European Monitoring Centre
for Drugs and Drug Addiction

JOINT REPORTS

ISSN 1977-7868

MT-45

EMCDDA–Europol Joint Report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine ('MT-45')

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

About this series

EMCDDA–Europol Joint Report publications examine the detailed information provided by the EU Member States on individual new psychoactive substances. Information is collected from the Reitox network, the Europol national units and the national competent authorities of the European Medicines Agency.

Each Joint Report serves as the basis upon which the decision to conduct a risk assessment of the new psychoactive substance is taken. It is part of the three-step procedure involving information exchange, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

EUROPOL

EMCDDA–Europol
joint publication

Contents

Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this publication:

- the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- the Europol national units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway and Iceland;
- the European Medicines Agency (EMA) and the European Commission;
- the World Health Organization;
- Dr István Ujváry for preparing a technical review on MT-45.

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1. Introduction

Article 5.1 of Council Decision 2005/387/JHA [1] (hereinafter referred to as 'the Council Decision') stipulates that '*Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the "Joint Report").*' The Joint Report shall be submitted to the Council of the EU, the European Medicines Agency (EMA) and the European Commission.

In April 2014 the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol examined the available information on the new psychoactive substance 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, commonly known as MT-45, through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and,
6. evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on MT-45 satisfied criteria 4, and, in particular, criteria 6. The two agencies therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on MT-45 as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 16 April 2014 the EMCDDA and Europol launched a procedure for the collection of information on MT45, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States, Turkey and Norway as well as the Europol national units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 28 May 2014; additional information and clarifications from some countries were received up to four weeks after this date.

Europol asked the Europol national units to provide information on:

- the level of MT-45 production in their country;
- the level of MT-45 distribution in their country;
- the level of MT-45 trafficking in their country, for internal, transit or export purposes;
- the number of seizures of MT-45 in their country, the total amount of the seizures, country of origin, details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution and trafficking of MT-45 in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of MT-45.

Europol received responses from 21 Member States [2].

According to Article 5.3 of the Council Decision, the EMA requested that the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein provide information on whether:

- the new psychoactive substance MT-45 has obtained a marketing authorisation;
- the new psychoactive substance MT-45 is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance MT-45 has been suspended.

The EMA received responses from 15 Member States and Norway [3]. The EMA also provided information as relevant to the central authorisation procedure.

Furthermore, in anticipation of Article 7.3 of the Council Decision in relation to the manufacturing of medicinal products in the European Union (EU), the EMA also requested information on whether the new psychoactive substance MT-45 is used to manufacture a medicinal product:

[1] OJ L 127, 20.5.2005, p. 32.

[2] Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovenia and Spain.

[3] Austria, Finland, Germany, Ireland, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Lithuania, the Netherlands and Spain provided a response in relation to human medicinal products. Belgium, France, Latvia, Poland, Portugal and Slovenia provided a response in relation to veterinary medicinal products. Norway provided a response in relation to human medicinal products.

- which has been granted a marketing authorisation;
- for which an application has been made for a marketing authorisation; and,
- for which a marketing authorisation has been suspended by a competent authority.

The EMA received responses from 15 Member States ([4]) and Norway. The EMA also provided information as relevant to the central authorisation procedure.

The EMCDDA collected data through:

1. a structured questionnaire to the Reitox national focal points. The EMCDDA received replies from the 28 Member States, Turkey and Norway;
2. information previously provided to the EU Early Warning System, including EMCDDA–Europol Reporting Forms, Progress and Final Reports;
3. a specific information request to the World Health Organization on whether or not MT-45 is under assessment by the United Nations system (see section 3.5);
4. a search of open source information which included: scientific and medical literature; official reports; grey literature; Internet drug discussion forums and related websites (hereafter, 'user websites'); and Internet suppliers (which typically appear to be manufacturers and/or wholesalers) and retailers selling MT45.

Thus, the information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2, 3.8.3 (in part), Annex 1 and Annex 2 ([5]). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusion of the Joint Report was prepared and agreed by the EMCDDA and Europol, the agencies responsible for the report.

3. Information required by Article 5.2 of the Council Decision

The order and titles of subsections 3.1 to 3.8 and section 4 below are as they appear in Article 5.2(a) to (h) and Article 5.3(a) to (c) of the Council Decision; sections are cross-referenced with those set down in the Council Decision.

([4]) Austria, Finland, Germany, Ireland, Sweden, and the United Kingdom provided a response in relation to human and veterinary medicinal products. Lithuania, the Netherlands, and Spain provided a response in relation to human medicinal products. Belgium, France, Latvia, Poland, Portugal and Slovenia provided a response in relation to veterinary medicinal products. Norway provided a response in relation to human medicinal products.

([5]) The sections on chemistry, pharmacology and toxicology, dependence liability and abuse potential were produced in cooperation with Dr István Ujváry.

3.1. Chemical and physical description, including the names under which the new psychoactive substance is known (Article 5.2(a) of the Council Decision)

Chemical description and names

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

MT-45 is an analgesic substance that was developed by the Japanese company Dainippon Pharmaceutical Co. Ltd, in the early 1970s while searching for analogues of the tricyclic tranquilizer-antipsychotic perathiepine and of the structurally related analgesic lefetamine ([6]) (Umemoto et al., 1972; Natsuka et al., 1975; Nishimura et al., 1976). The pharmacological properties of MT-45 have been extensively studied in animals; it appears that it has not been studied in humans. Limited mode of action studies were also undertaken *in vitro*. Based on the results of these experiments it appears that the pharmacology, including the analgesic activity, of MT-45 is complex and involves not only opioid receptors but also non-opioid targets that have not been fully characterised (section 3.4.1).

The systematic IUPAC name for MT-45 is 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine.

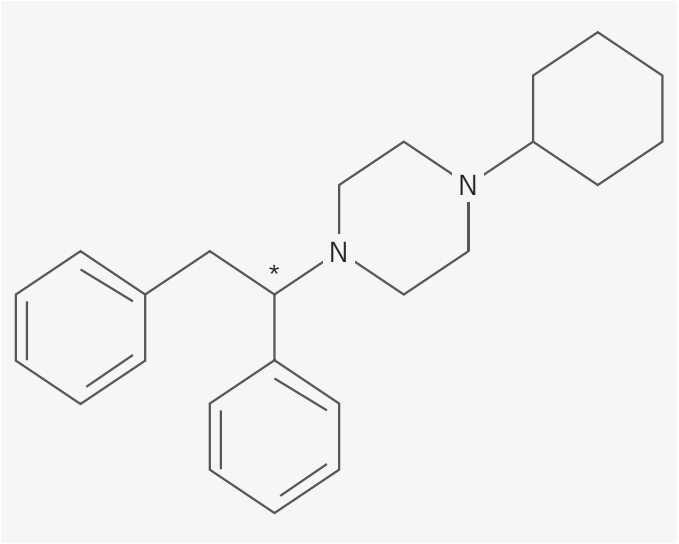
Other common names or codenames for MT-45 have also been reported: I-C6, CDEP and NSC 299236. It has not been possible to ascertain the origin of the commonly used name MT-45. The name I-C6 comes from the name used during the original research published in the scientific literature, with the C6 referring to the cyclohexane ring.

No additional chemical synonyms were reported.

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

([6]) Lefetamine is controlled under the 1971 United Nations Convention on Psychotropic Substances.

FIGURE 1
The molecular structure of MT-45. The asterisk (*) denotes a chiral centre



Molecular formula: $C_{24}H_{32}N_2$
Molecular weight: 348.54

MT-45 is a chiral molecule with one asymmetry centre, thus two enantiomers exist. The pure isomers may be obtained by resolution of the synthetic racemic mixture. The absolute configuration and the optical rotation ($[\alpha]^{22}_D$ values) 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 within the EU, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Of note in this respect is that optical rotation was found for MT-45 isolated from a collected sample of a liquid drug product purchased in Japan in early 2013 indicating that the product contained the racemic mixture (Uchiyama et al., 2014).

Chemical Abstract Service (CAS) registry numbers

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) was searched using the CAS registry numbers listed above. The searches returned no results.

Physical description

The free base of MT-45 is a solid, forming colourless prisms. The racemic substance is reported to have a melting point of 94–95°C. The dihydrochloride salt of the racemic substance has a melting point of 270–271°C (melts with decomposition) (Natsuka et al., 1975).

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 (Shroomery, 2014; Bluelight, 2014).

Information provided from seizures and a collected sample reported by the Member States have usually noted the presence of MT-45 in powder form. In one instance it was detected in a seized sample of brown heroin base. It 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 a collected sample that have been reported can be found in sections 3.2.1 and 3.2.2.

3.2. Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance (Article 5.2(b) of the Council Decision)

3.2.1. Information provided to Europol

Europol received replies from 21 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovenia and Spain). Belgium and Germany reported that they had information relating to MT-45.

Belgium provided information about a collected sample of powder, which was previously reported to the EMCDDA by the Belgian national focal point and is detailed in section 3.2.2.

Germany reported that MT-45 is known to drug users and is offered for sale on the Internet. There have been two seizures

where MT-45 was detected. The first seizure was in December 2013 and was 11.3 g of 'light brown chunky substance', which was identified as heroin base mixed with caffeine, paracetamol, sorbitol and MT-45. The second seizure was in March 2014, when 250.49 g of white powder was seized which was found to contain MT-45 at a concentration of 95 %.

The level of production, distribution and trafficking

No reports were received that indicated licit or illicit production of MT-45.

3.2.2. Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States, Turkey and Norway. Of these, two Member States (Belgium and Sweden) reported detections of MT-45 ([7]).

Seizures

Sweden reported 28 seizures of MT-45. In 26 of these, MT-45 was seized in either white or off-white powder form; the quantities seized ranged from 0.1 to 49.9 g. In two of these cases another new psychoactive substance was also present (α-PBP ([8]) in one case and 6-APDB ([9]) in another). In the remaining two seizures MT-45 was detected in plant material (0.55 g and 0.99 g) in the presence of another new psychoactive substance (the synthetic cannabinoid receptor agonists AB-FUBINACA ([10]) and AKB-48 ([11]) respectively).

Collected samples

Belgium reported a sample of white powder collected from a user in March 2014 that contained MT-45 and methylone ([12]). The powder was reportedly sold as 'a new thing, "wow"'. The user apparently experienced strong sedation and was concerned that he had ingested something toxic.

Biological samples

Sweden reported 33 detections where MT-45 was analytically confirmed in biological samples. These related to: 31 serious adverse events, comprised of 10 non-fatal intoxications and 21 deaths; and two cases where MT-45 was detected in people suspected of committing minor drug offences. The non-fatal intoxications and deaths are discussed in section 3.4.1.

3.3. Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance (Article 5.2(c) of the Council Decision)

No information was provided by Member States in relation to the involvement of organised crime in the manufacture or trafficking of MT-45.

Money laundering aspects

No information was received on money laundering in connection with the production and/or trafficking of MT-45.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of MT-45.

3.4. A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Council Decision

3.4.1. First indication of health risks

A total of 34 serious adverse events ([13]) associated with MT-45 were reported by Sweden. These comprised 13 non-fatal intoxications and 21 deaths.

Non-fatal intoxications

Sweden reported 13 non-fatal intoxications associated with MT-45 (Annex 1). These cases were reported by the Swedish

([7]) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. 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 collected from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).
([8]) 1-Phenyl-2-pyrrolidinobutanone.
([9]) 6-(2-Aminopropyl)-2,3-dihydrobenzofuran.
([10]) *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide.
([11]) *N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide.
([12]) 2-Methylamino-1-[3,4-methylenedioxyphenyl]propan-1-one.

([13]) 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. 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. Definition adapted from ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A.

Poison Information Centre ([14]) and occurred during 2013 (five cases) and 2014 (eight cases). All cases were male and aged between 18 and 37. MT-45 was analytically confirmed in 10 of the cases.

Ten of the cases were reported to be life-threatening and requiring treatment in hospital; two of the cases were not life-threatening ([15]) but required treatment in hospital; while in one case this detail was not known. In three of the analytically confirmed cases no other substances were detected.

The routes of administration were: oral (five cases); snorted (two); intravenous and intramuscular injection and snorted (one); oral and rectal (one). In four cases the route of administration was not known.

The dose/amount taken was available for three cases: 100 mg (oral); 3 g during a week (intravenous and intramuscular injection and snorted); and 50 mg (oral).

The reported symptoms were: somnolence (seven cases) or unconsciousness (four); tachycardia (seven); decreased respiratory rate (three) or apnoea (one); low oxygen saturation (two) or hypoxia (one) or cyanosis (one); hypotension (two); hearing loss (three); muscular symptoms (two); miosis (two); seizures (one); high body temperature (one); hypertension (one); hypokalemia (one); and vomiting (one). The opioid antagonist naloxone was administered in six of the cases as part of their clinical management.

Deaths

Sweden reported 21 deaths associated with MT-45 (Annex 2). These cases were reported by the Swedish National Board of Forensic Medicine (Department of Forensic Genetics and Forensic Toxicology), and occurred in a six-month period between November 2013 and April 2014. All cases were male, aged between 19 and 43 (mean 29, median 29). In all of these cases MT-45 was analytically confirmed and quantified. The concentration of MT-45 in post-mortem femoral blood ranged from 0.006 to 1.9 µg/g. In 17 of the cases, MT-45 was found in combination with at least one other psychoactive substance, including controlled substances, new psychoactive substances and medicines; in the remaining four cases no other substances were detected. In 17 of the cases it was reported that the deceased were found dead in a home/house. The cause of death was reported in 19 cases. In eight cases MT-45 was indicated as the cause of death; in eight cases the cause was reported as mixed intoxication; in two cases the cause was reported as pneumonia and intoxication; and in one case the cause was reported as injury. The investigations into the remaining two cases had not been completed at the time of writing the Joint Report.

Serious adverse events from open source information

Two deaths that occurred in August 2013 in the United States were identified in a news release by the US Immigration and Customs Enforcement's Homeland Security Investigations. These deaths involved a male and a female who were found dead in Hamburg, New York State. It was reported that the male died of acute intoxication with MT-45 and the female died of acute intoxication with MT-45 and ethanol ([16]).

Pharmacology and mode of action

The synthesis of a series of 1-substituted 4-(1,2-diphenylethyl) piperazines was described in the early 1970s and was based on structural analogies to the antipsychotic perathiepine and the analgesic-stimulant lefetamine (also known as (-)SPA). Among the first series of compounds prepared, MT-45 stood out as a promising analgesic agent as it was almost as potent as morphine. The pharmacology and toxicology of MT-45 has been extensively studied in animals; it appears that no studies have been published that have examined MT-45 in humans. Studies involving the racemate as well as the two individual stereoisomers revealed a complex mode of action (see below).

The analgesic activity of MT-45 was found to be comparable to morphine in several studies (Table 1). The results of a series of animal pharmacological studies (Nakamura and Shimizu, 1976; Fujimura et al., 1978; Imai, 1982; Nozaki et al., 1983) have also suggested that the modes of action of MT-45 and its individual stereoisomers are partly different from those of morphine. The analgesic activity of the (*S*) isomer is by an order of magnitude higher than that of the (*R*) isomer. In vitro studies with rat brain opioid receptor preparations also showed that the (*S*) isomer was a more potent inhibitor of the specific binding of naloxone or morphine. The (*R*) isomer had µ opioid receptor (MOP) agonist character although the molecular mechanisms appeared to be complex. The (*S*) enantiomer had particularly high affinity for δ and κ opioid receptors and interaction at an allosteric site of the receptor for the (*S*) enantiomer was also suggested (Fujimura et al., 1978; Imai, 1982; Nozaki et al., 1983).

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

([15]) In one of these cases, two different reporting agencies provided information on the severity of the intoxication. One agency described it as 'life-threatening' and the other described it as 'non-life-threatening'.

([16]) m.ice.gov/news/releases/1404/140411buffalo.htm?f=m, and personal communication to EMCDDA from US Immigration and Customs Enforcement's Homeland Security Investigations.

TABLE 1

Representative analgesic activity data (ED_{50} values in mg/kg) of morphine hydrochloride and MT-45 and its isomers as dihydrochloride salts, upon subcutaneous (s.c.) or oral administration (male animals; n=18–54) (Natsuka et al., 1975; Nakamura and Shimizu, 1976).

Drug	Mice				Rats	
	Thermal	Mechanical	Electrical	Chemical	Thermal	Mechanical
Morphine s.c. **oral**	2.39 29.4	2.41 15.4	1.22 7.70	0.58 4.20	3.79 41.0	1.17 32.0
Racemic MT-45 s.c. **oral**	3.09 20.9	2.15 11.9	1.54 30.8	2.24 12.5	6.62 29.5	0.73 36.4
(*R*)-MT-45 s.c. **oral**	50.7 no data	27.4 no data	38.3 41.0	36.0 73.3	~75 no data	45.0 no data
(*S*)-MT-45 s.c. **oral**	1.92 20.9	1.09 5.51	0.91 14.8	1.97 10.6	5.39 no data	0.73 26.0

The local anaesthetic activity of the (*R*) isomer MT-45, as determined in the corneal reflex in guinea pigs, was the highest compared to the racemic mixture, the (*S*) isomer and procaine with mean effective concentration values of 0.03, 0.092, 0.16 and 0.27, respectively (Nakamura and Shimizu, 1976).

At 3 mg/kg and 10 mg/kg subcutaneous doses, MT-45 dose-dependently reduced gastrointestinal propulsion in the mouse but its potency was somewhat weaker than that of morphine at the same dosages.

Upon intravenous administration of 1 mg/kg to rabbits, the racemic MT-45 and its (*S*) isomer caused respiratory depression by 59 % and 57 %, respectively; the (*R*) isomer failed to cause any respiratory depression even at 5 mg/kg. At 3 mg/kg, morphine depressed respiration by 63 % in this experiment.

A recent study by Matsuno et al. (1998) indicated the involvement of sigma receptors in the psycho/neuro/pharmacological activity of (*R*) isomer of MT-45 showing that the substance produced significant memory impairment in the mouse passive avoidance performance. Interestingly, this memory impairment could be alleviated by subcutaneous administrations of sigma receptor agonists. A receptor binding study revealed that the substances possessed high affinities for both sigma 1 and sigma 2 receptor subtypes (IC_{50} 1.4 nM and 1.8 nM, respectively).

Acute toxicity in rodents

The acute toxicity of MT-45 was determined in male mice and rats, observing mortality for seven days (Nakamura and Shimizu, 1976). The LD_{50} values are shown in Table 2. 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 would also appear that, with the exception of subcutaneous injection of the racemate, MT-45 preparations are more toxic to rodents than morphine.

TABLE 2

Representative acute toxicity data (LD_{50} values in mg/kg) of morphine and MT-45 and its isomers upon oral, subcutaneous (s.c.) or intravenous (iv) 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 HCl	1402	560	204	335	not tested	not tested
Racemic MT-45 2HCl	329	743	§17.8	150	136	7.8
(*R*)-MT-45 2HCl	not tested	not tested	17.9	288	97.7	12.9
(*S*)-MT-45 2HCl	274	320	18.5	not tested	not tested	8.0

It was remarkable that upon subcutaneous administration the stereoisomers of MT45 displayed different, dose-dependent symptoms indicating different modes of actions: animals receiving toxic doses of racemic MT-45 or its (*S*) isomer died with symptoms of severe sedation, muscle rigidity and shortness of breath (dyspnoea). Moreover, in lower, non-lethal doses the (*R*) isomer caused sedation while the racemic mixture and the (*S*) isomer caused excitation.

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

Dependence potential and abuse liability

The dependence potential of the racemic MT-45 and its (*S*) isomer was assessed in the mouse (Nishimura et al., 1976; see also Natsuka et al., 1987). Nalorphine-treatment of mice that had received repeated doses of the racemic substance precipitated jumping behaviour and other withdrawal signs similar to those noted for morphine in the same assay. The Straub tail indexes ([17]) for racemic MT-45, its (*S*) isomer and morphine were estimated to be 7.34, 30 and 33.1, respectively, indicating dependence potential for the synthetic piperazine derivatives. In addition, MT-45 substituted for morphine in morphine-dependent animals.

Some self-reported user experiences ('trip reports') on user websites suggest withdrawal-like symptoms (Bluelight, 2014).

3.4.2. Characteristics of users

No studies were identified that examined the characteristics of users of MT-45. The section below includes a discussion of the characteristics of users that includes self-reported use/experiences from user websites. As such, it is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose/amount, etc. Analysis 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 and over geographical areas and time. In addition, the information provided on user websites may not necessarily be representative of users of MT-45 in general and should be regarded as illustrative only.

Route of administration, dose, drug regimens and settings of use

Information from the non-fatal intoxications reported by Sweden and from user websites suggests that the route of administration for MT-45 includes oral and nasal ('snorting'), intravenous or intramuscular injection and rectal administration. Information from user websites suggests that a range of doses may be used: oral doses were between 25–75 mg with re-dosing reported; doses for nasal insufflation were between 15–20 mg (this route of administration was noted by several users to cause an intolerable level of irritation); one user reported rectal administration of '80 mg of MT-45 salt as the solution'; the same user also reported smoking 30–50 mg of MT-45 base, which he prepared from the dihydrochloride salt (Bluelight, 2014). Conversely, some user reports suggest that higher doses have been used.

Information from the serious adverse events reported by Sweden and from user websites suggests that MT-45 may be used on its own and in combination with other psychoactive substances.

Information from the deaths reported by Sweden and from user reports would suggest that MT-45 is used in the home environment.

Subjective effects

No studies were identified that have examined the subjective effects of MT-45 in humans; information is limited to self-reported experiences on user websites, which are briefly described.

Some users reported feeling high, a 'decent buzz' followed by sedation; some users added qualifying comments such as 'feels good like an opi but lacking euphoria or that good deep opi feeling' or 'nice calm opiate undertones'. Some typical opiate-like 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 were similar to methadone, one compared them to the synthetic opioid AH-7921, and one to codeine. No serious adverse events were mentioned in these reports (Shroomery, 2014; Bluelight, 2014; ChemsRus, 2014).

([17]) The 'Straub tail index' is defined as the ratio of the intravenous LD50 value and the Straub tail ED50 value, where the Straub tail ED50 is defined as the dose, injected intravenously through the tail vein of the animal, producing Straub-reaction in 50 % of the treated animals.

Availability, supply, price

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 ten cases the source was unknown.

A structured search by the EMCDDA of Internet suppliers (which typically appear to be manufacturers and/or wholesalers) and retailers ([18]) selling MT-45 identified 12 websites that appear to be based within the EU, Canada, China or India (Google, 2014). Five of the websites only provided quantities and prices for MT-45 on application. The remaining seven websites listed quantities and prices. Briefly: the minimum quantity offered was 1 g (n=2 websites) with a mean price of EUR 33.25 (EUR 22.16–44.34); the maximum quantity offered was 5 000 g (n=1 website) with a price of EUR 12,900. Most of the seven websites offered quantities ranging from 10 g to 1000 g. The mean price for 10 g (n=5 websites) was EUR 178.11 (EUR 129–311.01); the mean price for 100 g (n=5 websites) was EUR 778.37 (EUR 498.00–1 107.90); the mean price for 1 000 g (n=5 websites) was EUR 3 041.02 (EUR 2 363.52–3 914.58). MT-45 was typically sold by these websites as a 'research chemical'.

Prevalence of use

No prevalence surveys were identified that have examined the use of MT-45 either in targeted populations or in the general population.

3.5. Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system (Article 5.2(e) of the Council Decision)

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. On 14 May 2014 the World Health Organization informed the EMCDDA that MT-45 is currently not under assessment and has not been under assessment by the UN system and no such assessment is planned.

3.6. The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol (Article 5.2(f) of the Council Decision)

The first official notification to the EMCDDA–Europol of MT-45 dates from December 2013 from the Swedish national focal point. The Reporting Form details a seizure of 50 g of white powder in October 2013 by the Swedish customs authorities. The identification and analytical characterisation was based on GC-MS ([19]), FT-IR ([20]), LC-MS ([21]) and NMR ([22]) at the Swedish National Laboratory of Forensic Science.

MT-45 was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the EU Early Warning System and a profile of the substance was created on the European Database on New Drugs (EDND). Since then, analytical details, background information and public health alerts have been exchanged between the EMCDDA, Europol and the Member States on an ad hoc basis; the European Commission and the EMA have been kept duly informed.

3.7. Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State (Article 5.2(g) of the Council Decision)

Latvia reported that MT-45 is controlled under drug control legislation by being placed under temporary control for 12 months by the decision of the Centre for Disease Prevention and Control (control in force since 15 May 2014) according to the Law on Procedures for the Legal Trade of Narcotic and Psychotropic Substances and Medicinal Products.

Two Member States (Austria and Poland) reported that MT-45 is controlled under legislation prohibiting the unauthorised supply of defined or qualifying new psychoactive substances. In Austria MT-45 is categorised as a member of the '(1phenyl and 1-benzyl)piperazine' group in the new psychoactive substances law (NPSG law, Group II). In Poland MT-45 falls under the definition of a 'substitution drug' under the Act amending the Act on Counteracting Drug Addiction and the Act on State Sanitary Inspection, 2010, and as such its marketing and production is penalised with a fine (administrative sanctions).

In the Netherlands the sale of MT-45 in consumer amounts is treated as a medicinal product and must comply with medicines legislation.

([18]) 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.

([19]) Gas chromatography-mass spectrometry.
([20]) Fourier transform-infrared spectroscopy.
([21]) Liquid chromatography-mass spectrometry.
([22]) Nuclear magnetic resonance spectroscopy.

Spain reported that 'although there is no current specific legislation controlling production, commerce, imports, exports or use/consumption of this substance and given that it may cause harmful effects to those using it — the same way as illegal drugs do — there is generic legislation (administrative and criminal) on health protection which is fully applicable, if necessary.'

Twenty-three Member States (Belgium ([23]), Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Malta, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom), Turkey and Norway reported that MT-45 is not subject to control measures at the national level.

3.8. Further information (Article 5.2(h) of the Council Decision)

3.8.1. The chemical precursors that are known to have been used for the manufacture of the substance

No information was reported about the chemical precursors or manufacturing methods used to make the MT-45 that has been detected within the EU.

Two synthetic methods for the manufacture of MT-45 and closely related analogues have been described in the patent and scientific literature (Natsuka et al., 1975; Nishimura et al., 1976). In one of the routes the key precursor is the commercially available 1,2-diphenylethylamine, which upon alkylation with *N*,*N*-bis(2-chloroethyl)cyclohexanamine can be converted in one step to MT-45. Alternatively, MT-45 can be prepared by the alkylation of cyclohexylamine with *N*,*N*-bis(2-chloroethyl)-1,2-diphenylethanamine, which can be obtained by a multi-step process involving a Grignard reaction. Other synthetic methods are feasible. Note that these routes afford a 1:1 mixture of the (*S*) and (*R*) enantiomers each possessing distinct biological activities (section 3.4.1). The separation of the enantiomers from this racemic mixture requires optical resolution that has been accomplished.

3.8.2. The mode and scope of the established or expected use of the new substance

No studies were identified that have examined the mode and scope of established or expected use of MT-45. Given the limited information currently available, the relevant information has been included in the previous sections.

3.8.3. Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks

No information was provided by any Member State that indicated that MT-45 had any other use apart from in legitimate scientific research and in analytical reference materials.

From the available information, it does not appear that MT-45 is used in the manufacture of a medicinal product in the EU; however, the data collection is incomplete and some countries indicated that this information is not known. Six Member States (Finland, Lithuania, the Netherlands, Spain, Sweden and the United Kingdom) provided information that MT-45 is not used to manufacture a medicinal product for human use. Three Member States (Austria, Germany and Ireland) and Norway replied that they did not know this information. Seven Member States (Belgium, Finland, France, Latvia, Poland, Sweden and the United Kingdom) provided information that MT-45 is not used to manufacture a medicinal product for veterinary use. Five Member States (Austria, Germany, Ireland, Portugal and Sweden) replied that they did not know this information ([24]).

In addition, the EMA reported that it is not known if MT-45 is used in the manufacture of medicinal products for human or veterinary use in the EU. It is understood that the collection of such information is a challenge in the absence of a EU database on the synthetic routes of all medicinal products.

4. Information from the EMA (Article 5.3 of the Council Decision)

4.1. Marketing authorisation

Fifteen Member States and Norway responded to the EMA's information request (section 2). They reported that the new psychoactive substance MT-45 has not obtained a marketing

([23]) Belgium reported that MT-45 is included in the new generic drug legislation that will come into effect later in 2014 after the Royal Decree has been signed.

([24]) Austria, Finland, Germany, Ireland, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Lithuania, the Netherlands and Spain provided a response in relation to human medicinal products. Belgium, France, Latvia, Poland, Portugal and Slovenia provided a response in relation to veterinary medicinal products. Norway provided a response in relation to human medicinal products.

authorisation ([25]). The EMA also reported that the new psychoactive substance MT-45 has not obtained a marketing authorisation through the centralised procedure for authorising medicinal products.

4.2. Application for a marketing authorisation

Fifteen Member States and Norway responded to the EMA's information request (section 2). They reported that the new psychoactive substance MT-45 is not the subject of an application for a marketing authorisation ([24]). The EMA also reported that the new psychoactive substance MT-45 is not the subject of an application for a marketing authorisation through the centralised procedure.

4.3. Suspended marketing authorisation

Fifteen Member States and Norway responded to the EMA's information request (section 2). They reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance MT-45 ([24]). The EMA also reported that the new psychoactive substance MT-45 is not the subject of a suspended marketing authorisation through the central authorisation procedure.

5. Conclusion

MT-45 is a synthetic opioid. It has been available in the EU since at least October 2013 and has been detected in three Member States: Belgium, Germany and Sweden. In most cases it has been seized in small quantities as a powder. Over a short period of time MT-45 has been associated with 13 non-fatal intoxications and 21 deaths in Sweden. It is sold as a 'research chemical' online and offered in wholesale and consumer amounts. MT-45 is similar to morphine in some aspects of its pharmacology, although in some animal studies it exhibited a higher toxicity than morphine. There has been one case where MT-45 was detected in a seized sample of brown heroin base.

We conclude that the health and social risks caused by the manufacture, trafficking and use of MT-45, and the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

([25]) I.e. products that have been granted a marketing authorisation, or where an application for a marketing authorisation has been made, or where the marketing authorisation has been suspended.

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Annex 1

Non-fatal intoxications reported by Sweden where MT-45 was analytically confirmed in biological samples

Case	Toxicology results (biological matrix: blood and urine)	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, source for MT-45)	Details of the serious adverse event: – clinical symptoms, treatment – why the event was considered serious
1	MT-45 (+)	Oral; 100 mg	–	– Hypertension, tachycardia, muscular symptoms. – Non life-threatening event, but required treatment in hospital.
2	MT-45 (+) Dextromethorphan (+) Methiopropamine (+) THC (+)	–	–	– Constricted pupils, unconsciousness, cyanosis, tachycardia. Naloxone was administered. – Life-threatening event requiring treatment in hospital.
3	MT-45 (+) Flubromazepam (+) Pyrazolam (+) THC (+)	Injected (intravenous and intramuscular) and snorted; 3 g during a week	α-PBP (1 g) MT-45 obtained from the Internet	– Somnolence, hypotension, tachycardia, low oxygen saturation. Naloxone was administered. – Life-threatening event requiring treatment in hospital.
4	MT-45 (+) 3-MeO-PCP	Snorted	'Maybe some stimulating drugs' MT-45 obtained from the Internet	– Somnolence, apnoea, hearing loss. Naloxone was administered. – Life-threatening event requiring treatment in hospital.
5	MT-45 (+) Oxycodone (+) Pregabalin (+)	Oral; 50 mg	Flubromazepam MT-45 obtained from the Internet	– Somnolence, hypotension, tachycardia. – Life-threatening event requiring treatment in hospital.
6	MT-45 (330 µg/g, blood) THC (+)	–	–	– Somnolence, decreased respiratory rate, tachycardia, hearing loss, muscular symptoms. Naloxone was given. – Life-threatening event requiring treatment in hospital.
7	MT-45 (0.06 µg/g blood) Flubromazepam (+)	–	–	– Somnolence, tachycardia. – Described as both life-threatening and non-life-threatening event by two different reporting agencies; required treatment in hospital.
8	MT-45 (+)	Oral, rectal	–	– Somnolence, decreased respiratory rate, tachycardia. – Life-threatening event requiring treatment in hospital. – Outcome not known.
9	MT-45 (+)	–	–	– Unconsciousness, hypoxia, vomiting, hearing loss. – Life-threatening event requiring treatment in hospital.
10	MT-45 (+) 3-MMC/4-MMC (+) Flubromazepam (+) Pyrazolam (+)	Oral (powder)	–	– Unconsciousness, decreased respiratory rate, hypokalaemia. Naloxone was given. – Life-threatening event requiring treatment in hospital.

Note: Intoxications occurred during 2013 (four cases) and 2014 (six cases). All cases were males, aged between 18 and 37.

Annex 2

Deaths reported by Sweden where MT-45 was analytically confirmed in biological samples (quantified in femoral blood using LC/MS/MS) and for which cause of death is stated

Case	Toxicology results for MT-45	Toxicology results for other substances		Circumstances	Cause of death
1	1.9 µg/g	No other substances detected		Found dead at home	MT-45 intoxication
2	0.82 µg/g	0.51 µg/g	quetiapine	Found dead at home	MT-45 intoxication
3	0.46 µg/g	27 µg/g 1.3 µg/g 0.43 µg/g + +	gabapentin methiopropamine flubromazepam pyrazolam ethylphenidate	Found dead at home	Mixed intoxication
4	0.008 µg/g	0.06 µg/g 5.5 µg/g 0.02 µg/g 0.6 ng/g	alprazolam gabapentin morphine THC	Not known	Pneumonia + intoxication
5	0.38 µg/g	0.16 µg/g 0.1 µg/g 0.3 µg/g +	flubromazepam sertraline desmethylsertraline pyrazolam	Found dead at home	Pneumonia + intoxication
6	0.35 µg/g	0.03 µg/g 0.02 µg/g 0.6 µg/g	mirtazapine desmethylmirtazapine APDB ([26])	Found dead at home	Mixed intoxication
7	0.93 µg/g	0.57 µg/g 0.51 µg/g	fluoxetine norfluoxetine	Found dead at home	MT-45 intoxication
8	1.0 µg/g	0.02 µg/g 0.12 µg/g	oxycodone flubromazepam	Found outside, cardiac arrest, died in hospital	MT-45 intoxication
9	0.51 µg/g	0.1 µg/g 0.3 µg/g 0.6 µg/g 0.79 µg/g	flubromzepam sertraline desmethylsertraline tramadol	Found dead at home	Mixed intoxication
10	0.39 µg/g	2.3 µg/g 1.0 µg/g 0.08 µg/g +	gabapentin lamotrigine amphetamine ethanol	Found unconscious, died in hospital	Mixed intoxication
11	0.27 µg/g	4 µg/g 0.03 µg/g + +	gabapentin codeine methiopropamine 2-aminoindane	Found dead at home	MT-45 intoxication
12	0.16 µg/g	0.09 µg/g +	flubromazepam diclazepam	Died at a friend's house	Mixed intoxication
13	0.19 µg/g	0.6 µg/g 5.3 ng/g 0.3 µg/g 0.24 µg/g 0.05 µg/g 0.01 µg/g 0.04 µg/g	alimemazine fentanyl fluoxetine norfluoxetine bupropion alprazolam nordiazepam	Found dead at home	Mixed intoxication (opioids)
14	0.09 µg/g	0.61 µg/g 0.06 µg/g 0.03 µg/g 0.03 µg/g 0.10 µg/g 0.08 µg/g 0.05 µg/g +	codeine morphine hydrocodone diazepam nordiazepam olanzapine desmethylolanzapine ethanol	Found dead at home	Mixed intoxication (ethanol and drugs)
15	0.2 µg/g	No other substances detected		Found dead at home	MT-45 intoxication

([26]) 4,5 or 6-(2-aminopropyl)-2,3-dihydrobenzofuran

Case	Toxicology results for MT-45	Toxicology results for other substances	Circumstances	Cause of death
16	0.35 µg/g	0.5 µg/g alimemazine 0.5 µg/g desmethylalimemazine + diclazepam	Found dead at home	Mixed intoxication (alimemazine, MT-45 and diclazepam)
17	0.15 µg/g	No other substances detected	Jumped off a building	Injury
18	0.77 µg /g	No other substances detected	Found dead at home	MT-45 intoxication
19	0.46 µg/g	5.9 µg/g gabapentin 0.12 µg/g diazepam 0.008 µg/g alprazolam 1.1 µg/g venlafaxine 0.4 µg/g desthylvenlafaxine 3.02 µg/g carbamazepine 0.06 µg/g alimemazine 0.07 µg/g levomepromazine	Found dead at home	MT-45 intoxication

Note: Deaths occurred between November 2013 and April 2014. All cases were male, aged between 19 and 43.

TD-AS-14-007-EN-N

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2014), *EMCDDA–Europol Joint Report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine ('MT-45')*, Joint Reports, Publications Office of the European Union, Luxembourg.

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Luxembourg: Publications Office of the European Union
doi: 10.2810/54074 | ISBN 978-92-9168-745-9

This publication is only available in electronic format.

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