

**MT-45**  
**Critical Review Report**  
**Agenda item 5.1**

**Expert Committee on Drug Dependence**  
**Thirty-seventh Meeting**  
**Geneva, 16-20 November 2015**





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## Summary

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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 developed along with other 1-Substituted-4-(1,2-diphenylethyl)piperazine derivatives by the Japanese company, Dainippon Pharmaceutical Co. Ltd, in the mid-1970s with the objective of obtaining compounds with analgesic, anti-tussive, and anti-inflammatory effects but without opiate-like abuse liability. Structurally, MT-45 is somewhat similar to lefetamine (SPA; (-)-N,N-dimethyl-1,2-diphenylethylamine), a stimulant with analgesic effects, that is controlled as a Schedule IV drug under the U.N. 1971 Convention on Psychotropic Substances, but conversion into SPA is considered difficult. It has no known approved medical or industrial applications.

MT-45 is being used for non-medical reasons. MT-45 has been detected in seized material in Japan, the United States and in Europe (Sweden, Belgium and Germany). It is sold on the Internet, often presented as a "research chemical". Use of MT-45 has toxic consequences including respiratory depression, unconsciousness, paraesthesia, balance and vision disturbances. Persistent hearing loss has been associated with its use. Twenty-eight deaths have been associated with MT-45's use in Sweden alone. Fatalities have also been reported in the United States as well. Users report using MT-45 via several different routes of administration including oral, insufflation, inhalation, and rectally.

MT-45 is a chiral molecule and has stereoisomers that differ in their pharmacological effects. MT-45 (the racemate) binds to the  $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptors, respectively. The S(+) isomer binds less potently to the  $\mu$ -opioid receptor, but more potently to the  $\delta$ - and  $\kappa$ -opioid receptors than the racemate. The R(-)-enantiomer also binds to all three receptors, but less potently than either the racemate or the S(+)-enantiomer. The R(-)-isomer has also been reported to bind to both the  $\sigma_1$  and  $\sigma_2$  receptors at 1.4 nM and 1.8 nM, respectively, a 1000-fold higher affinity than that found for the opioid receptor subtypes. Targeting the  $\sigma_1$  receptor subtype with antagonists has been proposed as an approach for combating the effects of several drugs of abuse especially the psychostimulants.

MT-45 has many of the effects of a classical opiate such as morphine. It inhibits electrically induced contractions of the guinea pig ileum, it has antinociceptive effects in thermal, mechanical, electrical and chemical pain models, it reduces GI transit time, depresses respiration, produces Straub tail in mice, and induces hyperglycemia. The S(+)-isomer can also produce these effects, but the R(-)-isomer was reported not to depress respiration, produce Straub tail, or to have hyperglycemic effects. Also similar to the racemate, the S(+)-isomer produces stimulation at low doses, and unlike the R(-)-isomer that produces sedation.

The mixed opiate agonist-antagonist, nalorphine, is able to precipitate opiate-like withdrawal jumping in MT-45-treated mice. MT-45 is also able to attenuate signs of morphine withdrawal in mice thus demonstrating cross-dependency with morphine. Controlled studies examining the potential physical dependence effects of MT-45 in human subjects have not been reported;

however, withdrawal-like symptoms have been reported following use of MT-45 on user websites.

MT-45 is clearly being abused for non-medical reasons in several countries, most often apparently for its opiate-like effects, although its isomers markedly distinguish themselves from each other in terms of their opiate-related effects and MT-45 should not be just considered "another morphine". Recognizing the abuse of MT-45 and its associated toxicity, several European countries have brought MT-45 under some level of regulatory control. Unfortunately, as is true with many NPS's, scholarly reports documenting the prevalence and incidence of MT-45's abuse are not available.

## 1. Substance identification

### A. *International Nonproprietary Name (INN)*

None

### B. *Chemical Abstract Service (CAS) Registry Number*

41537-67-1 (free base); 57377-70-5 ((R)-isomer); 52694-54-9 ((S)-isomer dihydrochloride salt); 52694-55-0 (racemic free base); 57314-55-3 (diHCl salt); 52694-54-9 ((S)-isomer diHCl salt); 57426-38-7 ((R)-isomer diHCl salt);

### C. *Other Names*

(±)-1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine  
 1-Cyclohexyl-4-(1,2-diphenylethyl)piperazin [German] [ACD/IUPAC Name]  
 1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine [ACD/IUPAC Name]  
 1-Cyclohexyl-4-(1,2-diphényléthyl)pipérazine [French] [ACD/IUPAC Name]  
 4-cyclohexyl-1-(1,2-diphenylethyl)piperazine  
 CDEP  
 NSC 299236.  
 IC-6  
 MT-45  
 Piperazine, 1-cyclohexyl-4-(1,2-diphenylethyl)- [ACD/Index Name]  
 Piperazine, 1-cyclohexyl-4-(1,2-diphenylethyl)-, (±)-  
 (±)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine  
 41537-67-1 [RN]  
 IC 6  
 41537-67-1  
 AC1L8SAC; IC 6;  
 SCHEMBL11504649;  
 CTK1C8936

### D. *Trade Names*

none

### E. *Street Names*

MT-45, IC-6, "Wow" in combination with methylone

### F. *Physical properties*

The free amine and the hydrochloride salts are solid. Seizures within the European Union have usually found MT-45 in white powder form.<sup>1</sup> User report indicated, "... fluffy, slightly off-white (perhaps eggshell or faint cream) powder; soft and very sticky. Will coat my fingers if I handle it. Taste: Extremely bitter....Smell – extranasally/wafting: faint earthiness. Essentially no smell."<sup>2</sup> It has also been



detected in samples of plant material in the presence of synthetic cannabinoid substances. In two non-fatal intoxications reported by Sweden the physical form used by the patients included a tablet in one case and a capsule in the other.<sup>3</sup> In Japan, MT-45 was identified as a white solid after precipitation from a colorless liquid.<sup>4</sup>

**G. WHO Review History**

Not previously reviewed.

**2. Chemistry**

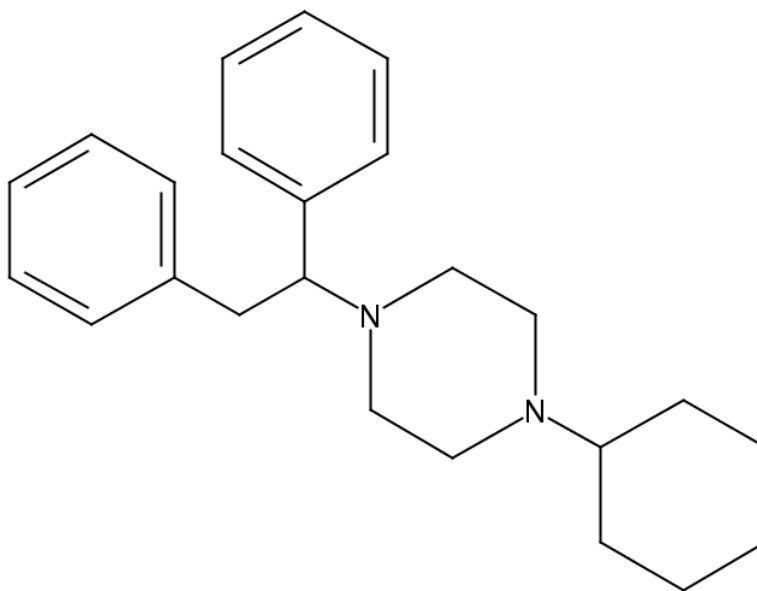
**A. Chemical Name**

**IUPAC Name:** 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine

**CA Index Name:** Piperazine, 1-cyclohexyl-4-(1,2-diphenylethyl)-

**B. Chemical Structure**

**Free base:**



**Molecular Formula:** C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>

**Molecular Weight:** 348.52428 g/mol for base; 421 g/mol for •2HCl

**Melting point:** 94-95°C for free base<sup>5</sup>; 270-271°C for diHCl salt<sup>6</sup>

**Boiling point:** 450.8°C at 760mmHg

**C. Stereoisomers**

MT-45 is chiral and thus has stereoisomers. In presumably the first instance in which MT-45 was detected as a designer drug in Japan, the racemate was only found.<sup>(4)</sup> This evidence from Japan has led to the suggestion that MT-45 sold in Europe is also most likely the racemate.<sup>7</sup>

**D. Synthesis**Methods of manufacturing:

Natsuka and colleagues reported one route of synthesis using the following steps: "In DMF (30-40 ml) was dissolved N,N-bis(2-chloroethyl)-1,2-diphenylethylamine.HCl (20 mmol) and the appropriate primary amine (80 mmol) was added to the mixture. The mixture was refluxed for 5 hr with stirring. After the solvent and excess of amine were removed, the residue was dissolved in aqueous 10% HCl and the solution was cooled. The resulting crystals were collected, washed with a small amount of cold H<sub>2</sub>O and acetone, and dried. The product was recrystallized from MeOH or EtOH."<sup>6</sup> Other methods of synthesis have been described by Ward and colleagues.<sup>8</sup> These methods of syntheses have been identified as requiring readily available starting materials that require conventional laboratory equipment, and that require "no special chemical expertise" for production.<sup>9</sup>

**E. Chemical description.**

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 developed along with other 1-Substituted-4-(1,2-diphenylethyl)piperazine derivatives by the Japanese company Dainippon Pharmaceutical Co. Ltd in the mid-1970s with the objective of obtaining compounds with, "... excellent analgesic, anti-tussive and anti-inflammatory activities, without undesirable side effect such as narcotic activity...".<sup>10</sup>

**F. Chemical properties**

MT-45 (hydrochloride) is a crystalline solid which is sparingly soluble in aqueous solutions. It is soluble in chloroform at approximately 1.4 mg/ml.<sup>11</sup> Other pertinent information regarding chemical properties can be found in section 2B above.

**G. Chemical identification**

MT-45 could not be detected (i.e. it showed no cross reactivity) using the standard set of immunoassay urine screening tests for drugs of abuse.<sup>12, 13</sup> MT-45 could be identified and quantified by a liquid chromatographic-tandem mass spectrometric (LC-MS/MS) multi-component method<sup>14</sup> based upon that described by Al-Saffar and colleagues.<sup>15</sup> Reference standards of the racemate and its enantiomers for analytical methodologies are commercially available.<sup>11</sup>

**3. Ease of convertibility into controlled substances**

Published literature could not be found in which expert medicinal chemists provided comment regarding the ease of convertibility of MT-45 into known, controlled substances. In the absence of this literature, the reviewer contacted two, eminent opioid medicinal chemists: Dr. F. Ivy Carroll, Distinguished Fellow, Medicinal Chemistry of the Research Triangle Institute, NC, U.S.A., and Dr. Andrew Coop, Vice Chair for Academic Affairs, Department of Pharmaceutical Sciences, University of Maryland, MD, U.S.A. and asked their opinion. Both medicinal chemists indicated it would be difficult converting MT-45

into any known, scheduled substance. Structurally, MT-45 is somewhat similar to lefetamine (SPA; (-)-N,N-dimethyl-1,2-diphenylethylamine), a stimulant with analgesic effects, that is controlled as a Schedule IV drug under the 1971 Convention, but conversion into SPA is considered extremely difficult as well.<sup>16</sup>

## 4. General pharmacology

### A. Pharmacodynamics

**Receptor binding:** The inhibitory effect of MT-45 and its enantiomers on the stereospecific binding of  $5 \times 10^{-9}$  M  $^3\text{H}$ -naloxone or  $1 \times 10^{-8}$  M  $^3\text{H}$  morphine to homogenates of rat brain without cerebellum was determined by Fujimura and colleagues.<sup>17</sup> The IC<sub>50</sub> (μM) against naloxone binding was 0.74, 0.14 and 1.18 for the racemate, S(+)-, and R(-)-isomers, respectively. The corresponding IC<sub>50</sub> value for morphine was much more potent than the other compounds at 0.0055 μM. Against tritiated morphine binding the values for the racemate, S(+)-, and R(-)-isomers were 0.064, 0.072 and 1.60, respectively. Hill's coefficient in these binding assays for R(-)-isomer and morphine were close to 1.0, non-cooperativity. This value was about half for the S(+)-isomer, namely negative cooperativity. These results suggested to Fujimura and colleagues that, "... R(-)-enantiomer interacts with the opiate receptor in a mode similar to that seen with morphine, but the S(+)-enantiomer acts in a different mode and the racemate in a two-way mode".<sup>17</sup> Note below for their *in vivo* effects, however, that it is more often the case that the S(+)-enantiomer is more similar in its effects than the R(-)-enantiomer.

In other studies, Fujimura evaluated MT-45 and its enantiomers for their binding affinities at μ, δ, and κ opioid receptors using tritiated  $^3\text{H}$ -dihydromorphine (70 Ci/mmol),  $^3\text{H}$ -D-Ala<sup>2</sup>-D-Leu<sup>5</sup>-enkephalin (DADLE, 27.4 Ci/mmol), and  $^3\text{H}$ -ethylketocyclazocine (EKC, 21.8 Ci/mmol), respectively.<sup>18</sup> Morphine bound to the μ, δ, and κ opioid receptor sites with IC<sub>50</sub>s (nM) of 4.6, 78.6, and 242 nM, respectively. The S(+)-enantiomer bound to the δ and κ sites with IC<sub>50</sub>s of 70.6 and 78.0 nM, respectively, and more potently than morphine, but less potently at the μ receptor binding site with an IC<sub>50</sub> of 736 nM. MT-45 (the racemate) bound to the μ receptor more potently than its S(+) isomer at 644 nM, but less potently at δ, and κ opioid receptor sites with IC<sub>50</sub>s of 156 and 176 nM, respectively. The R(-)-enantiomer bound to all three receptors less potently than either the racemate or the S(+)-enantiomer with IC<sub>50</sub>'s of 644, 156, and 176 for the μ, δ, and κ receptor sites, respectively.<sup>18</sup>

(R)-MT-45 binds with high affinity (IC<sub>50</sub>'s) to both the σ<sub>1</sub> and σ<sub>2</sub> receptors at 1.4 nM and 1.8 nM, respectively, 1000-fold higher than that found for the opioid receptor subtypes, using guinea pig brain membrane and [ $^3\text{H}$ ]pentazocine as the radioligand.<sup>19</sup> Targeting the σ<sub>1</sub> receptor subtype with antagonists has been proposed as an approach for combating the effects of several drugs of abuse especially the psychostimulants (refer to review<sup>20</sup>)

**Inhibition of the guinea pig ileum:** Morphine inhibits electrically induced contractions of the longitudinal muscle of the guinea pig ileum. When tested in this assay, MT-45, its S(+)-, and R(-)-isomers inhibited stimulation of the guinea pig ileum with IC<sub>50</sub>'s of 0.0153, 0.0127 and 0.107 μM, respectively.<sup>17</sup>

Analgesia: Nakamura and colleagues conducted extensive analgesia tests with MT-45 and its enantiomers in mice and rats.<sup>21</sup> MT-45 demonstrated analgesic activity in a number of pain procedures in mice and rats. The analgesic ED50-values of MT-45 were 3.09, 2.15, 1.54 and 2.24 mg/kg, s.c. in mice against thermal, mechanical, electrical and chemical pains, respectively, and the activity was almost as potent as that of morphine except for chemical pain in which it was less potent. In rats, analgesic ED50-values of MT-45 were 6.62 and 0.73 mg/kg, s.c. against the thermal and mechanical pains, respectively. MT-45 was more effective than morphine against mechanical pain, but less effective against thermal pain. MT-45 was orally active in the four pain models in mice with similar or greater potency to morphine except for electrical and chemical pain. The activity of the S(+)-isomer was 1.14 to 1.97 times in mice and 1.00 to 1.23 times in rats as potent as MT-45, and 18.3 to 61.6 times as potent as the R(-)-isomer dependent upon the route of administration and pain model.

Gastrointestinal propulsion: Subcutaneous administration of 3 and 10 mg/kg of MT-45 significantly ( $P < 0.01$ ) reduced GI transit time in mice with a potency slightly weaker than that of morphine. The S(+)-isomer was more potent than the racemate, and nearly 10x more potent than the R(-)-isomer.<sup>21</sup>

Miosis: In contrast to tests with 10 mg/kg s.c. morphine, neither the racemate nor its isomers showed any effect on pupil size in rabbits. The mydriatic activity of MT-45 was determined to be superior to that of morphine in mice at 10 mg/kg, s.c., but much less at 3 mg/kg, s.c. At a dose of 10 mg/kg, s.c., the activity of the S-isomer was comparable to that of MT-45. The mydriatic activity of the R-isomer was almost negligible at 30 mg/kg, s.c.<sup>21</sup>

Respiratory depression: In anesthetized rabbits, 3 mg/kg i.v. morphine caused a 63% reduction in respiration. The racemate and the S(+) isomer caused a respiratory depression by 59% and 57% at 1 mg/kg, respectively, but the R(-)-isomer was without effect up to 5 mg/kg.<sup>21</sup>

Morphine-like Straub tail: The racemate and the S(+)-isomer, but not the R(-)-isomer produced a characteristic morphine-like Straub tail in rodents.<sup>21</sup>

Body temperature: MT-45 and its S(+)-isomer produced an  $\sim 1^{\circ}\text{C}$  increase in rectal temperature in rats when given at an identical dose of 10 mg/kg s.c.<sup>21</sup>. In contrast, the R(-)-isomer was without effect up to 30 mg/kg s.c.

Hyperglycemia: Morphine can induce hyperglycemia in rabbits (increase in plasma glucose levels). MT-45 and its S(+)-isomer increased blood glucose levels by  $\sim 1/3$  the level that morphine did when tested at identical doses of 10 mg/kg s.c.<sup>21</sup> The R(-)-isomer was without effect up to 30 mg/kg s.c.

Memory: Intraperitoneal administration of 20 mg/kg (R)-MT-45 immediately after a passive avoidance training task produced significant memory impairments in male ddy mice.<sup>19</sup> Curiously, a higher dose of 40 mg/kg was ineffective. These memory impairments were alleviated by subcutaneous administrations of sigma receptor agonists, (+)-N-

allylnormetazocine ((+)-SKF-10,047), (+)-3-(3-hydroxyphenyl)-N-(J-propyl)piperidine ((+)-3-PPP), and 1,3-di(2-tolyl)guanidine (DTG).<sup>19</sup>

Controlled human studies: This reviewer could not find any published reports of controlled studies on the pharmacology of MT-45 using human subjects. Similarly, Siddiqi and colleagues canvassed the literature in June of 2014 and reported that, "There have been no formal studies in humans assessing MT-45 as a potential analgesic or to determine its pharmacology."<sup>22</sup>

### ***B. Routes of administration and dosage***

MT-45 appears to be used through most routes of administration normally accessible to users including the oral, nasal, intravenous and rectal routes of administration.

The route of administration was reported in six of nine non-fatal intoxications in patients with verified MT-45 use by the Swedish STRIDA project, a collaborative project between the Karolinska University Laboratory, the Karolinska Institutet, and the Swedish Poisons Information Centre that monitors the occurrence and health hazards of newly emerging drugs of abuse in Sweden.<sup>14</sup> Two of these patients reported administering the drug orally, one combined oral and intravenous use, one reported use by insufflation, one reported combined use by insufflation and the intravenous route, while one reported combined oral and rectal use.<sup>14</sup> The rectal route of administration deserves further comment. One website report by a user explained, "I've experimented with several ROAs, including smoked, oral, intranasal and intrarectal (though not intravenous/intramuscular injection). I've found that intrarectal administration is ideal, if I use a proper needleless syringe and go about it right. There's an immediate euphoric rush which doesn't exist for other ROA's I've tried, and it uses less material, which is always a massive boon when it comes to opioids."<sup>2</sup>

Following searches on the user websites of the Bluelight, Shroomery and the UK Chemical Research forums in June of 2014, Siddiqi and colleagues found the most commonly reported route of use of MT-45 by users to be oral ingestion (13 user reports), followed by nasal insufflation (4 reports), inhalation (2 reports) and finally rectal insertion (1 report).<sup>22</sup> Information from these websites indicated that oral doses of MT-45 had ranged from 20 to 500 mg, although the majority of users reported limiting the dose to less than 100 mg. Doses of nasal insufflation ranged from 1 to 50 mg. The one report of rectal use identified by Siddiqi and colleagues was found on the Bluelight forum in which MT-45 was used by insertion of "80 mg of MT-45 salt as the solution".<sup>22</sup>

### ***C. Pharmacokinetics***

The analgesic effects of MT-45 and both isomers after s.c. administration in rats attained the highest peaks within 30 min, followed by significant activities lasting for 60 min or more.<sup>21</sup> More detailed accounts of the pharmacokinetics in animals could not be found in the published literature.

Literature searches in Medline and in the Web of Science resulted in no published reports of controlled pharmacokinetic studies in humans, and estimates of MT-45's kinetics must currently be based mainly upon user reports. From user reports of oral administration, little relationship could be observed between dose and time to the emergence of intended effects.

Emergence of desired effects following oral administration as reported on websites of the Bluelight, Shroomery and the UK Chemical Research forums (June 2014 poll) occurred between 25 and 400 min, with the duration of action extending from 300-630 min. Time to desired effect is much faster following insufflation to be within 15 min of administration, and lasts much shorter than oral use extending only from 150-180 min.<sup>22</sup> Following rectal use, one user reported desired effects occurring as fast as 5 min following intra-rectal administration of ~25 mg suspended in 2 ml propylene glycol.<sup>2</sup>

This reviewer could find no published reports on the metabolism of MT-45, as did the EMCDDA in their report in 2014.<sup>9</sup>

## 5. Toxicology

Rats and mice receiving high doses of either the racemate or the S(+)-isomer died with symptoms of severe sedation, muscle rigidity and dyspnea. In lower doses, the R-isomer caused sedation, while the S(+)-isomer and racemate caused excitation.<sup>21</sup> Representative LD<sub>50</sub>s for the racemate via the intravenous route were 17.8 and 7.8 mg/kg in male mice and rats, respectively, and for the S(+)-isomer of 18.5 and 8.0. The LD<sub>50</sub> for the R(-)-isomer i.v. was similar to the S(+)-isomer in the two species at 17.9 and 12.9 mg/kg, but the progression of effects were different. At low doses the R(-)-isomer caused sedation, while the racemate and the S(+)-isomer caused excitation.

Carcinogenicity reports on MT-45 could not be found, however it was evaluated for its antitumor activity using the P388 Leukemia (intraperitoneal) assay using B6D2F1 (BDF1) and CD2F1 (CDF1) mice bearing transplantable tumors. Survival tumor size was measured after 30 days and the results were expressed as the measurement made in the treated group (T) divided by the measurement made in the vehicle treated control group (C). MT-45 was inactive in this assay.<sup>23</sup>

## 6. Adverse reactions in humans

In September of 2014 a European-level risk assessment was conducted on MT-45. During a nine month period following October 2013 MT-45 was detected (analytically confirmed) in 28 deaths, and 12 non-fatal intoxications in Sweden. In 19 of the deaths, MT-45 was either reported as the cause of death or contributing to death.<sup>1</sup> In a slightly earlier joint report by the EMCCDA/Europol, in which comment was presumably made on a subset of these deaths, the concentration of MT-45 in post-mortem femoral blood was reported to range from 0.006 to 1.9 µg/g. In 17 of the mortality cases, MT-45 was found in combination with at least one other psychoactive substance, including controlled substances, new psychoactive substances and medicines; in the remaining four cases no other substances were detected.<sup>3</sup>

Based upon open source information (<http://www.ice.gov/>) and communications to the EMCDDA from US Immigration and Customs Enforcement's Homeland Security Investigations, it was reported that a male and a female died in New York from acute intoxication with MT-45 and a combination of MT-45 and ethanol in August of 2013.<sup>3</sup>

In nine MT-45-positive patients included in the STRIDA project in Sweden (see 4.B above) most presented with opioid-like symptoms, including seven with respiratory depression and decreased consciousness, five of which were deeply unconscious, two of whom were awake on admission to hospital but became unconscious in the emergency room.<sup>14</sup> Apnea was documented in two cases and another two had cyanosis. Miosis was notable in three patients. Four patients had paraesthesia in hands and feet, difficulties to grip and hand coordination, balance disturbances, and vision impairments (e.g. blurred and double vision). Although improvements were achieved during hospital care, symptoms still were reported to persist upon discharge.<sup>14</sup> The competitive opioid receptor antagonist, naloxone, was administered to seven of these nine patients of which four responded well. In three patients, a low oxygen saturation and/or depressed respiratory rate exceeding 24 h was recorded. Three of these nine patients complained of bilateral hearing loss that persisted for over two weeks. Helander and colleagues have noted that, "Ototoxicity is a very infrequent adverse reaction to chronic heavy consumption or acute overdose of opioids, reported in rare cases of heroin, methadone, oxymorphone, or hydrocodone/acetaminophen intake."<sup>14</sup>

## 7. Dependence potential

### A. *Animal Studies*

Precipitated opiate-like withdrawal jumping was observed when ddN male mice were given increasing increments of 8, 16, 25, 50 and 100 mg/kg of MT-45 "subcutaneously and/or orally ... until a maximally tolerated dose was reached within that range" and then 2 h after the last injection were challenged with 50 mg/kg nalorphine.<sup>10</sup> Additionally, MT-45 was able to attenuate the signs of morphine withdrawal and exhibited morphine-like Straub tail in ddN mice.<sup>10</sup>

### B. *Human Studies*

Reports of signs or symptoms of withdrawal during abstinence from chronic use of MT-45 indicative of physical dependence, as observed by trained medical personnel, were not found in the published scientific literature. However, withdrawal-like symptoms have been reported following use of MT-45 on user websites.<sup>3</sup>

## 8. Abuse potential

### A. *Animal Studies*

Published reports involving controlled laboratory studies involving drug discrimination, self-administration, conditioned place preference, or intracranial self-stimulation procedures, which are considered primary preclinical procedures addressing the abuse liability of drugs, could not be found.

### B. *Human Studies*

Similar to the lack of relevant, published, controlled laboratory animal studies pertinent to estimating the abuse liability of drugs, none could be found involving human subjects such

as those involving drug discrimination, self-administration, or paper-and-pencil drug-liking inventories, which are considered primary clinical procedures addressing the abuse liability of drugs.

## 9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are no known approved therapeutic applications for MT-45.

## 10. Listing on the WHO Model List of Essential Medicines

MT-45 is not listed on the WHO Model List of Essential Medicines.

## 11. Marketing authorizations (as a medicinal product)

None that could be determined. Similarly, in a survey conducted by the EMA and reported in a joint report by the EMCDDA and Europol, fifteen EU member states, as well as Norway, reported that MT-45 had not obtained a marketing authorization, nor had one been applied for.<sup>3</sup>

## 12. Industrial use

MT-45 has no current known legitimate industrial, agrochemical, cosmetic, human or veterinary medical use.<sup>9</sup>

## 13. Non-medical use, abuse and dependence

Evidence in seizures or other detections: The first instance in which MT-45 was detected as a designer drug in Japan was in 2013.<sup>4</sup> Sweden reported 28 seizures of MT-45 during a EMCDDA/Europol survey that concluded May 28, 2014.<sup>3</sup> Only two other member states, Belgium and Germany, reported detections (seizures or confirmed biological samples) of MT-45. In 26 of the 28 seizures Sweden reported, MT-45 was seized as a white/off white powder in quantities ranging from 0.1 to 49.9 g. In one of these cases 1-Phenyl-2-pyrrolidinobutanone ( $\alpha$ -PBP) was also present, and in another 6-(2-Aminopropyl)-2,3-dihydrobenzofuran (6-APDB). In the remaining two seizures MT-45 was detected in plant material (0.55 g and 0.99 g) in the presence of *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) in one and *N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (AKB-48) in the other.

In the EMCDDA/Europol survey described above, Sweden reported 33 detections in which MT-45 was confirmed in biological samples.<sup>3</sup> These biological samples were associated with 33 patients having serious adverse events, including 21 deaths.

Using the standardized EMCDDA methodology for monitoring internet sales of new psychoactive substances, 12 websites presumably based within the EU, Canada, China or India were identified selling what was presumably MT-45 and was typically presented as a "research chemical".<sup>3</sup>

## 14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Prevalence of use: In June 2014 Siddiqi and colleagues reported searching the published literature and found that they were unable to identify any studies reporting the prevalence



of use of MT-45.<sup>22</sup> In addition, a technical report of the EMCDDA found, "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."<sup>9</sup> This reviewer also could not find published reports documenting the prevalence of use of MT-45 as of August 22, 2015.

Toxicity and mortalities associated with MT-45's use: (See Section 6 above)

## 15. Licit production, consumption and international trade

Based upon information available as of May of 2014, the EMCDDA and Europol reported they could not find licit production for MT-45 apart for its legitimate scientific research and production in analytical reference materials.<sup>3</sup> Licit production of MT-45, other than for the two limited reasons above, could also not be identified in other countries for this review.

## 16. Illicit manufacture and traffic and related information

An Internet snapshot study conducted in English in May of 2014 by Siddiqi and colleagues identified 17 Internet sites selling MT-45.<sup>22</sup> Information on price was available from 9 sites, with the mean price of MT-45 decreased with increasing purchase amounts from US \$57.60 ± 19.37 per gram for a 1-g purchase to US \$3.36 ± 1.83 per gram for a 1-kg purchase. Of these 17 internet sites the country of origin was identified in 13 including eight from China, two from Canada, and one each from Germany, India and Sweden.<sup>22</sup> Using the standardized EMCDDA methodology for monitoring internet sales of new psychoactive substances, 12 websites presumably based within the EU, Canada, China or India were identified selling what was presumably MT-45 and was typically presented as a "research chemical".<sup>3</sup>

## 17. Current international controls and their impact

MT-45 is not controlled under the 1961, 1971 or 1988 United Nation Conventions. Structurally, MT-45 is somewhat similar to lefetamine (SPA; (-)-N,N-dimethyl-1,2-diphenylethylamine), a stimulant with analgesic effects, which is controlled as a Schedule IV drug under the U.N. 1971 Convention on Psychotropic Substances.

## 18. Current and past national controls

Following a survey ending May 28, 2014, a joint report by the EMCDDA and Europol reported the following regarding national controls of MT-45 in Europe:<sup>3</sup> this report was updated by the EMCDDA Risk Assessment Report on MT-45.<sup>7</sup>

- (i) Twenty-two European countries (Belgium, 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 was not under national control.
- (ii) Latvia had placed MT-45 under temporary control for 12 months beginning 15 May 2014
- (iii) Austria controlled MT-45 as a member of the '(1phenyl and 1-benzyl)piperazine' group in the new psychoactive substances law (NPSG law, Group II)
- (iv) Poland had MT-45 regulated under acts that penalized its marketing and production with fines

- (v) In the Netherlands the sale of MT-45 is treated as a medicinal product and must comply with medicines legislations
- (vi) Spain had reported that there was generic legislation (administrative and criminal) regarding health protection that was likely applicable
- (vii) 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.
- (viii) Ireland and Romania MT-45 is controlled under legislation prohibiting the unauthorized supply of defined or qualifying new psychoactive substances

**19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance**

None.

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