

Alpha-methyltryptamine (AMT)

Critical Review Report

Agenda item 4.20

Expert Committee on Drug Dependence

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**World Health
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Summary

Alpha methyltryptamine (AMT) is a tryptamine (indole ethylamine) derivative that shares several similarities with various scheduled tryptamine hallucinogens. Human subjects using AMT report euphoria, stimulation, visual effects such as blurry vision, bright colors, after images and amphetamine-like mood elevating effects. Oral AMT has a slow onset of action of 3-4 h but an extended duration of 12-24 h although some users have reported effects for 2 days. Although essentially unknown as a recreational drug until the late 1990s, AMT has slowly appeared in various countries as users seek legal highs and alternate hallucinogens. AMT is less frequently used than other hallucinogenic tryptamines although it has recently seen a relatively low but stable baseline of use globally. Pharmacologically, AMT has high affinity for the serotonin (5-HT) transporter, a number of 5-HT receptors, and potently inhibits reuptake of monoamines dopamine, 5-HT, and norepinephrine reuptake. Furthermore, AMT was similar to methamphetamine in its effectiveness to release these monoamines. AMT is also a monoamine oxidase A inhibitor which conceivably could contribute to its pharmacological effect. The finding that AMT activates 5-HT_{2A/C} receptors likely contributes to its hallucinogenic activity. In animals, AMT produced discriminative stimulus effects similar to DOM and MDMA. Some deaths have been associated with AMT especially in combination with other substances and a number of countries have recently added AMT to their controlled substances list. In summary, despite the general lack of preclinical or clinical data on AMT, it appears that AMT produces effects and toxicities similar to other tryptamine derivatives with hallucinogenic and stimulatory properties and therefore should be scheduled as such.

1. Substance identification

A. International Nonproprietary Name (INN)

α -Methyltryptamine

B. Chemical Abstract Service (CAS) Registry Number

299-26-3

879-36-7 (hydrochloride)

C. Other Names

α -Methyltryptamine; alpha-Methyltryptamine; Indopan; IT-290; IT-403; U-14; 164E; 3-IT; (\pm)- α -Methyltryptamine; α -Methyl-3-indoleethanamine; 1H-Indole-3-ethanamine; α -methyl-2-(1H-Indol-3-yl)-1-methylethylamine; 3-(2-Aminopropyl)-1H-indole; 3-(2-Aminopropyl)indole; Indole, 3-(2-aminopropyl)-; NSC 97069; Ro 3-0926;

DL-3-(2-aminopropyl)indole (English, French) (REACH, EINECS)

DL-3-(2-Aminopropyl)indol (German) (EINECS)

DL-3-(2-aminopropil)indol (Spanish) (EINECS)

DL-3-(2-amminopropil)indolo (Italian)

DL-3-(2-aminopropyl)indol (Danish, Swedish)

DL-3-(2-aminopropyl)indool (Dutch)

DL-3-(2-aminopropyli)indoli (Finnish)

DL-3-(2-aminopropil)indole (Portuguese)

D. Trade Names (hydrobromide salt)

Currently, there are no trade names for AMT. Originally developed by Upjohn in the 1960s as a potential antidepressant, α -Methyltryptamine was labelled Indopan.

E. Street Names

Alpha, Digital, Spirals

F. Physical properties

White, crystalline powder.

G. WHO Review History

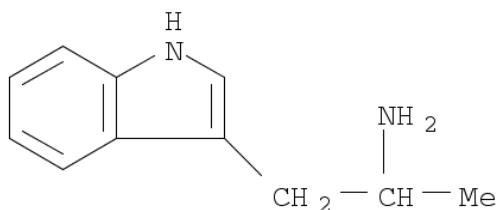
AMT was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that AMT is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

A. Chemical Name

IUPAC Name: 2-(1H-indol-3-yl)-1-methyl-ethylamine

CA Index Name: 1H-Indole-3-ethanamine, α -methyl-

B. Chemical Structure**Free base:****Molecular Formula:** C₁₁ H₁₄ N₂**Molecular Weight:** 174.24**Melting point:** 151-153 °C**Boiling point:** 344.5±17.0 °C**Fusion point:** 189.0±8.1 °C**C. Stereoisomers**

Two stereoisomers exist for α -methyltryptamine: (R)- α -methyltryptamine and (S)- α -methyltryptamine.

D. Synthesis

There are a number of published synthesis strategies for α -methyltryptamine^(1, 2). Probably the most relevant strategy for the synthesis of illicit AMT comes from the highly referenced text TiHKAL⁽³⁾. Briefly, an indole solution was added to a second solution of dimethylformamide and phosphoryl trichloride. Next, an intermediate solution of indole-3-carboxaldehyde was treated with ammonium acetate and the excess reagent was removed yielding yellow solids which were washed and air dried. After trituration, filtration, and air-drying, an intermediate, 1-(3-indolyl)-2-nitropropene-1, remains. A reaction mixture of lithium aluminium hydride, anhydrous tetrahydrofuran, and 1-(3-indolyl)-2-nitropropene-1 was obtained and the excess hydride was removed and buffered until no further solids formed. After filtration, washings, and drying, the solvent was removed under vacuum and the residue was distilled to yield a white oil that crystallized. This residue was recrystallized from an ethyl acetate/petroleum ether mixture, dissolved in methanol, treated with glacial acetic acid, and dried under vacuum to give the acetate salt which, on recrystallization from ethyl acetate and air drying yielded the product α -methyltryptamine (α -MT; AMT) as fine white crystals.

E. Chemical description

AMT contains a tryptamine backbone, which is structurally characterized by an indole ring substituted at the third position by an ethanamine. Specifically, AMT is tryptamine with a methyl substituent at the alpha carbon.

F. Chemical properties

AMT is available as the free base or either the hydrochloride or fumarate salt. AMT has 3 freely rotatable bonds, three H donors and two H acceptors with logD of -1.20 and logP of 1.895 at 25°C. As the free base, AMT is not particularly water soluble but it is soluble in alcohol and other solvents.

G. Chemical identification

As a class, tryptamines have an indole ring structure - a bicyclic combination of a benzene ring and pyrrole ring, joined to an amino group by a two carbon side chain. Most designer substitutions occur at the amino group, side chain and aromatic ring at positions 4 or 5. AMT is classified as simple, unsubstituted synthetic tryptamines⁽⁴⁾.

3. Ease of convertibility into controlled substances

AMT is a tryptamine (indole ethylamine) derivative that shares several similarities with the Schedule I tryptamine hallucinogens such as alpha-ethyltryptamine, N,N-dimethyltryptamine (DMT), 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT), 5-Methoxy-N,N-diallyltryptamine (5-MeO-DALT), 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT), and 5-methoxy- α -methyltryptamine (5-MeO-AMT)⁽⁴⁾. The ease of convertibility varies but generally occurs prior to the methylation on the α carbon as once this carbon group is methylated it is no longer easily altered. From AMT, there are five possible chain relocations, from the normal 3-position to the 2, the 4, the 5, the 6 or the 7-positions with the 5-isomer, 5-(2-aminopropyl)indole (5-IT) used in man for psychotropic effects⁽³⁾ and has been responsible for fatalities⁽⁵⁾.

4. General pharmacology

4.1. Pharmacodynamics

AMT has high affinity for the 5-HT transporter, a number of human, cloned 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇), and α_{2A} and β_1 adrenergic receptors⁽⁶⁾. In rat brain synaptosomes, AMT potently inhibits monoamines dopamine, 5-HT, and norepinephrine reuptake. Furthermore, AMT was similar to methamphetamine for its effectiveness to release these some monoamines with release being more dominant than reuptake inhibition. AMT's effects on the serotonergic system were stronger than that of methamphetamine but the effects on dopaminergic and adrenergic systems were similar to methamphetamine⁽⁷⁾. AMT is also a potent monoamine oxidase A inhibitor⁽⁸⁾ which conceivable would contribute to its pharmacological effect. In vitro screening of AMT in [³⁵S]GTP γ S binding in rat cortical membranes receptors revealed only 39% of 5-HT-stimulated maximal binding i.e., less than half of a maximal effect⁽⁹⁾. However, in a more recent study, AMT was very potent for activating 5-HT_{2A/B/C} receptors with E_{max} values of 89%, 84%, and 95%, respectively. This profile is likely contributing to the hallucinogenic activity AMT⁽⁶⁾.

A dose of 10 mg/kg, i.p., to rats or rats produced lateral head weaving, hindlimb abduction, and Straub tail for one hour which was followed by pronounced running activity for 4-6 h^(10, 11). These behavioural effects were reduced by nonselective 5-HT antagonists methiothepin and metergoline or by the 5-HT releaser p-chlorophenylalanine while the running activity was blocked by pimozide suggesting both 5-HT and DA stimulation⁽¹²⁾.

4.2. Routes of administration and dosage

AMT is generally available in powder, tablet, or capsule and is most commonly ingested but can also be smoked or rectally administered. Snorting appears to be a infrequent route of administration due to burning and a bad odour. The inadequate solubility and lack of increased pharmacological effects limits intravenous administration. Oral doses generally range from 15-40 mg but can be higher (50-200 mg) while smoked doses range from 5-20 mg.

4.3. Pharmacokinetics

Little pharmacokinetic information is available on AMT. After oral administration of a dose of 10 mg/kg AMT, the metabolites 2-oxo-AMT, 6-hydroxy-AMT, 7-hydroxy-AMT and 10-hydroxy-AMT were detected in the urine of male, Wistar rats after 24h. The peak intensities of these metabolites detected were smaller compared with that of unchanged AMT, indicating AMT was poorly metabolized in rats. The authors proposed metabolic pathways for AMT in rats that consist of hydroxylation or oxidation on the indole ring at the 2-, 6- and 7-positions, whereas the 4- and 5-positions remain unchanged. However, it is also possible that deamination to indole-3-acetone and deamination followed by oxidation to indole-3-carboxylic acid are possible metabolic pathways of AMT in rats⁽¹³⁾.

In humans, 20 mg AMT has a slow onset of action of 3-4 h but an extended duration of 12-24 h although some users have reported effects for 2 days^(14, 15). After ingestion, the alpha methyl group protects AMT from degradation by MAO which would contribute to its oral activity and longer duration⁽⁸⁾.

5. Toxicology

Although tryptamines are considered not to produce life-threatening cardiovascular, renal or hepatic toxicity because of their lack of affinity for the relative targets and receptors^(16, 17), there have been deaths associated with AMT use especially in combination with other agents such as 3,4-methylenedioxypropylamphetamine, cocaine, amphetamine, cathinones, MDMA, and cannabinoids⁽¹⁷⁾ as investigated by ROAR Forensics laboratory, UK. Other deaths related to AMT have been reported in the US⁽¹⁸⁾, Isle of Man, Sweden, Norway, Scotland, UK, and Japan.

A closely-related tryptamine, alpha-ethyltryptamine, is neurotoxic causing a reduction in a number of serotonin brain markers⁽¹⁹⁾. AMT may cause serotonin syndrome due to its ability to inhibit MAO^(8, 14).

6. Adverse reactions in humans

AMT produces various negative physical and psychological effects in users. Physical effects of AMT include mild increases in blood pressure or respiration rate, tachycardia, mydriasis, diaphoresis, salivation, severe nausea, severe vomiting, deep tendon reflexes, impaired coordination, visual and auditory disturbances and distortions. Subjects report uncomfortable feelings, muscular and nervous tension, irritability, restlessness, upset stomach, and inability to sleep or relax. Psychological effects associated with the use of AMT can include terrifying hallucinations, emotional distress, nervousness, tension,

irritability, restlessness, and inability to sleep^(3, 20). AMT also diminishes user inhibitions and hallucinations, which can result in high-risk sexual activity or accidental injury, respectively.

7. Dependence potential

As a class of agents, tryptamines are generally not physically addicting or likely to cause psychological dependence⁽²¹⁾. This generalization is supported by users that report a lack of withdrawal effects following the discontinuation of use although some users have reported a short period of tolerance or feelings of depression after AMT. The users report that use for two days in a row is likely to lead to a diminished experience the second day, although spaced 3-4 or more days apart, this effect is nearly non-existent⁽³⁾ and (Erowid Vault, accessed March 2014). However, without human pharmacokinetic and controlled pharmacology data, dependence or tolerance potential is essentially unknown for AMT.

8. Abuse potential

In animals, AMT produced discriminative stimulus effects similar to DOM and MDMA^(22, 23). AMT has only been tested in the drug discrimination procedure; no results are available for self-administration or conditioned place preference animal models of abuse liability. The abuse potential in humans has relied on anecdotal reports⁽³⁾, subjective effect reports, or retrospective reports. Human subjects using AMT report euphoria, stimulation, visual effects such as blurry vision, bright colors, after images, primarily hallucinogenic effects similar to 50 µg of LSD. AMT also produces amphetamine-like mood elevating effects^(14, 24) and indeed AMT is used as a substitute for MDMA (DEA Federal Register, 2004). Apparently, lower doses produce stimulant effects and increasing the dose causes more hallucinogenic effects. The fact that AMT shares many similarities to other hallucinogenic tryptamines and MDMA suggests it has potential for abuse.

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

Historically, AMT was first developed in the 1960s as an antidepressant and MAOI with a related compound alpha-ethyl-tryptamine which was sold for a short while by Upjohn before being placed in Schedule I in 1971. AMT was available in the Soviet Union in the 1960s as an antidepressant under the commercial name Indopan in 5 and 10 mg tablets. There is no current legitimate medical or therapeutic use for AMT.

10. Listing on the WHO Model List of Essential Medicines

AMT is not listed on the WHO List of Essential Medicines.

11. Marketing authorizations (as a medicine)

There are no marketing authorizations as a medicine for AMT.

12. Industrial use

AMT remained an obscure chemical until the late 1990s when began being sold commercially around the world as a research chemical. AMT has no industrial uses although it may be used as an intermediate reactant or reagent for other chemicals or agents.

13. Non-medical use, abuse and dependence

The US DEA database, National Forensic Laboratory Information System collects information on drugs and cases submitted to by US state and local forensic laboratories and indicates its first record of AMT appeared in 1999. The recreational use of tryptamines remains limited but has increased over the past five years. The DEA estimated the number of tryptamine reports to State and local laboratories in the United States rose from 42 reports in 2006 to 474 reports in 2010. From January 2006 to December 2010, an estimated 1,302 reports of tryptamines were submitted to NFLIS from as many as 35 States although most tryptamines were either DMT (79%) or 5-MeO-DIPT (13%) with the remainder including AMT and some other variants. In 2010, there were 71 reports of various tryptamines including AMT in the West, 105 reports in the Midwest, 102 reports in the Northeast, and 196 reports in the South (NFLIS, 2012).

Similarly, AMT was first reported through the European Monitoring Centre for Drugs and Drug Addiction's (EMCDDA) Early Warning System in Finland in 2001 and since that time, 11 additional neighbouring countries have detected AMT. Respondents to the UNODC questionnaire on New Psychoactive Substances up to the year 2012 reported the incidence of both natural and synthetic tryptamines including, 5-MeODMT, 5-MeO-DPT, and AMT.

According to the 2010 SAMHSA's annual National Survey on Drug Use and Health (NSDUH), lifetime use of DMT, AMT, or 5-MeO-DIPT among persons aged 12 or older remained stable between 2006 and 2009, at 0.3% annually, but increased significantly in 2010 to 0.5%. Among persons aged 18 to 25, 1.3% were lifetime users in 2010, which was higher than the percentages in 2006 (0.9%) to 2008 (0.8% in 2007 and 2008). The prevalence of use among persons aged 26 or older also increased significantly between 2009 and 2010, from 0.2% to 0.4%. In 2010, 0.7% of males and 0.3% of females were lifetime users. Between 2009 and 2010, lifetime use of DMT, AMT, or 5-MeO-DIPT increased significantly among males, from 0.5% to 0.7%. The past year use of DMT, AMT, or 5-MeODIPT among persons aged 12 or older remained the same between 2008 and 2010, at 0.1% annually.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

The patterns of illicit sales and abuse have mostly been through internet sources. Recently, the availability, cost, and sale of AMT have been monitored using EMCDDA's Internet snapshot methodology in March and October of 2012. In this

study, the authors found a small decrease in the number of Internet sites selling AMT in powder, capsules, and pellets and prices were decreasing and cheaper for bulk/potential dealer sales compared to recreational, smaller purchases⁽²⁵⁾.

Patterns of use, clinical effects and possible harm of acute toxicity following recreational use of AMT in the UK was reported by the National Poisons Information Service (NPIS) and compared to mephedrone, a common NPS in the UK. There were increasing numbers of telephone enquiries from 2009 to 2013 with most patients being male (68%) with a median age of 20 years. The route of exposure was ingestion in most cases and clinical effects recorded more frequently in AMT (n = 55) compared with those of mephedrone (n = 488) users including acute mental health disturbances (66% vs. 32%), stimulant effects (66% vs. 40%) and seizures (14% vs. 2%). The authors concluded that although AMT use is still infrequent, toxicity following reported exposure to AMT has been encountered in the UK since January 2011. Stimulant features, acute mental health disturbances and seizures are more frequently reported than in those presenting following reported use of another NPS, mephedrone⁽²⁶⁾.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

There are approximately 44 commercial vendors for AMT located in many countries across the different continents (e.g., CA, CH, CN, DE, GB IN, RU, UA, UK, US).

16. Illicit manufacture and traffic and related information

Synthetic tryptamines such as AMT found their way into recreational use in the late 1990s as powder, capsules, or pellets. Although the use of tryptamines and specifically AMT remains limited at the present time, the use appears to have increased over the past five years. For example, the US DEA reported that the estimated number of tryptamine reports (including AMT) to State and local laboratories in the United States rose from 42 reports in 2006 to 474 reports in 2010. UN Member States reported the incidence of natural and synthetic tryptamines including, 5-MeODMT, 5-MeO-DPT, AMT, 4-AcO-DMT, 4-AcODiPT, and 5-HTP. Of the tryptamines reported in the UNODC questionnaire on NPS in 2012, AMT was 4-5th most commonly reported. The Global Emergence of NPS (December 2013) reported the emergence of AMT in the following countries: Estonia, Finland, France, Italy, Lithuania, Netherlands, Norway, Russian Federation, and United Kingdom..

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

AMT is not under international Control.

18. Current and past national controls

In Australia, the 5-methoxy analogue, 5-MeO- α MT is schedule 9 and AMT is controlled as an analogue of this compound. In Sweden (2005), the health ministry has classified AMT as a "health hazard" under the Act on the Prohibition of Certain Goods Dangerous to Health making AMT illegal to sell or possess. In Denmark (2010), the Danish Minister for the Interior and Health placed AMT to their lists of controlled substances (List B). AMT is listed under Narcotics Act, schedule 1 (narcotics not eligible for trade and medical prescriptions) in Germany and AMT is placed under Austrian law (NPSG) Group 6. AMT was controlled: on the Schedule C list in Hungary; on the List of Hazardous Substances in Annex, § 2 in Slovakia (2013); on the Decree on Classification of Illicit Drugs in Slovenia (2013); and in Spain (2005) according to the Act on the Prohibition of Certain Goods. In Lithuania (2012), AMT is controlled as a tryptamine derivative put under control in the 1st list of Narcotic Drugs and Psychotropic Substances which use is prohibited for medical purposes.

In the United Kingdom, however, AMT does not fall under the tryptamine clause as its substituent is not on the nitrogen position and therefore AMT remained legal. Similarly, Canada has no mention of AMT in its Controlled Drugs and Substances Act. However, AMT is on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) list of pre-registered substances as of March 2009 and the European Commission has recently proposed stricter rules to implement restriction of new psychoactive substance in September 2013.

The US DEA monitored AMT and placed AMT temporarily in schedule I of the Controlled Substances Act (CSA) on April 4, 2003 and on September 29, 2004, AMT was permanently controlled as a Schedule I substance. At least nineteen states in US have scheduled AMT as Schedule I since 2003.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

There is no medical use of AMT at the present time. There is very little primary literature in animals or humans on the pharmacology, pharmacokinetics, or toxicology of AMT. Most of our understanding of the effects of AMT in humans relies on anecdotal, retrospective or self-reports. Therefore, when scheduling AMT, judgement must depend on literature and findings pertaining to other tryptamine compounds (although these compounds are also understudied).

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Annex 1:**Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Alpha-methyltryptamine (AMT)**

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3SEAR, 4 WPR).

A total of 65 Member States answered the questionnaire for Alpha-methyltryptamine (AMT). Of these, only 27 (AMR 5, EUR 19, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that AMT was currently authorized or in the process of being authorized/registered as a medical product in their country. Three respondents stated that this substance was used in medical and scientific research. One respondent stated that there was use in animal/veterinary care.

HARMFUL USE

Seventeen respondents confirmed there was recreational/harmful use of AMT; eight stated that the common route of administration was oral, four oral, inhaling/sniffing and one inhaling/sniffing. Eleven respondents stated this was obtained only via trafficking, one via clandestine manufacturing and one via diversion and trafficking. Thirteen respondents reported on the common formulations of AMT available with six reporting powder, five powder and tablet, one powder, liquid and one powder, tablet and liquid forms. When asked on use by special populations one respondent stated that it was used by the general population and in clubs, two each only in clubs and only by general population. One respondent reported 3 emergency room visits in 2012 and 1 visit in 2013. Three respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by AMT. Effects include hyper reflexia, jaw tightness, irritability, nervous tension, restlessness, nausea, increased heart rate, blood pressure increase, dilated pupils, psychosis, agitated delirium, etc.

Additional information provided include ‘in 2003, there were two published case reports describing the instances of emergency department admissions resulting from the abuse of AMT and 5-MeO-DIPT (Long et al., *Vet. Human Toxicol.*, 45:149, 2003; Meatherall and Sharma, *J. Anal. Toxicol.*, 27: 313-317, 2003). In 2003, there was one more confirmed death caused by the abuse of AMT.’ ‘there were several cases of death in 2012 in the EU in connection with 5-IT, an isomer of AMT.’

CONTROL

Of those with information on the substance, 19 reported that AMT was controlled under legislation that was intended to regulate its availability; 12 under “controlled substance act”, three under “medicines law”, one “temporary ban”, one under “analogue legislation” and two “other” laws. Only one respondent stated that there were challenges with the implementation of this legislation. On illicit activities related to AMT, one respondent reported clandestine manufacture. Three respondents reported processing into the consumer product, 10 reported trafficking, two reported diversion and 10 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	16 (5)	154 (9)
Total quantity seized (kg)	0.03	37.52
Total quantity seized (tablets/pills)	1 (1)	226 (4)

IMPACT OF SCHEDULING

Twenty-five respondents reported that if AMT was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use.

