ACMD

Advisory Council on the Misuse of Drugs

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Lynne Featherstone MP, Minister for Crime Prevention
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14 November 2014

Dear Minister,

RE: ACMD's recommendation on the synthetic opioid MT-45

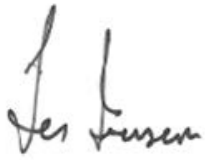
The Advisory Council on the Misuse of Drugs (ACMD) is continuing to review materials which may present sufficient risk to the UK to merit control under the Misuse of Drugs Act 1971. The materials being monitored include the synthetic opioids, a diverse range of compounds which, by their ability to suppress respiratory function, can present a particular and potentially lethal hazard to users. I am pleased to enclose the ACMD's report on a synthetic opioid known as "MT-45".

MT-45 has been reported in a number of serious adverse events and deaths in other European countries since 2013, most notably in Sweden. Two deaths related to MT-45 have also been reported from the USA. Although the ACMD has not seen evidence to indicate the current availability of MT-45 in the UK, the Council recommends the permanent control of this opioid, based on its potential to cause harm in the UK and the fatalities reported in other countries within a short time period. Like other opioids, MT-45 has a high addictive potential and abuse liability.

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol have published a joint report on the potency and toxicity of MT-45. The potency of racemic MT-45 is comparable to morphine, which itself is controlled under the Misuse of Drugs Act 1971 as a Class A substance.

The ACMD recommends that MT-45 be controlled under the Misuse of Drugs Act 1971 as a **Class A** substance and scheduled under **Schedule 1** of the Misuse of Drugs Regulations 2001 (as amended).

Yours sincerely,



Professor Les Iversen

ACMD Chair

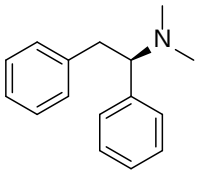
CC: Rt Hon Theresa May MP, Home Secretary

ACMD's review of the synthetic opioid MT-45

1. Introduction

1.1. MT-45 is a potent opioid, available in some European countries outside the UK, and reported in a number of deaths and cases of significant acute toxicity in Sweden (EMCDDA-Europol report, 2014; EMCDDA Risk Assessment MT 45, 2014 (Annex 1)).

1.2. MT-45 is structurally related to lefetamine, an analgesic drug, which is controlled as a Class B material under the Misuse of Drugs Act 1971 (see figure 1). Although it does not appear to be widely used as yet in the United Kingdom, it clearly has the potential to cause harm to users.



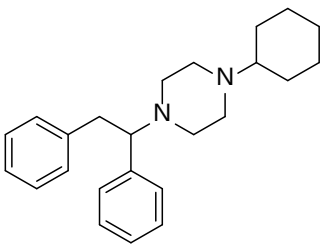
Lefetamine

Figure 1: Chemical structure of lefetamine

2. Chemical description

2.1. MT-45 is an N,N-disubstituted piperazine compound. The IUPAC name is 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (see figure 2). The compound has two enantiomers S(-) and R(+) but the substance appears to be usually sold as the hydrochloride salt of the racemate.

2.2. In addition to "MT-45" the compound is also known as I-C6, CDEP, and NSC 299236.



MT-45

Figure 2: Chemical structure of MT-45

3. Availability

3.1. MT-45 is offered for sale in USA, Canada, Hong Kong, Japan, China and India, and is offered for sale or has been detected in several European countries (Belgium, Sweden and Germany). In Sweden, MT-45 has been detected in white powders both as lone MT-45 and in combination with other psychoactive substances; it has also been detected in herbal smoking material together with synthetic cannabinoids.

3.2. Drugs Early Warning System (DEWS) surveys in July/August 2014 and October 2014 failed to find any UK-based “Clearnet” websites openly offering MT-45 for sale.

3.3. Forensic Early Warning System (FEWS) surveys have also failed to detect MT-45 in UK samples.

3.4. An Internet snapshot survey undertaken using EMCDDA methodology in June 2014 identified seventeen Internet sites offering MT-45 for sale (personal communication: Dr David Wood and Dr Paul Dargan).

4. Consultation on legitimate uses

4.1. The ACMD consulted with the Department for Business Innovation and Skills (BIS) and the Medicines and Healthcare products Regulatory Agency (MHRA) and found no legitimate medicinal, industrial or commercial use for MT-45.

4.2. The EMCDDA risk assessment on MT-45 states that there are “no known uses of MT-45 as a component in industrial, cosmetic or agricultural products. There are currently no other indications that MT-45 may be used for other legitimate purposes. MT-45 has no established or acknowledged medical value or use (human or veterinary) in the European Union.”

5. Pharmacology

5.1. The Japanese company Dainippon Pharmaceutical Co. Ltd developed MT-45 in the 1970’s (Japan patent 4704907 [1972209]). Racemic MT-45 is an analgesic in a variety of animal tests, with potency comparable to morphine. The (S)-enantiomer appears to be more potent than the (R)-enantiomer, although both isomers bind with high affinities to all three opioid receptors, including the mu-opioid receptor, considered critical in mediating the euphoric effects and many of the clinically significant acute toxic effects of opioid drugs (Fujimara *et al*, 1978; Nozaki *et al,*1983). In animal models racemic MT-45 produces similar magnitude respiratory depression to morphine suggesting a similar potential for acute toxicity (Nakamura *et al*, 1976).

5.2. The results of animal tests showed that animals treated with MT-45 displayed typical behavioural signs of opioid withdrawal when challenged with the receptor antagonist nalorphine; other animal studies have shown that MT-45 substitutes for morphine in morphine-dependent animals (Nishimura *et al*, 1976; Natsuka *et al*, 1987). These results suggest that like other opioids, MT-45 has addictive potential and abuse liability.

6. Adverse events and deaths

6.1. A total of 46 serious adverse events associated with MT-45 have been reported in Sweden. These include 18 non-fatal intoxications and 28 deaths. Of the 18 non-fatal intoxications, MT-45 was analytically confirmed in 12 cases. In one case series of analytically confirmed MT-45 acute intoxication, nine individuals required treatment in hospital for life-threatening clinical features, including coma and respiratory depression characteristic of opioid toxicity; in three cases bilateral hearing loss was reported, that in one case persisted for more than two weeks (Helander *et al*, 2014).

6.2. All of the 28 deaths associated with MT-45 reported from Sweden occurred in a 9-month period between November 2013 and July 2014. In all these cases MT-45 was analytically confirmed, and in 24 cases MT-45 was present with one or more other psychoactive substances. In 19 cases MT-45 was reported to be the cause of death or contributing to death. (EMCDDA-Risk Assessment, 2014).

6.3. Two deaths were reported in the USA in August 2013.

7. Social Harms

7.1. MT-45 has only been available for a short time in Europe, so it is too early to document any social harms associated with its use. However, extensive knowledge of the dangers of other opioids suggests the potential for social harm. Opioid use can lead to addiction, acquisitive crime, family disruption and loss of employment, and these could be predicted as potential consequences if MT-45 were to gain widespread used.

8. Control

8.1. MT-45 is subject to control under drug legislation in Latvia, Austria and Poland and potentially in Spain. However, 23 EU Member States reported that MT-45 is not subject to control measures at the national level.

8.2. The EMCDDA/EUROPOL issued a joint report on MT-45 (EMCDDA-Europol Report, 2014) and the EMCDDA have published a formal risk assessment of this which has been approved by EU Council (Annex 1)

9. Conclusion

9.1. Given the serious adverse events and deaths already reported in the short period that MT-45 has been available in Europe – and given knowledge of the abuse potential characteristics of other potent opioid drugs, the ACMD believes that MT-45 should be subject to control in the UK.

10. Recommendation

10.1. The ACMD recommends that 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) be controlled as a Class A compound under the Misuse of Drugs Act 1971 and scheduled as Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).

References

EMCDDA-Europol (2014) Joint report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, ”MT45”

Fujimura, H., Tsurumi, K. Nozaki M., Hori, M., Imai, E. (1978) Analgesic activity and opiate receptor binding of 1-cyclohexyl-4(1,2-diphenylethyl)piperazine. *Japan J.Pharmacol*.,28:505-506

Helander, A., Backberg, M., Beck, O. (2014) MT-45, a new psychoactive substance associated with hearing loss and unconsciousness. *Clinical Toxicology* Early Online 1-4

Nakamura, H. & Shimizu, M. (1976) Comparative study of 1-(cyclohexyl-4-(1,2-dipphenyl)-piperazine (MT-45) and its enantiomorphs on analgesic and other pharmacological activities in experimental animals. *Archives Internationales de Pharmacdynamie et de Therapie* 221:105-21

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Natsuka, k., Nakamura, H., Nishikawa, Y., Negoro, T., Uno, H. & Nishmura, H. (1987) Synthesis and structure-activity relationships of 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives having narcotic agonist and antagonist activity. *Journal of Medicinal Chemistry* 30:1179-1787.

Nishimura,H., Hitoshi, U., Imai,E., Hori,M., Fujimara, H. (1976) US Patent 3,957,788 to Dainippon Phamaceutical Co.

Nozaki, M., Niwa, M., Imai, E., Hori, M., Fujimura, H. (1983) (1,2-diphenylethyl)piperazines as potent opiate-like analgesics ; the unusual relationship between stereoselectivity and affinity to opiate receptor. *Life Sciences*, 33,Suppl 1: 431-434.

Annex 1 – EMCDDA Risk Assessment of MT-45

1. Introduction

This risk assessment report presents the summary findings and the conclusions of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, commonly called **MT-45**. The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ([1]). It is written as a stand-alone document presenting a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on MT-45, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]) (hereafter 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ([3])) that may pose public-health and social threats, including the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ([4]) that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ([5]).

MT-45 was first detected in a seizure by customs in Sweden in October 2013 and formally notified to the Early Warning System in December 2013. Following an assessment of the available information on MT-45, and in accordance with Article 5 of the Council Decision, on 25 June 2014 the EMCDDA and Europol submitted to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) a *Joint Report* on MT-45 ([6]).

([1]) EMCDDA (2009), *Risk assessment of new psychoactive substances: operating guidelines*, The Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

([2]) OJ L 127, 20.5.2005, p. 32.

([3]) The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New Psychoactive Substances ('Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Reitox National Focal Points and Europol National Units in the Member States, the European Commission and the European Medicines Agency.

([4]) According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

([5]) In compliance with the provisions of the 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.

([6]) EMCDDA and Europol (2014), *EMCDDA–Europol Joint Report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine 'MT-45'*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-reports/MT-45

Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision, on 26 September 2014, the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of MT-45 was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of five additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of MT-45, including health and social risks. Furthermore, two experts from the Commission, one expert from Europol and one expert from the European Medicines Agency (EMA) participated in the risk assessment. For logistical reasons, the meeting took place on 16 September 2014 at the EMCDDA in Lisbon with the risk assessment report being completed after the formal request from the Council was received by the EMCDDA. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the list of participants attending the risk assessment meeting, is annexed to this report (Annex 2). For the risk assessment, the extended Scientific Committee considered the following information resources:

i. Technical report on 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) (Annex 1);

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

iii. Scientific articles, official reports, grey literature, Internet drug discussion forums and related websites (hereafter 'user websites');

iv. Data from EMCDDA Internet monitoring of suppliers (that typically appear to be manufacturers and/or wholesalers) and retailers selling MT-45;

v. Risk assessment of new psychoactive substances: Operating guidelines; and

vi. Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances.

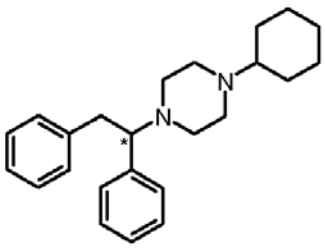
Finally, it is important to note that this risk assessment report contains a discussion of the available information on non-fatal intoxications and deaths associated with MT-45. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

2. Physical, chemical and pharmacological description of MT-45 and its mechanism of action, including its medical value

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 (Figure 1). MT-45 is one of a series of 1-(1,2-diphenylethyl)piperazine analgesics invented in the early 1970s. Its systematic (International Union of Pure and Applied Chemistry, IUPAC) name is (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine. Another abbreviation encountered in the literature is 'I-C6' ([7]).

The free amine of MT-45 is a colourless solid; the hydrochloride salt of MT-45 is also a solid. Seizures and collected samples within the European Union have usually noted the presence of MT-45 in white powder form; it is unknown whether the samples contained the free amine or a salt. MT-45 contains an asymmetry centre thus it is a chiral molecule. Studies on MT-45 from the literature have found that the pharmacological effects of racemic MT-45 and its (*S*) and (*R*) enantiomers were somewhat different. The stereoisomeric composition of the MT-45 currently on the drug market within the European Union is currently unknown but evidence from Japan suggests that the products sold in Europe are most likely racemic.

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 typically administered orally or by nasal insufflation; the vapours of the heated free base can be inhaled while the water-soluble hydrochloride salt can be administered by injection.

The tentative single doses reported by users are 15–30 mg for nasal intake and 25–75 mg for oral administration; redosing is common. The desired effects reportedly manifest within 15 minutes after nasal intake or 60 minutes after oral intake and may last for up to 2 hours; redosing may extend the effects.

Detailed information on the analytical profile of MT-45 is provided in Annex 1. Briefly, the detection ([8]) of MT-45 by gas chromatography and liquid chromatography coupled with mass

([7]) In the name I-C6, 'I' refers to structural 'Group I', while 'C6' indicates the six-membered cyclohexane ring in the molecule.

([8]) '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.).

spectrometry is straightforward. Infrared spectroscopy may also be used for the analysis of MT-45 in bulk samples. There is no information on presumptive colour tests with MT-45. No immunoassay field test for MT-45 is currently available. MT-45 does not appear to show cross-reactivity in standard drug immunoassay tests. Analytical reference materials facilitating the quantification of MT-45 in biological matrices are available.

No data are available on the pharmacokinetics of MT-45, and no metabolites of the substance have been identified.

There have been several animal model studies and *in vitro* experiments investigating the pharmacodynamics, in particular the analgesic mode of action of racemic MT-45 as well as the individual (*S*) and (*R*) enantiomers. Studies with rodents established racemic MT-45 and the (*S*)-MT-45 enantiomer to be opioid-like analgesics, with the (*S*) isomer being more potent than morphine in most rodent assays. In a receptor study, (*S*)-MT-45 appeared to be an opioid receptor agonist showing selectivity towards the δ and κ opioid peptide (DOP and KOP, respectively) receptor types, and with affinities comparable to or higher than those of morphine. The (*R*) isomer, however, displayed lower potency and diminished selectivity.

Knowledge of the activity of MT-45 at pharmacological targets other than the opioid system is limited. In mice, the (*R*) isomer of MT-45 induced learning and memory impairment that was independent of the opioid system and was due to antagonism at sigma receptors.

Studies on the side effect and adverse effect profiles of MT-45 in rodents and rabbits revealed opioid-like adverse effects, including respiratory depression and constipation.

The acute toxicity of MT-45 upon oral or intravenous administrations to rodents is several-fold higher than that of morphine.

There are no clinical studies on the (psycho)pharmacological effects of MT-45 in humans. Self-reported experiences from user websites as well as information from non-fatal intoxications and deaths associated with the substance suggest that its effects are similar to those of other opioids.

MT-45 is available as an analytical reference standard and for use in scientific research. There are no known uses of MT-45 as a component in industrial, cosmetic or agricultural products. There are currently no other indications that MT-45 may be used for other legitimate purposes.

MT-45 has no established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for MT-45 in the European Union or in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision. In addition, there is no information that MT-45 is used for the manufacture of a medicinal product or an active pharmaceutical ingredient (API) of a medicinal product in the European Union. It is important to note that the data collection is incomplete and some countries indicated that this information is not known. 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 European Union. It should be noted that

there is no European Union database on the synthetic routes of all registered medicinal products. Therefore, the use of MT-45 cannot be ruled out with certainty.

3. Chemical precursors that are used for the manufacture of MT-45

There is no information regarding the manufacturing sites, the precursors or the synthetic methods employed for MT-45 detected on the drug market within the European Union. As such, the impurities and side-products are also unknown.

In the 1970s, two methods for the synthesis of MT-45 and its closely related analogues were published in the scientific and patent literature ([9]). In one of the methods, the key precursor is the commercially available racemic 1,2-diphenylethylamine from which MT-45 is obtained by ring-forming alkylation with *N*,*N*-bis(2-chloroethyl)cyclohexanamine, which must be prepared separately ([10]). Alternatively, MT-45 can be prepared by ring-forming alkylation of cyclohexylamine with *N*,*N*-bis(2-chloroethyl)-1,2-diphenylethanamine, which is obtained by a multi-step process.

Precursors and other chemicals needed for the manufacture of MT-45 are inexpensive and are readily available or can be routinely prepared. The procedures require conventional equipment and, apart from necessary precautions when using toxic synthetic intermediates ([11]), no specialised chemical expertise is needed for the production of the substance.

4. Health risks associated with MT-45

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of MT-45, as well as its dependence potential, and its similarities to and differences from other chemically or pharmacologically related substances.

It is important to note that when interpreting the information from non-fatal intoxications and deaths reported by Member States as well as information from user websites, that individuals may have used other pharmacologically active substances in addition to MT-45. The presence of and/or interaction with other substances may account for some of the reported effects.

The acute toxicity of MT-45 has been assessed in rodents. In general, MT-45, regardless of stereoisomeric composition, is several-fold more toxic to rodents than morphine. For example, upon oral administration to rats the median lethal (LD_{50}) values for racemic MT-45 and morphine are 150 and 335 mg/kg, respectively. Data from some experimental pain models in mice suggests that the difference between analgesic and toxic doses for MT-45 are smaller than those for morphine indicating higher risk of overdose. It was observed that in sub-lethal doses the racemic mixture and the (*S*) isomer caused excitation, whereas the (*R*) isomer caused

([9]) It may be noted that later syntheses of analogues of MT-45 relied on alternative routes that may, in principle, be used for 'nitrogen mustard-free' production of MT-45.

([10]) Such bis(2-chloroethyl)amine derivatives (nitrogen mustards) are dangerous (blister-producing) substances.

([11]) See footnote 10 on the toxicity of nitrogen mustards.

sedation which is consistent with *in vitro* studies suggesting different modes of action for the individual stereoisomers.

No human studies were identified that investigated the pharmacological or behavioural effects of MT-45. Information on adverse effects from non-fatal intoxications and deaths is discussed below.

Based on users' self-reports, the effects of MT-45 resemble those of classical opioids with the feeling of mild euphoria and relaxation; miosis, sweating, itching and nausea appear to be typical adverse effects. Self-medication with MT-45 to relieve pain or to alleviate withdrawal symptoms due to cessation of the use of another opioid has also been reported.

There have been 18 non-fatal intoxications associated with MT-45, of which 12 were analytically confirmed, reported from one Member State, Sweden. The typical clinical features included miosis, tachycardia, somnolence, unconsciousness, decreased respiratory rate, and cyanosis. In some cases neurological disturbances such as paraesthesia, blurred vision and bilateral hearing loss were also noted.

In life-threatening MT-45 poisoning cases the administration of the opioid receptor antagonist naloxone may be valuable in reversing overdose features.

There have been 28 deaths associated with MT-45 reported from one Member State, Sweden, all of which were analytically confirmed. These deaths occurred within a nine-month period between November 2013 and July 2014, typically in a home environment; the routes of drug administration are not known.

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 medicinal products and unauthorised products), stimulants, and other prescription medicines (including anti-psychotics, anti-depressants, and anti-convulsants) ([12]).

Data from animal models suggest that MT-45 may have a dependence potential in humans. The opioid receptor antagonist nalorphine elicited withdrawal signs similar to those noted for morphine in mice that had received repeated doses of MT-45. Furthermore, MT-45 substituted for morphine in morphine-dependent rats. No self-administration studies in animals have been published.

([12]) Authorised medicinal products are those medicines which have received a marketing authorization by a competent authority within the EU, e.g. diazepam and alprazolam. Unauthorised benzodiazepines that have not received such authorization include diclazepam, pyrazolam and flubromazepam which have appeared on the new psychoactive substance market in recent years.

No studies have examined the abuse and dependence potential of MT-45 in humans. A limited number of self-reported user experiences suggest the development of mild withdrawal-like symptoms.

There are no data on the interaction of MT-45 with other substances, including medicinal products. In this context, it is worth noting that the sedative effects of opioid analgesics are enhanced when used with anti-psychotics as well as central nervous system depressants including hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

There is no information on the psychosocial consequences of (chronic) use of MT-45.

No studies have been published on the neurotoxicity, reproductive toxicity, genotoxicity or carcinogenic potential of single or repeated doses of MT-45. No studies have examined the chronic toxicity of MT-45 in animals or humans.

Public health risks

The public health risks associated with MT-45 may be categorised in terms of: pattern of use (extent, frequency, route of administration, etc.); availability and quality of the drug; availability and degree of information relevant to the effect of the drug amongst users; and negative health consequences.

According to user reports, MT-45 appears to have been available since 2012. It is openly marketed on the Internet as a 'research chemical'. Since October 2013, when MT-45 was first detected in Sweden, two additional Members States have reported detections (Belgium and Germany). EMCDDA monitoring of Internet suppliers and retailers identified twelve sites, including some apparently based in the European Union that offered MT-45 for sale, including in kilogram quantities.

As noted, the preferred route of administration appears to be oral and nasal. Injection has also been reported. As such, sharing of needles and syringes carries the risk of transmission of blood-borne viruses. People who experimented with the drug often reported repeated intake of MT-45 to maintain its effects for up to eight hours. Similar to other drugs, users may combine MT-45 with other psychoactive substances.

There are no prevalence data on the use of MT-45 in the European Union or elsewhere but available information does not suggest wide use of the substance. Based on the available information, MT-45 is mostly used in a home environment either by people who experiment with any drug that is new and readily available (such as 'psychonauts') or opioid dependent users having no access to heroin or any other opioid.

Based on limited information available on user websites, it appears that for MT-45, as with any newly occurring psychoactive substance, vendors and (potential) users rely on non-professional information, such as user reports, accessible on the Internet. Forum discussion participants appear to be generally aware of the opioid-like (wanted and unwanted) effects of and risks associated with the use of the substance.

5. Social risks associated with MT-45

There is limited information on the social risks associated with MT-45.

There is no information on whether the use of MT-45 affects education or career, family or other personal or social relationships, including marginalisation.

Although there are no relevant studies, it may be assumed that the acute behavioural (e.g., sedative) effects of MT-45 on operating machinery and driving are of a similar impairing nature to those caused by other opiate-type narcotic analgesics.

Data related to the social risk associated with the distribution and trafficking of MT-45 are lacking.

It is not possible at this time to estimate whether the use of MT-45 is associated with greater healthcare costs than other opioid drugs.

6. Information on the level of involvement of organised crime and information on seizures and/or detections by the authorities, and the manufacture of MT-45

MT-45 was first identified in a seizure of 49.9 g by customs in Sweden in October 2013 and reported to the Early Warning System in December 2013. Since then, Germany has also reported two seizures of 11.3 g and 250.5 g; in the former, MT-45 was detected as a component of a sample of brown heroin base. Belgium also reported the detection of MT-45 in a sample that also contained methylone.

There is no specific information to suggest the involvement of organised crime or criminal groups in the manufacture, distribution and supply of MT-45. It is noted that the largest seizure of MT-45 reported so far was 250 g that is not indicative of large-scale organised trafficking.

There is no information regarding the sites or the methods used to manufacture MT-45 detected in the Member States. Suppliers that advertise MT-45 on the Internet, including wholesale amounts, might not necessarily be the manufacturers of the chemical.

7. Information on any assessment of MT-45 in the United Nations system

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.

8. Description of the control measures that are applicable to MT-45 in the Member States

MT-45 is not listed for control in the 1961 UN Single Convention on Narcotic Drugs and the 1971 UN Convention on Psychotropic Substances (together 'UN drug conventions').

One Member State (Sweden) reported that MT-45 is subject to control measures under drug control legislation that is in accordance with the UN drug conventions. The remaining 27 Member States, Turkey and Norway do not control MT-45 under such legislation; however seven Member States (Austria, Ireland, Latvia, the Netherlands, Poland, Romania and Spain) report other legislative measures that control MT-45.

Sweden reported that MT-45 is a controlled narcotic substance (SFS 2014:1032; in force since 19 August 2014) according to the Act on the Control of Narcotic Drugs.

Austria, Ireland, Latvia, Poland and Romania reported that MT-45 is controlled under legislation prohibiting the unauthorised supply of defined or qualifying new psychoactive substances. In Austria, MT-45 is controlled under the new psychoactive substances law (NPSG, Group II), categorised as member of the '(1-phenyl and 1-benzyl)piperazine' group. In Latvia, MT-45 is controlled by being placed under temporary control for 12 months (control in force since 15 May 2014) by the decision of the Centre for Disease Prevention and Control according to the Law on Procedures for the Legal Trade of Narcotic and Psychotropic Substances and Medicinal Products. Laws were passed in Ireland (in 2010), Poland (2010) and Romania (2011) that prohibit the unauthorised supply of any psychoactive substance that qualifies by conforming to certain criteria. It was reported that national authorities may find that MT-45 meets such criteria. Of those, Poland reported that 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 may be subject to an administrative fine.

In the Netherlands, the sale of MT-45 may be subject to control under the Commodities Act, which describes the rules for food and consumer products to safeguard public health. It provides for both administrative and prison penalties for offences.

Spain reported that although there is no current specific legislation controlling production, commerce, imports, exports or use/consumption of this substance, given that it may cause harmful effects to those using it, there is general legislation on consumer health protection which is fully applicable, if necessary.

Twenty Member States (Belgium ([13]), Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, Malta, Portugal, Slovakia, Slovenia, and the United Kingdom), Turkey and Norway reported that MT-45 is not subject to control measures at the national level.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance MT-45 to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the UN drug conventions. There are no studies on the possible consequences of such control measures on MT-45. If this option of control is pursued, the Committee

([13]) Belgium reported that MT-45 is included in the new generic drug legislation which will come into effect in 2014 once the Royal decree has been signed.

considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of MT-45 and hence the further expansion of the current open trade in this substance within the European Union. However, this may have little impact on the manufacturers and suppliers outside of this jurisdiction.

- A health consequence that might result from this control is the benefit brought about by the presumed reduction of availability and use of MT-45.

- This control option could facilitate the detection, seizure and monitoring of MT-45 related to its unlawful manufacture, trafficking and use by facilitating cooperation between the judicial authorities and law enforcement agencies across the European Union.

- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement and the courts.

- This control option could lead to replacement with structurally related or other (established or new) psychoactive substances, which may in themselves have public health consequences.

- This control is not expected to impact on current and future research by the pharmaceutical or chemical industries.

- This control option could create an illicit drug market in MT-45 with increased risk of associated criminal activity, including organised crime.

- It is not expected that this control option could impact on the quality/purity of any MT-45 still available on the market. However, it is of concern that Internet retailers within the European Union may offer price discounts or other promotions in order to dispose of remaining stocks of MT-45 when control measures are impending. Therefore, this control option could lower the price of any MT-45 that is still available on the market and temporarily increase its availability. The extent to which this will impact on public health, criminality or levels of use is difficult to predict.

In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of MT-45 on the market post-control, should this option be pursued.

Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to the Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

10. Conclusions

MT-45 is a synthetic opioid investigated as an analgesic in the 1970s. Its structure is unique and contains a piperazine core bearing a cyclohexyl group on one of the nitrogen atoms and a 1,2-

diphenylethyl moiety on the other. The dihydrochloride salt of MT-45 is typically found as a powder. The substance is administered orally, by nasal insufflation, or, to a lesser extent, by injection or inhaling the vapours of its free base.

Animal models studies and experiments *in vitro* established MT-45 to be an opioid receptor agonist with analgesic potency similar or higher than morphine in some pain models. Animal studies indicate that the adverse-effect profile of MT-45 is similar to that of morphine. The acute toxicity, including the respiratory inhibitory effect, of MT-45 is higher than that of morphine.

Data from animal models suggest that MT-45 may have a dependence potential in humans. The pharmacological and behavioural activities of MT-45 in humans have not been studied. Limited information available from non-fatal intoxications and deaths as well as from user websites indicates that the physiological and psychological effects of MT-45 are similar to those of opioids.

The substance has no recognized medical (human or veterinary) use in the European Union nor, it appears, elsewhere. There are no indications that MT-45 may be used for any other purpose aside from as an analytical reference standard and in scientific research.

MT-45 has emerged on the new psychoactive substances market where it is sold as a 'research chemical'. It appears to be mostly sold on the Internet. MT-45 was first detected in a powder by Swedish customs in October 2013 and was formally reported to the Early Warning System in December 2013; since then, two other Member States have reported detections of the substance. In general, analyses of seizures have found MT-45 to be the sole psychoactive substance present. In a few small seizures, however, other controlled drugs or new psychoactive substances have been detected: Germany reported MT-45 in a seized sample of brown heroin; Belgium reported the detection of MT-45 along with methylone in a collected powder; Sweden reported the detection of MT-45 along with synthetic stimulants in two powder samples and along with synthetic cannabinoids in two herbal preparations.

In the non-fatal intoxications reported by Sweden, the clinical features were similar to those of opioid intoxication and in some cases responded to the opioid receptor antagonist naloxone.

A total of 28 deaths where the presence of MT-45 in biological samples was analytically confirmed have been reported from a single Member State, Sweden. These deaths occurred within a nine-month period between November 2013 and July 2014, typically in a home environment but information on the route of administration is lacking.

In 19 of the 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 the one remaining case (the deceased jumped off a building). In the cases where other substances were found these included opioids, benzodiazepines (both authorised medicines and unauthorised), stimulants, and other prescription medicines (including anti-psychotics, anti-depressants, and anti-convulsants).

There are no prevalence data on the use of MT-45. Limited information suggests that there may be some interest in using MT-45 among people who are familiar with licit or illicit opioids. It is often used in combination with other psychoactive substances. However, further information on the size and demand and the characteristics of these groups of people is not available. There is no specific information on the social risks that may be related to MT-45.

There is no specific information to suggest the involvement of organised crime in the manufacture, distribution (trafficking) and supply. There is no information to suggest that MT-45 is currently manufactured in any of the Member States. The chemical precursors and the synthetic routes used to manufacture the MT-45 detected in Member States are unknown. The starting materials used in the documented synthetic route are commercially available and not under international control.

MT-45 is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs or in the 1971 United Nations Convention on Psychotropic Substances. MT-45 is not undergoing assessment by the United Nations system. One Member State controls MT-45 under drug control legislation and seven Member States control MT-45 under other legislation.

Many of the questions posed by the lack of evidence on the health and social risks of MT-45, as for any new psychoactive substance, could be answered through further research. Areas where additional information would be important include: prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); market studies; chemical profiling studies; receptor profiling studies; metabolic pathway studies; behavioural studies; clinical patterns of acute and chronic toxicity in humans; the potential interaction between MT-45 and other substances; the dependence and abuse potential in humans; and the social risks associated with its use.

The Committee notes that a decision to control MT-45 has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of MT-45. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Although information is limited both on the human (psycho)pharmacological effects that may make MT-45 appealing and on the prevalence of its use, the emergence of chemically analogous substances to replace MT-45 is a possibility. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Finally, control measures should not inhibit the gathering and dissemination of accurate information on MT-45 to users, practitioners and decision makers.