol	found dead at home	mixed intoxication (ethanol + opioids)
15	0.2	no other substance detected	found dead at home	MT-45 intoxication
16	0.35	0.5 alimemazine (*) 0.5 desmethylalimemazine (*) + diclazepam (*)	found dead at home	mixed intoxication (alimemazine (*), MT-45 and diclazepam (*))
17	0.15	no other substance detected	jumped off a building	injury
18	0.77	no other substance detected	found dead at home	MT-45 intoxication
19	0.46	5.9 gabapentin 0.12 diazepam 0.008 alprazolam 1.1 venlafaxine 0.4 desvenlafaxine 3.02 carbamazepine 0.06 alimemazine (*) 0.07 levomepromazine (*)	found dead at home	MT-45 intoxication

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	Toxicology results for MT-45 µg/g	Results for other substances µg/g (*) name of drug	Circumstances	Cause of death
20	0.006	0.023 fentanyl 0.07 metoclopramide 0.26 mirtazapine 0.11 desmethylmirtazapine 0.06 zopiclone 13 gabapentin + flubromazepam	found dead at home	not finished
21	0.31	0.07 duloxetine 0.007 morphine 0.01 ethylmorphine	found dead at home	not finished
22	0.14	0.38 methadone 0.2 alimemazine (*) 0.09 mirtazapine 0.5 promethazine 0.1 desmethylprometazine 0.51 diazepam 0.63 nordiazepam 0.14 flubromazepam (*) 0.42 4-F-PVP (*)	found dead at home	mixed intoxication
23	0.51	0.03 propranolol	found dead at home	not finished
24	1.5	0.04 olanzapine + 6-MAPB (*) + 6-APB (*) + N-ethylbuphedrone (**)	found dead at home	mixed intoxication with opiates and illicit drugs

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	Toxicology results for MT-45 µg/g	Results for other substances µg/g (*)	name of drug	Circumstances	Cause of death
25	0.15	2.1 0.31	tramadol desmethyltramadol	found dead at home	intoxication with tramadol and MT-45
26	0.05	0.11 0.23 1.5 0.8 3.1 0.3 0.89	diazepam nordiazepam fluoxetine norfluoxetine pregabalin methylphenidate ritanilic acid	died visiting girlfriend	not finished
27	1.7	+	ethanol	found dead at home	not finished
28	0.47	3.5 0.3 0.22 0.02 0.1 +	lamotrigine citalopram quetiapine 7-hydroxyquetiapine propranolol ethanol	found dead at home	not finished

(*) A '+' sign in this column indicates that the given drug was detected but not quantified.

(*) 'Methiopropamine' is a name for a thiophene-containing amphetamine-type stimulant reported first as 'new psychoactive substance' to EMCDDA in January 2011.

(*) 'Flubromazepam' is a name for a benzodiazepine derivative reported first as 'new psychoactive substance' to EMCDDA in March 2013.

(*) 'Pyrazolam' is a name for a benzodiazepine derivative reported first as 'new psychoactive substance' to EMCDDA in August 2012.

(*) 'Ethylphenidate' is a name for a methylphenidate analogue reported first as 'new psychoactive substance' to EMCDDA in November 2011.

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() 'APDB' stands for 4-, 5- or 6-(2-aminopropyl)-2,3-dihydrobenzofuran derivatives reported first as 'new psychoactive substances' to EMCDDA in March 2012.

(*) 'Diclazepam' is a name for a benzodiazepine derivative reported first as 'new psychoactive substance' to EMCDDA in August 2013.

() Alimemazine, or trimeprazine, is a sedating antihistamine with antiemetic properties; it is used, among others, as an antipruritic agent to prevent itching.

() Levomepromazine, or methotrimeprazine, is the levorotatory stereoisomer of alimemazine with indications similar those of its racemic mixture and extending to the treatment of schizophrenia and as an adjunct to opioid pain medications.

() '4-F-PVP' is an acronym for a cathinone derivative reported first as 'new psychoactive substance' to EMCDDA in February 2014.

() '6-MAPB' is an acronym for aralkylamine derivative stimulant reported first as 'new psychoactive substance' to EMCDDA in September2013.

() '6-APB' is an acronym for aralkylamine derivative stimulant reported first as 'new psychoactive substance' to EMCDDA in June 2011.

(*) 'N-Ethylbuphedrone' is a name of a cathinone derivative first reported as 'new psychoactive substance' to EMCDDA in January 2009.

In an attempt to evaluate the toxicological significance of MT-45 in the deaths reported, an assessment of the following evidence was considered in each case: presence and concentration (and pharmacological nature) of MT-45; presence and concentration (and pharmacological nature) of other drugs present (including alcohol); circumstances of death; and, cited cause of death. This allowed categorisation of the significance of MT-45 in the deaths as being of low significance (i.e. alternative cause of death), medium significance (i.e. MT-45 may have contributed to toxicity/death but other drugs present may have been more toxicologically significant) or high significance (i.e. MT-45 was cited as the cause of death or was assessed to have likely contributed to toxicity/death even in the presence of other drugs). In order to highlight potential interactions or contributing toxicology the other substances found in the cases were characterised.

In 19 deaths, MT-45 was either reported as the cause of death or contributing to death (even in presence of other substances); in three of these deaths MT-45 was the sole drug present. In 8 deaths, MT-45 may have contributed to toxicity but other substances were present that may have been more toxicologically significant. An alternative cause of death was recorded in one case (deceased had jumped off a building). In the cases where other substances were found these included opioids, benzodiazepines (both authorised and unauthorised medicinal products), stimulants, and other prescription medicines (including anti-psychotics, anti-depressants, and anti-convulsants).

Deaths from open source information

Two deaths from the United States of America that occurred between 7 and 10 August 2013 were identified in a news release by the US Immigration and Customs Enforcement's Homeland Security Investigations (EMCDDA-Europol, 2014). These deaths involved a male (aged 34 years) and a female (aged 33 years) who were found dead in their apartment in Hamburg, New York State; white powder identified as MT-45 was recovered at the scene. The medical examiner determined that the male had died of acute intoxication with MT-45 and the female had died of acute intoxication with MT-45 and ethanol ([54]). Documented evidence showed that 3 g of MT-45 had been ordered through the Internet on 29 July 2013 and received by the victims on 5 August 2013. Diazepam and oxycodone were also collected at the scene.

D2. Chronic health effects

D2.1. Animal data

There is no animal data in the scientific or grey literature on the chronic health effects of MT-45.

There are no data on the neurotoxicity or carcinogenicity of MT-45 *in vitro*. It could be relevant to mention, however, that in the *in vivo* anticancer drug screening programme of the National

([54]) http://www.ice.gov/news/releases/1404/140411buffalo.htm, and personal communication to EMCDDA from US Immigration and Customs Enforcement's Homeland Security Investigations.

Cancer Institute (NCI), USA, intraperitoneally administered MT-45, under NCI number code 'NSC 299236', did not show antitumour activity in two strains of mice bearing transplantable tumours (P388 leukemia) (NCBI, 2014).

D2.2. Human data

There are no published studies investigating the chronic health effects of MT-45 in humans.

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market (purity, adulterants etc)

MT-45 is offered for sale in (multi)gram as well as in bulk (kg) quantities on the Internet by several suppliers as a drug in its own right (Section C). The purity of these products is claimed to be high (>95%) but this has rarely been tested by forensic analysis. Racemic and enantiopure MT-45 have become commercially available as analytical standards or experimental research chemicals from several fine chemical suppliers ([55]).

Analyses of seized products indicate that adulterants are not typically present in the powder products offered as MT-45. (Adulterants or contaminants arising from manufacture could be present in products but these are either not detected or not reported.) However, in two powder samples (0.1 g and 9 g) seized by customs in Sweden the stimulants 6-APDB and α-PBP were also detected. Furthermore, MT-45 was detected as an added component in powder, herbal and liquid products along with other psychoactive substances as noted in Belgium and Germany as well as in Japan. For details on seized and collected samples, see Section C.

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

There is limited information on commonly used user websites regarding the effects and potential health / adverse effects related to the use of MT-45 (Section D1.2.1). The users and forum discussion participants appear to be generally aware of the opioid-like (wanted and unwanted) effects of this substance.

D3.3. Characteristics and behaviour of users (including risk factors, vulnerability, etc.)

No studies were identified that have examined the characteristics and behaviours of users of MT-45 use. Available information, including forensic reports from Sweden (see also Helander et al., 2014) and from self-reports originating from user websites, indicate that MT-45 is typically used in the home environment. Some users are simply experimenting with this new drug, some use it to self-medicate pain or opioid-withdrawal symptoms. It also apparent from these reports that polydrug use is common.

([55]) For example, http://bioreagent.bertinpharma.com or http://www.caymanchem.com

D3.4. Nature and extent of health consequences (e.g. acute emergencies, road traffic accidents)

The limited information on the acute health effects of MT-45 in humans has been discussed in Section D1.2. Based on animal model experiments (Section A2) as well as on self-reports and clinical cases (Section D1.2), it may, however, be assumed that the acute behavioural effects of MT-45 on operating machinery and driving are similar to those caused by other opioid-type narcotic-analgesics.

There is insufficient information in the reported deaths where MT-45 has been detected to discuss in detail the circumstances of these deaths. From the information available, it does not appear that any of these were related to work or road traffic accidents. MT-45 was the sole drug detected in a fatal accident (a 22-year old male jumped or fell off a building) but the events preceding to or the circumstances of the accident are unknown.

D3.5. Long-term consequences of use

As discussed in Sections D2.1 and D2.2, there are no animal or human data on the chronic health effects of MT-45 use.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

Based on user reports and Internet searches, MT-45, being an unregulated substance in most Member States, is openly advertised as 'new research chemical' or 'legal opioid'. The amounts offered by Internet retailers range from 1 g to kg quantities (see also Section C).

As mentioned, the available information suggests that MT-45 is typically used in the home environment alone or in the company of a close friend (i.e., MT-45 does not appear to be a 'party drug').

Section E. Social risks

E1. Individual social risks

There are no published data to be able to determine the impact of MT-45 in this area.

E2. Possible effects on direct social environment

There are no published data to be able to determine the impact of MT-45 in this area.

E3. Possible effects on society as a whole

There are no published data to be able to determine the impact of MT-45 in this area.

One Member State (Sweden) reported the detection of MT-45 in two 'petty drug offence' cases. In one case, which occurred in December 2013, MT-45 was found in blood (0.08 µg/g) along with alprazolam, buprenorphine, flubromazepam, flunitrazepam, morphine and pyrazolam. The other case occurred in March 2014 and MT-45 was confirmed by LC/MS (TOF) in the urine but no quantification was done; buprenorphine and its nor-metabolite were also detected.

E4. Economic costs

Given the lack of data available on acute health emergencies and healthcare utilisation related to the use of MT-45, it is not possible at this time to estimate whether this substance is associated with greater healthcare costs than other opioid drugs.

E5. Possible effects related to the cultural context, for example marginalisation

There are no published data to be able to determine the impact of MT-45 in this area.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

At this time, there does not appear to be any appeal related to the use of MT-45 within the general population, or even within sub-populations that are usually associated with higher use of recreational drugs and new psychoactive substances.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

There is no specific information that criminal groups are systematically involved in the production, trafficking and/or distribution of MT-45 for financial gain (EMCDDA–Europol, 2014).

There is no information indicating the production of MT-45 in any of the Member States, Turkey or Norway.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

There is nothing to suggest that distribution networks established for heroin are being used. Based on the information available to ECMDDA and Europol, the production, trafficking and distribution of MT-45 does not appear to have any impact on other existing psychoactive substances or new psychoactive substances. However, the detection in Germany of MT-45 in a 'brown heroin' mixture also containing typical adulterants (caffeine, paracetamol and sorbitol) could be an indication of MT-45 and heroin having a common source possibly associated with a criminal organisation.

F3. Evidence of the same groups of people being involved in different types of crime

There is no information available in this area.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

No information has been received by Europol on incidents of violence in connection specifically with MT-45.

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

No information has been received by Europol on incidents of money-laundering specifically in connection with MT-45.

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

There are no published data to be able to determine the impact of MT-45 in this area.

F7. Use of violence between or within criminal groups

There are no published data to be able to determine the impact of MT-45 in this area.

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

There are no published data to be able to determine the impact of MT-45 in this area.

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European Monitoring Centre for Drugs and Drug Addiction

Annex 2. List of participants at the Risk Assessment meeting on MT-45 16 September 2014

A. Extended Scientific Committee

Scientific Committee Members

Dr. Henri BERGERON
Centre National de la Recherche Scientifique (CNRS), Institut d'Études Politiques de Paris (IEP), Paris

Dr. Anne-Line BRETTEVILLE JENSEN
Norwegian Institute for Alcohol and Drug Research, Oslo
Vice-Chair of the Scientific Committee

Prof. Dr. Gerhard BUEHRINGER
Addiction Research Unit, Dep. of Clinical Psychology and Psychotherapy, Technische Universität Dresden
Institut für Therapieforschung (IFT), Munich
Chair of the Scientific Committee

Dr. Paul DARGAN
Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Prof. Dr. Matthew HICKMAN
Social Medicine, Bristol

Prof. Dr. Dirk J. KORF
Universiteit of Amsterdam, Law Faculty, Amsterdam

Prof. Dr. Krzysztof KRAJEWSKI
Department of Criminology, Jagiellonian University, Krakow

Prof. Letizia PAOLI
LINC, Leuven Institute of Criminology, University of Leuven Faculty of Law, Leuven

Dr. Fernando RODRIGUEZ de FONSECA
Fundación IMABIS, Hospital Carlos Haya, Málaga

Prof. Dr. Brice De RUYVER
Department of Criminal Law and Criminology, Faculty of Law, Universiteit Gent

Prof. Dr. Rainer SPANAGEL
Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Additional Experts to the Scientific Committee

Dr. Wim BEST
Utrecht University, Faculty of Science, Department of Pharmaceutical Sciences, Utrecht

Dr. Simon BRANDT
School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Prof. Gaetano DI CHIARA
Cagliari University, Biomedical Sciences Department, Cagliari

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Dr. Kalervo KIIANMAA
Addiction Prevention Unit, Department of Alcohol, Drugs and Addiction, National Institute for Health and Welfare, Helsinki

Representatives of the institutions

European Commission
Elsa MAIA
Anti-Drugs Policy Unit, European Commission, Brussels

Fabiano RENIERO
Institute for Health and Consumer Protection (IHCP), Joint Research Centre, Ispra

European Medicines Agency (EMA)
Dr. Leon Van AERTS
Section Pharmacology, Toxicology and Biotechnology (FTBB), College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht

Europol
Daniel DUDEK
Project SYNERGY, Europol, The Hague

EMCDDA
Paul GRIFFITHS
Scientific Director, EMCDDA, Lisbon

Roumen SEDEFOV
Head of unit, Supply reduction and new drugs unit, EMCDDA, Lisbon

B. Invited Experts

Dr. Simon ELLIOTT
(ROAR) Forensics Ltd, Worcestershire

Dr. István UJVÁRY
Budapest University of Technology and Economics, Budapest

Dr. David WOOD
Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

C. EMCDDA Staff

Anabela ALMEIDA
Project assistant, Action on new drugs, Supply reduction and new drugs unit

Rachel CHRISTIE
Scientific analyst, Action on new drugs, Supply reduction and new drugs unit

Andrew CUNNINGHAM
Scientific analyst, Action on new drugs, Supply reduction and new drugs unit

Michael EVANS-BROWN
Scientific analyst, Action on new drugs, Supply reduction and new drugs unit

Ana GALLEGOS
Head of Sector, Action on new drugs, Supply reduction and new drugs unit

Brendan HUGHES
Senior Scientific analyst - national legislation ELDD Supply reduction and new drugs unit