European Monitoring Centre
for Drugs and Drug Addiction

Risk Assessment Report of a new psychoactive substance:

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

In accordance with Article 6 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

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1. Introduction

This Risk Assessment Report presents the summary findings and 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 that presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion 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 the 'Council Decision'). The Council Decision established a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ([3])) that may pose public-health and social risks, including the involvement of organised crime. The Council Decision therefore 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 ([5]).

MT-45 was first detected in a seizure by customs authorities in Sweden in October 2013, and the Early Warning System was formally notified 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 a Joint Report on MT-45 to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) ([6]). Taking into account the conclusion of the Joint Report, and in accordance with Article 6 of the

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([1]) EMCDDA (2009), *Risk assessment of new psychoactive substances: operating guidelines*, Publications Office of the European Union, Luxembourg (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 operationalised 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, '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 Schedules 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 Schedules 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 (www.emcdda.europa.eu/publications/joint-reports/MT-45).

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 12 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 and the other participants attending the risk assessment meeting is annexed to this report (Annex 2).

The extended Scientific Committee considered the following information resources during the risk assessment:

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 and grey literature, and Internet drug discussion forums and related websites (hereafter 'user websites');

iv. data from EMCDDA monitoring of Internet suppliers (which 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.

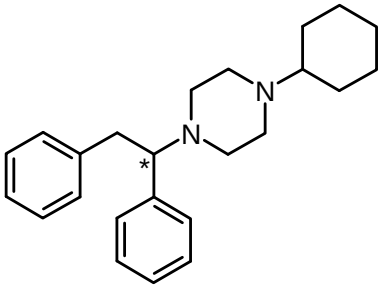
Finally, it is important to note that this Risk Assessment Report contains a discussion of the available information on non-fatal intoxications and deaths associated with MT-45. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify and report these events differs both within and between Member States. Some Member States have introduced programmes in the past few years 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 that is 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; re-dosing is common. The desired effects reportedly manifest within 15 minutes of nasal intake or within 60 minutes of oral intake and may last for up to two hours; re-dosing 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 and 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, its dependence potential and its similarities to and differences from other chemically or pharmacologically related substances.

It is important to note, when interpreting the information on non-fatal intoxications and deaths reported by Member States and 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 feelings 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.

A total of 18 non-fatal intoxications associated with MT-45, of which 12 were analytically confirmed, have been reported by a single 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 intoxications the administration of the opioid receptor antagonist naloxone may be valuable in reversing overdose features.

Twenty-eight deaths associated with MT-45 have been reported by a single 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 reported either as the cause of death or as contributing to death (even in presence of other substances); in three of these deaths MT-45 was the sole drug present. In eight 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 (the 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 antipsychotics, antidepressants and anticonvulsants) ([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 that have received a marketing authorisation by a competent authority within the EU, e.g. diazepam and alprazolam. Benzodiazepines that have not received such authorisation include diclazepam, pyrazolam and flubromazepam, all of 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 antipsychotics and 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, 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. In such instances, 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, MT-45 may be combined with other psychoactive substances by users.

There are no prevalence data on the use of MT-45 in the European Union or elsewhere, but available information does not suggest widespread 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 who have no access to heroin or any other opioid.

Based on limited information available on user websites, it appears that, as with any new psychoactive substance, vendors and (potential) users rely on non-professional information about MT-45, such as user reports that are 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 MT-45.

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 risks 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, 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 authorities 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; this 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 United Nations system, and that 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 United Nations 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) reported 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 custodial 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 that is fully applicable, if necessary.

Twenty Member States (Belgium ([13]), Bulgaria, Croatia, Cyprus, the 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

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

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 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 that may also have public health consequences.

- This control option 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 imminent. 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 model studies and experiments *in vitro* established MT-45 to be an opioid receptor agonist with analgesic potency similar to 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 and from user websites indicates that the physiological and psychological effects of MT-45 are similar to those of opioids.

The substance has no recognised 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 psycho-active 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 by 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 reported as either 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 eight 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 antipsychotics, antidepressants and anticonvulsants).

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, demand and 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.

11. List of annexes

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

Annex 2: List of participants attending the risk assessment meeting.

European Monitoring Centre for Drugs and Drug Addiction

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

Prepared by: Dr István Ujváry, Budapest, Hungary

EMCDDA contract: CC.14.SAT.006

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Annex 1 to the Risk Assessment Report of a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45)

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Summary

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

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

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

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

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

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

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

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

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

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

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

Eighteen non-fatal intoxications were reported from a single Member State, Sweden; 12 of these were analytically confirmed. In life-threatening intoxications the opioid receptor antagonist naloxone was valuable in reversing overdose symptoms.

Twenty-eight deaths where MT-45 was analytically confirmed post mortem have been reported. All occurred in Sweden between November 2013 and July 2014. In 19 deaths MT-45 was reported either as the cause of death (8 cases) or as contributing to death (even in presence of other substances); in three of these deaths MT-45 was the sole drug present. In eight 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.

In conclusion, MT-45, first described in the scientific literature in 1975, is a recently emerged synthetic opioid analgesic with a novel chemical structure. The powder products currently sold are presumed to be racemic mixtures of the hydrochloride salts of (*S*) and (*R*) stereoisomers of MT-45. The pharmacological properties of MT-45, including dependence liability and toxicity, are similar to morphine. Currently, the use of MT-45 in European Union (EU) Member States, Norway and Turkey appears to be limited. Between October 2013 and July 2014 MT-45 was seized in two Member States, Sweden and Germany; it was also detected in a single sample in Belgium. Fatal and non-fatal intoxications, occurring within a period of six months, have been reported from a single EU Member State, Sweden. Between November 2013 and April 2014 MT-45 was detected in a number of non-fatal poisonings. There have been 28 deaths where MT-45 was detected post mortem. In 19 deaths MT-45 was reported either as the cause of death (8 cases) or as contributing to death (even in presence of other substances).

Section A. Physical, chemical, pharmaceutical and pharmacological information

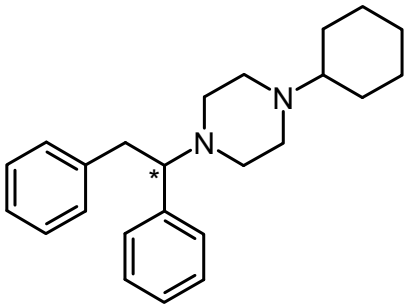
A1. Physical, chemical and pharmaceutical information

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

Chemical description and names

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

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



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

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

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

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

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

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

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

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

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

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

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

52694-55-0 racemic free base

57314-55-3 dihydrochloride (2 x HCl) salt

57377-70-5 (*R*)-isomer

57426-38-7 (*R*)-isomer dihydrochloride salt

52694-52-7 (*S*)-isomer

52694-54-9 (*S*)-isomer dihydrochloride salt

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

Identification and analytical profile

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

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

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

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

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

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

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

mass spectrometry (MS) is straightforward ([10]) (see also Uchiyama et al., 2014). The electron impact mass spectrum of MT-45 contains the following characteristic fragments (m/z): 347 $[M-1]^+$, 257 (base peak), 175, 166, 146, 124, 107, 91 and 55. The electrospray ionisation mass spectrum of MT-45 contains the following characteristic fragments (m/z): 349 $[M+1]^+$, 182, 181 and 169 (analytical data reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)).

The ultraviolet and visible spectrum of MT-45 has λ_{max} value at 258 nm (Uchiyama et al., 2014).

The Fourier Transform infrared spectrum of the hydrochloride salt of MT-45 contains the following characteristic bands: 441, 531, 558, 696, 748, 760, 780, 905, 916, 934, 1007, 1071, 1199, 1265, 1274, 1496, 2448, 2562, 2644, 2945, and 3470 cm^{-1} (see spectral data submitted to the EMCDDA; see also Hori and Fujimura, 1975).

The proton and ^{13}C nuclear magnetic resonance (NMR) spectra used for the structure identification in the first detection of the substance in Japan and Sweden are available (Uchiyama et al., 2014; analytical data reported to EMCDDA; see also Hori and Fujimura, 1975; Imai, 1982).

There is no information on presumptive colour tests with MT-45.

Urinary MT-45 did not show cross-reactivity in standard immunoassay urine screening tests for drugs of abuse (Helander et al., 2014). As of August 2014 there is no immunoassay field test for MT-45.

Certified reference materials of racemic and enantiomerically pure MT-45 suitable for forensic analysis and biological studies are commercially available ([11]).

Physical description

The dihydrochloride salt of MT-45, as obtained by recrystallization from methanol, is a solid melting at 270–271 ºC with decomposition; the free amine forms colourless prism upon crystallisation from 95 % ethanol and has a melting point of 94–95 ºC (Natsuka et al., 1975).

According to a product information data sheet available from a supplier of analytical standards ([12]), the hydrochloride salt of racemic MT-45 is sparingly soluble in water; its solubility in chloroform is approximately 1.4 mg/ml.

([10]) https://db12.designer-drugs.de

([11]) For example, bioreagent.bertinpharma.com or www.caymanchem.com

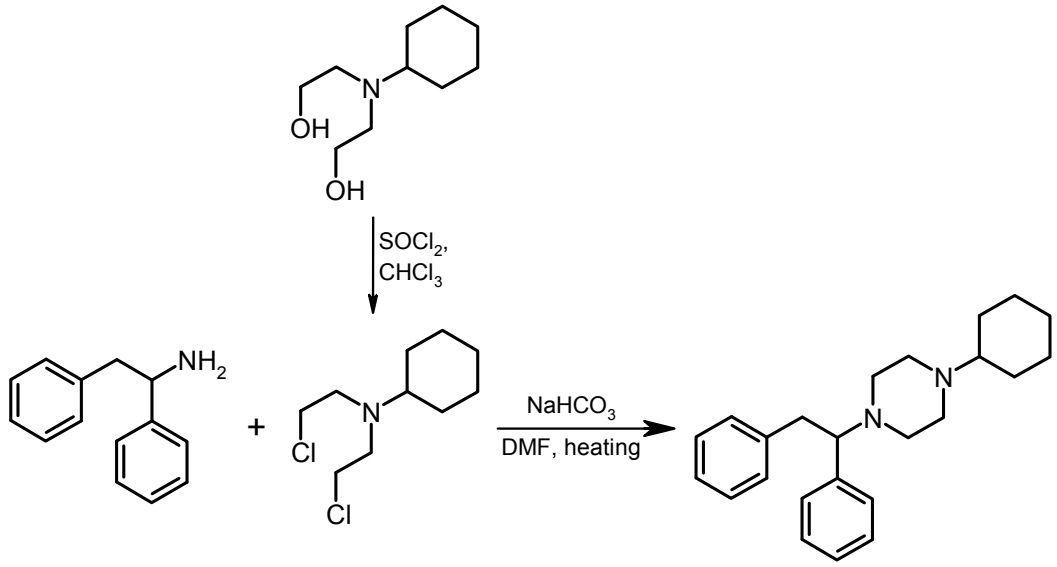
([12]) www.caymanchem.com/catalog/14082

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

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

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

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



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

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

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

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

Typical impurities encountered in seized samples

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

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

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

A1.2. Physical/pharmaceutical form

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

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

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

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

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

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

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

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

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

A1.3. Route of administration and dosage

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

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

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacokinetics

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

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

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

Pharmacodynamics

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

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

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

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

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

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

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

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

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

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

([a]) Phenylquinone-induced pain (Natsuka et al., 1975; Nakamura and Shimizu, 1976).
([b]) Acetic acid-induced pain (Kobayashi, 1991).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Abbreviations: s.c.: subcutaneous injection; i.c.v.: intracerebroventricular injection.

Table 3. Affinities of morphine hydrochloride, MT-45 and its stereoisomers, all as dihydrochlorides, and lefetamine hydrochloride to binding sites of various tritiated ligands in rat brain homogenates (Fujimura et al., 1978; Imai, 1982; Nozaki et al, 1983).

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

Abbreviations: DHM: [$^3H_2$]dihydromorphine; NLX: [^{3}H]naloxone; DADLE: [^{3}H](D-Ala^2,D-Leu^5]enkephalin; EKC: [^{3}H]ethylketocyclazocine.

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

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

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

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

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

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

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

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

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

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

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

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

inhibition (Nakamura et al., 1985).

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

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

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

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

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

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

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

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

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

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

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

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

A3. Psychological and behavioural effects

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

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

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

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

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

A4. Legitimate uses of the product

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

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

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

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

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

Section B. Dependence and abuse potential

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

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

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

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

B2. Human data

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

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

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

Section C. Prevalence of use

Information from seizures, collected and biological samples

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

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

Country	Amount and details of the seizure/collected sample
Belgium	

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

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

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

Availability from Internet retailers

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

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

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

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

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

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

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

Five of the sites only provided quantities and prices for MT-45 on application. The remaining seven sites listed quantities and prices. Briefly: the minimum quantity offered was 1 g (n=2 sites) with a mean price of EUR 33.25 (EUR 22.16–44.34); the maximum quantity offered was 5 000 g (n=1 site) with a price of EUR 12,900. Most of the seven sites offered quantities ranging from 10–1 000 g. The mean price for 10 g (n=5 sites) was EUR 178.11 (EUR 129–311.01); the mean price for 100 g (n=5 sites) was EUR 778.37 (EUR 498.00–1 107.90); the mean price for 1 000 g (n=5 sites) was EUR 3 041.02 (EUR 2 363.52–3 914.58). On these sites MT-45 was typically sold as a 'research chemical'. Repeating the search in August 2014 gave similar results. For example, 10 g, 100 g or 1 kg of MT-45 were offered for USD 180, 700 or 3 200, respectively ([45]); another supplier offered 1 kg of MT-45 for USD 6 716 ([46]).

An Internet snapshot survey undertaken in English during June 2014 identified 17 sites selling MT-45 (16 were common to both google.co.uk and google.com; one identified on google.com only). The country of origin was identifiable from the Internet site as follows: China eight; Canada two; Germany one; India one; and Sweden one; it was not possible to identify the country of origin for four Internet sites. Nine Internet sites had no information directly available on cost and this was only available to registered users and/or on request. Of the eight Internet sites where information was available on cost, six were selling in dollars (assumed to be US dollars, although not explicitly stated), one in Euros and one in Swedish Krona. MT-45 was for sale in amounts ranging from 500 mg to 5 kg. The mean price of MT-45 decreased with increasing purchase amounts from USD 57.6 ± 19.37 per gram for a 1 g purchase to USD 3.36 ± 1.83 per gram for a 1 kg purchase (personal communication to the EMCDDA from David Wood) ([47]).

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

Prevalence of use

There are currently no coordinated national or European surveys on the prevalence of use of MT-45 in the general population or in targeted populations. Further, neither the European School Survey Project on Alcohol and Other Drugs (ESPAD) nor other school/college/university surveys have investigated or reported on MT-45 use.

Section D. Health risks

D1. Acute health effects

([45]) www.lsresearchchems.com/views.asp?hw_id=155

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

([47]) These data has now been published, see: Siddiqi, S., Verney, C.H., Dargan, P., Wood, D.M. (2014), 'Understanding the availability, prevalence of use, desired effects, acute toxicity and dependence potential of the novel opioid MT-45', *Clin Toxicol (Phila)* 2014; In press.

D1.1. Animal data

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

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

Drug	Mice			Rats		
	oral	s.c.	i.v.	oral	s.c.	i.v.
Morphine	1402	560	204	335	Not tested	Not tested ([48])
Rac. MT-45	329	743	17.8	150	136	7.8
(*S*)-MT-45	274	320	18.5	Not tested	Not tested	8.0
(*R*)-MT-45	250	Not tested	17.9	288	97.7	12.9
Lefetamine	176	104	32.6	~300	148	Not tested

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

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

The RTECS Number for the dihydrochloride of MT-45 is TL3486500 ([49]).

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

D1.2. Human data

No clinical studies were identified that have systematically examined the toxicity or adverse effects of MT-45 in humans. The sub-sections that follow summarise selected, though typical, user reports and reports from Sweden on 18 non fatal-intoxications requiring emergency treatment following MT-45 use ([50]). The clinical findings reported by Sweden on 28 deaths are also presented.

D1.2.1. User reports

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

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

Bluelight:

The first user report appeared in September 2012 on this user website (Bluelight, 2014). One user who had previously experimented with inhaling the vaporised base of MT-45 'tried 80 mg of MT-45 salt solution rectally. I expected this to be a full dose and was surprised to find

([49]) RTECS stands for Registry of Toxic Effects of Chemical Substances, which is a compendium of toxicity data extracted from the scientific literature. The database was originally developed by The US National Institute of Occupational Safety and Health (www.cdc.gov/niosh/rtecs/RTECSaccess.html) but it is now maintained by Accelrys-BIOVIA of Dassault Systèmes.

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

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

Flashback:

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

Chems’R’us:

Discussions of MT-45 started on this website in the ‘legal opioids’ category early in 2013

(Chems'R'us, 2014). One experience report described how, by rubbing over the gums ('dabbing') a few milligrams of powdery MT-45, the effects 'within 5 mins … kicked in. Very trippy, no warm opiate sensation'; 30 minutes later 'sweaty palms and feet, little anxiety' were noted. Another user commented later that a mixture of AH-7921 and MT-45 in a 1:1 ratio was as euphoric and addictive as oxycodone.

Shroomery:

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

D.1.2.2. MT-45 associated acute toxicity

The Swedish national focal point reported 46 serious adverse events ([51]) associated with MT-45 between November 2013 and July 2014. Of the 46 cases, 18 were non-fatal intoxications (12 have been analytically confirmed) and 28 were deaths. In one of these deaths MT-45 was detected in biological samples and the cause of death was reported as 'injury'.

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

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

Non-fatal cases reported by Sweden:

There have been 12 cases where MT-45 was analytically confirmed in non-fatal intoxications associated with MT-45 as reported by the Swedish Poison Information Centre or National

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

Laboratory of Forensic Chemistry ([52]). The cases occurred during 2013 (four cases) and 2014 (eight cases). All these cases were males aged between 17 and 37. The forensic and clinical results for these cases are summarised in Table 6.

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

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

- somnolence or unconsciousness;

- tachycardia;

- shortness of breath (apnoea) or decreased respiratory rate;

- cyanosis;

- miosis.

In four of the nine cases described by Helander et al. (2014), various neurological disturbances, such as paraesthesia in hands and feet, difficulties in grip and coordinating hand movements, balance disturbances, and/or blurred and double vision were also noted. Furthermore, bilateral hearing loss developed in three cases as a result of MT-45 exposure; in two of the cases the hearing impairment was transient, but in one case the unusual ototoxicity ([53]) persisted for two weeks after discharge, as documented at a follow-up audiology testing.

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

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

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

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

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

Case	Toxicology results for MT-45	Results for other substances detected	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, sources of MT-45)	Details of serious adverse event - Clinical symptoms, treatment - Why the event was considered serious?
1	Detected	None	Oral; 100 mg	-	- Hypertension, tachycardia, muscular symptoms - Non life-threatening event, but required treatment in hospital
2	Detected	Dextromethorphan, methiopropamine ([a]), THC	Not known	-	- Constricted pupils, cyanosis, unconsciousness, tachycardia. Naloxone was administered - Life-threatening event, requiring treatment in hospital
3	Detected	Pyrazolam ([b]), THC	Injected (intravenous and intramuscular) and snorted; 3 g during a week	α-PBP (1 g) ([c]); MT-45 was obtained from the Internet	- Somnolence, hypotension, tachycardia, low oxygen saturation. Naloxone was administered - Life-threatening event, requiring treatment in hospital
4	Detected	3-MeO-PCP	Snorted	'Maybe some stimulating drugs'; MT-45 was obtained from the Internet	- Somnolence, apnoea, hearing loss. Naloxone was administered - Life-threatening event requiring treatment in hospital

Case	Toxicology results for MT-45	Results for other substances detected	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, sources of MT-45)	Details of serious adverse event - Clinical symptoms, treatment - Why the event was considered serious?
5	330 μg/g in blood	None	Not known	–	- Somnolence, decreased respiratory rate, tachycardia, hearing loss, muscular symptoms. Naloxone was administered - Life-threatening event requiring treatment in hospital
6	0.06 μg/g in blood	Flubromazepam ([d]), THC	Not known	–	- Somnolence, tachycardia - Described both as life-threatening and non life-threatening event by two different reporting agencies; required treatment in hospital
7	Detected	None	Oral, rectal	–	- Somnolence, decreased respiratory rate, tachycardia. - Life-threatening event, requiring treatment in hospital. Outcome not known
8	Detected	None	Not known	–	- Unconsciousness, hypoxia, vomiting, hearing loss - Life-threatening event, requiring treatment in hospital

Case	Toxicology results for MT-45	Results for other substances detected	Route of administration (physical form) and amount of MT-45 taken	Contextual information (self-reported intake of other substances, sources of MT-45)	Details of serious adverse event - Clinical symptoms, treatment - Why the event was considered serious?
9	Detected	3-MMC/4-MMC ([e]), flubromazepam ([d]), pyrazolam ([b])	Oral (powder)	–	- Unconsciousness, decreased respiratory rate, hypokalaemia. Naloxone was given - Life-threatening event, requiring treatment in hospital
10	Detected	α-PPP ([f]), N-ethyl-buphedrone ([g]), α-PBP ([c]), 3-MeO-PCP, methio-propamine ([a])	Oral (tablet)	Flubromazepam ([d])	- Somnolence - Life-threatening event, requiring treatment in hospital
11	Detected	4-hydroxy-midazolam	Not known	–	- Unconsciousness, cyanosis - Life-threatening event, requiring treatment in hospital
12	Detected	DPT ([h]), des-methyldiazepam	Not known	APB ([i])	- Anxiety, tachycardia, hallucinations - Non life-threatening event but required treatment in hospital

([a]) Methiopropamine is a name for a thiophene-containing analogue of methamphetamine; it was first reported to the EMCDDA as a new psychoactive substance in January 2011.

([b]) Pyrazolam is a name for a benzodiazepine derivative; it was first reported to the EMCDDA as a new psychoactive substance in August 2012.

([c]) α-PBP is an acronym of a cathinone derivative; it was first reported to the EMCDDA as a new psychoactive substance in December 2011.

([d]) Flubromazepam is a name for a benzodiazepine derivative; it was first reported to the EMCDDA as a new psychoactive substance in March 2013.

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

([f]) *N*-Ethylbuphedrone is a name of a cathinone derivative; it was first reported to the EMCDDA as a new psychoactive substance in January 2009.

([g]) α-PPP is an acronym of a cathinone derivative; it was first reported to the EMCDDA as a new psychoactive substance in January 2009.

([h]) DPT is an acronym for *N*,*N*-dipropyltryptamine; it was first was reported to the EMCDDA as a new psychoactive substance in November 2004.

([i]) APB probably stands for an isomer of aminopropylbenzofurans; the first of such substances was reported to the EMCDDA in December 2010.

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

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

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

Case	Reported or suspected substances ([a])	Reported dose and route of MT-45 intake	MT-45 in blood (ng/ml)	MT-45 in urine (ng/mmol creatinine)	Other substances detected in urine ([a])	Main clinical symptoms ([b]); naloxone treatment ([c]), if any
9	MT-45	100 mg, oral	56	132	3-MMC, pyrazolam	Deep unconsciousness (RLS 8), prolonged respiratory depression; 3 x 0.4 mg naloxone

([a]) For explanation of names and abbreviations, see Table 6.

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

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

([d]) THC-COOH refers to the major urinary metabolite of THC indicating cannabis use.

([e]) α-PVP is an acronym for a cathinone derivative; it was first reported to the EMCDDA as a new psychoactive substance in April 2011.

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

D1.2.3. MT-45 associated deaths

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

MT-45 was analytically confirmed in all the death cases reported by the Swedish National Board of Forensic Medicine (Department of Forensic Genetics and Forensic Toxicology, Linköping). In four of these cases MT-45 was the sole detected drug in post-mortem femoral blood at concentrations ranging from 0.2 to 1.9 μg/g ([54]). In one additional case where MT-45 was the sole detected drug in post-mortem femoral blood (0.15 μg/g), death was due to an accident ('injury'). In the remaining 24 cases at least one other psychoactive substance was detected. These included: THC (one case); ethanol (four cases); stimulants (six cases); benzodiazepines and/or their metabolites (13 cases); other opioids (10 cases); as well as other medicines and, in some cases, their metabolites: alimemazine (also known as trimeprazine) or levomepromazine (also known as methotrimeprazine), bupropion, citalopram, duloxetine, fluoxetine, gabapentin, lamotrigine, metoclopramide, mirtazapine, olanzapine, promethazine, propranolol, quetiapine, sertraline, venlafaxine and/or zopiclone (one or more of these in 14 cases). In the polydrug intoxications, the concentration of MT-45 in post-mortem femoral blood ranged from 0.006 to 1.7 μg/g. (See Table 8 for further details.)

For 22 cases the cause of death was given as follows: 'MT-45 intoxication' (eight cases); 'mixed intoxication' (six cases); 'mixed intoxication' specifying 'opioids' (one case), 'opiates and illicit drugs' (one case) and 'tramadol and MT-45' (one case); 'ethanol and drugs' intoxication (one case); 'alimemazine, MT-45 and diclazepam' intoxication (one case); and 'pneumonia + intoxication' (two cases). As mentioned in the previous paragraph, one death was due to a fatal accident. For six cases the cause of death has not been declared (as of September 2014).

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

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

	Toxicology results for MT-45 μg/g	**Results for other substances** μg/g ([a]) name of drug	**Circumstances**	**Cause of death**
1	1.9	No other substance detected	Found dead at home	MT-45 intoxication
2	0.82	0.51 quetiapine	Found dead at home	MT-45 intoxication
3	0.46	27 gabapentin 1.3 methiopropamine ([b]) 0.43 flubromazepam ([c]) + pyrazolam ([d]) + ethylphenidate ([e])	Found dead at home	Mixed intoxication
4	0.008	0.06 alprazolam 5.5 gabapentin 0.02 morphine 0.0006 THC	Not known	Pneumonia and intoxication
5	0.38	0.16 flubromazepam ([c]) 0.1 sertraline 0.3 desmethylsertraline + pyrazolam ([d])	Found dead at home	Pneumonia and intoxication
6	0.35	0.03 mirtazapine 0.02 desmethylmirtazapine 0.6 APDB ([f])	Found dead at home	Mixed intoxication
7	0.93	0.57 fluoxetine 0.51 norfluoxetine	Found dead at home	MT-45 intoxication

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

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

	Toxicology results for MT-45 μg/g	Results for other substances μg/g ([a]) name of drug	Circumstances	Cause of death
20	0.006	0.023 fentanyl 0.07 metoclopramide 0.26 mirtazapine 0.11 desmethylmirtazapine 0.06 zopiclone 13 gabapentin + flubromazepam	Found dead at home	Not finished
21	0.31	0.07 duloxetine 0.007 morphine 0.01 ethylmorphine	Found dead at home	Not finished
22	0.14	0.38 methadone 0.2 alimemazine ([h]) 0.09 mirtazapine 0.5 promethazine 0.1 desmethylprometazine 0.51 diazepam 0.63 nordiazepam 0.14 flubromazepam ([c]) 0.42 4-F-PVP ([j])	Found dead at home	Mixed intoxication
23	0.51	0.03 propranolol	Found dead at home	Not finished

	Toxicology results for MT-45 μg/g	Results for other substances μg/g ([a]) name of drug	Circumstances	Cause of death
24	1.5	0.04 olanzapine + 6-MAPB ([k]) + 6-APB ([l]) + N-ethylbuphedrone ([m])	Found dead at home	Mixed intoxication with opiates and illicit drugs
25	0.15	2.1 tramadol 0.31 desmethyltramadol	Found dead at home	Intoxication with tramadol and MT-45
26	0.05	0.11 diazepam 0.23 nordiazepam 1.5 fluoxetine 0.8 norfluoxetine 3.1 pregabalin 0.3 methylphenidate 0.89 ritanilic acid	Died visiting girlfriend	Not finished
27	1.7	+ ethanol	Found dead at home	Not finished
28	0.47	3.5 lamotrigine 0.3 citalopram 0.22 quetiapine 0.02 7-hydroxyquetiapine 0.1 propranolol + ethanol	Found dead at home	Not finished

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

([b]) Methiopropamine is a name for a thiophene-containing amphetamine-type stimulant; it was first reported to the EMCDDA as a new psychoactive substance in January 2011.

([c]) Flubromazepam is a name for a benzodiazepine derivative; it was first reported to the EMCDDA as a new psychoactive substance in March 2013.

([d]) Pyrazolam is a name for a benzodiazepine derivative; it was first reported to the EMCDDA as a new psychoactive substance in August 2012.

([e]) Ethylphenidateis a name for a methylphenidate analogue; it was first reported to the EMCDDA as a new psychoactive substance in November 2011.

([f]) APDB stands for 4-, 5- or 6-(2-aminopropyl)-2,3-dihydrobenzofuran derivatives; it was first reported to the EMCDDA as a 'new psychoactive substances' in March 2012.

([g]) Diclazepam is a name for a benzodiazepine derivative; it was first reported to the EMCDDA as a new psychoactive substance in August 2013.

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

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

([j]) 4-F-PVP is an acronym for a cathinone derivative; it was first reported to the EMCDDA as a new psychoactive substance in February 2014.

([k]) 6-MAPB is an acronym for an aralkylamine derivative stimulant; it was first reported to the EMCDDA as a new psychoactive substance in September2013.

([l]) 6-APB is an acronym for an aralkylamine derivative stimulant; it was first reported to the EMCDDA as a new psychoactive substance in June 2011.

([m]) *N*-Ethylbuphedrone is a name of a cathinone derivative; it was first reported to the EMCDDA as a new psychoactive substance in January 2009.

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

In 19 deaths MT-45 was reported either as the cause of death or as contributing to death (even in presence of other substances); in three of these deaths MT-45 was the sole drug present. In eight 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 (the deceased had jumped off a building). In the cases where other substances were found these included opioids, benzodiazepines (both authorised and unauthorised medicinal products), stimulants and other prescription medicines (including antipsychotics, antidepressants, and anticonvulsants).

Deaths identified in open source information

Two deaths from the United States of America that occurred between 7 and 10 August 2013 were identified in a news release by the US Immigration and Customs Enforcement's Homeland Security Investigations (EMCDDA and Europol, 2014). These deaths involved a male (aged 34) and a female (aged 33) who were found dead in their apartment in Hamburg, New York State; white powder identified as MT-45 was recovered at the scene. The medical examiner determined that the male had died of acute intoxication with MT-45 and the female had died of acute intoxication with MT-45 and ethanol ([55]). Documented evidence showed that 3 g of MT-45 had been ordered through the Internet on 29 July 2013 and received by the victims on 5 August 2013. Diazepam and oxycodone were also collected at the scene.

D2. Chronic health effects

D2.1. Animal data

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

There are no data on the neurotoxicity or carcinogenicity of MT-45 *in vitro*. It could be relevant to mention, however, that in the *in vivo* anticancer drug screening programme of the National Cancer Institute (NCI), USA, intraperitoneally administered MT-45, under NCI number code

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

NSC 299236, did not show antitumour activity in two strains of mice bearing transplantable tumours (P388 leukemia) (NCBI, 2014).

D2.2. Human data

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

D3. Factors affecting public health risks

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

MT-45 is offered for sale in small (multi gram) and in bulk (kilogram) quantities on the Internet by several suppliers as a drug in its own right (Section C). The purity of these products is claimed to be high (>95 %) but this has rarely been tested by forensic analysis. Racemic and enantiopure MT-45 have become commercially available as analytical standards or experimental research chemicals from several fine chemical suppliers ([56]).

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

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

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

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

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

([56]) For example, bioreagent.bertinpharma.com or www.caymanchem.com

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

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

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

D3.5. Long-term consequences of use

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

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

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

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

Section E. Social risks

E1. Individual social risks

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

E2. Possible effects on direct social environment

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

E3. Possible effects on society as a whole

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

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

E4. Economic costs

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

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

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

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

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

Section F. Involvement of organised crime

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

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

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

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

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

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

There is no information available in this area.

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

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

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

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

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

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

F7. Use of violence between or within criminal groups

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

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

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

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European Monitoring Centre
for Drugs and Drug Addiction

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

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