



European Monitoring Centre
for Drugs and Drug Addiction



ISSN 1977-7868

EMCDDA–Europol Joint Reports

EMCDDA–Europol Joint Report on a new psychoactive substance: 5-(2-aminopropyl)indole

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

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Luxembourg: Publications Office of the European Union, 2013

ISBN 978-92-9168-596-7

doi: 10.2810/85464

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Cais do Sodré, 1249-289 Lisbon, Portugal

Tel. +351 211210200 • Fax +351 218131711

info@emcdda.europa.eu • www.emcdda.europa.eu

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Eisenhowerlaan 73, 2517 KK, The Hague, the Netherlands

Tel. +31 703025000; Fax +31 703455896

File No: EDOC#645400

Publications: <https://www.europol.europa.eu/latest-publications>

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1. Introduction

Article 5.1 of Council Decision 2005/387/JHA ⁽¹⁾ (hereinafter referred to as the 'Decision') stipulates that 'Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the 'Joint Report').' The Joint Report shall be submitted to the Council, the European Medicines Agency (EMA) ⁽²⁾ and the Commission.

At the end of September 2012, the EMCDDA and Europol examined the available information on a new psychoactive substance 5-(2-aminopropyl)indole (commonly known by the abbreviation '5-IT'), through a joint assessment based upon the following criteria:

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

The EMCDDA and Europol agreed that the information collected on 5-(2-aminopropyl)indole satisfied criteria 1, 4, 5 and 6. The two organisations therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on 5-(2-aminopropyl)indole as stipulated by Article 5.1 of the Decision.

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

⁽²⁾ Formerly referred to as the EMEA.

2. Information collection process

In compliance with the provisions of the Decision, on 3 October 2012 the EMCDDA and Europol launched a procedure for the collection of information on 5-(2-aminopropyl)indole, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States and Croatia, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the Member States' national competent authorities responsible for human and veterinary medicinal products. The information collection process was largely concluded by 14 November 2012; however, additional information and clarifications from some countries were received up to four weeks after this date.

Europol asked the Europol National Units to provide information on:

- the level of production of 5-(2-aminopropyl)indole in their country;
- the level of distribution of 5-(2-aminopropyl)indole in their country;
- the level of trafficking of 5-(2-aminopropyl)indole in their country, both for internal, transit or export purposes;
- the number of seizures of 5-(2-aminopropyl)indole in their country, the total amount of the seizures, country of origin, details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution and trafficking of 5-(2-aminopropyl)indole in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of 5-(2-aminopropyl)indole.

Europol received responses from 22 Member States and Norway.

According to Article 5.3 of the Decision, the EMA asked the Member States' national competent authorities responsible for human and veterinary medicinal products to provide information on whether:

- the new psychoactive substance 5-(2-aminopropyl)indole has obtained a marketing authorisation;
- the new psychoactive substance 5-(2-aminopropyl)indole is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance 5-(2-aminopropyl)indole has been suspended.

17 Member States, Iceland and Norway replied to the EMA's request regarding human and/or veterinary medicinal products.

Furthermore, in anticipation of Article 7.3 of the Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested whether the new psychoactive substance 5-(2-aminopropyl)indole is used to manufacture a medicinal product:

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

The same 17 Member States, Iceland and Norway replied to the EMA's request in this regard.

A list of the information sources used to inform the Joint Report are listed in Annex 1, and include data collected by the EMCDDA through:

1. a structured questionnaire from the Reitox national focal points. The EMCDDA received replies from 27 Member States as well as Croatia, Norway and Turkey;
2. a specific information request to the World Health Organization on whether or not 5-(2-aminopropyl)indole is under assessment by the United Nations system (see section 3.5); and,
3. a structured literature review that included a chemical sub-structure search and Internet search.

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (partly). The information included in sections 3.4.1 (partly), 3.8.3 (partly), 4.1, 4.2 and 4.3 was provided by the EMA. The summary findings and the conclusion of the Joint Report were prepared and agreed by the two organisations responsible — the EMCDDA and Europol. Further details of the seizures and collected samples (including images where available) reported to the EMCDDA are provided in Annex 2. The details of deaths associated with 5-(2-aminopropyl)indole that have been reported to the EMCDDA are provided in Annex 3.

3. Information required by Article 5.2 of the Decision

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

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

Chemical description and names

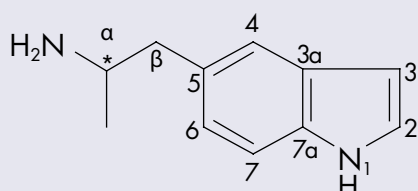
5-(2-Aminopropyl)indole is a synthetic derivative of indole substituted at the phenyl side of the indole ring system (position 5). It is a positional isomer of alpha-methyltryptamine (AMT) which belongs to the tryptamine family, many of which are hallucinogenic. However, 5-(2-aminopropyl)indole also contains the sub-structure of alpha-methylphenethylamine and therefore could be considered to be a substituted phenethylamine, many of which are stimulants. Limited data suggests that 5-(2-aminopropyl)indole has stimulant effects.

The structural core of 5-(2-aminopropyl)indole is formed by the indole nucleus. Additional names that may be encountered include 1-(1H-Indol-5-yl)propan-2-amine, α -methyl-1H-indole-5-ethanamine and 2-(1H-indol-5-yl)-1-methyl-ethylamine. A common abbreviation used for 5-(2-aminopropyl)indole is 5-IT. To a lesser extent the abbreviation 5-API is also used. Both these abbreviations are used by Internet retailers advertising 5-(2-aminopropyl)indole as well as in discussion on Internet drug forums. This suggests that '5-IT' and '5-API' are used as 'street names'.

Excluding the abstractable proton on the nitrogen atom, a total number of six positional isomers exist that can carry the 2-aminopropyl side chain. With the exception of the 3-(2-aminopropyl)indole isomer (alpha-methyltryptamine: AMT ⁽³⁾) relatively little has been reported in the published literature about the five remaining analogues.

⁽³⁾ Other abbreviations and code names for AMT found in the literature include: α -methyltryptamine, AMT, α -MT, 3-IT, IT-290, IT-403, U-14, 162-E, Ro 3-0926, NSC 97069, Indopan

Figure 1. The numbered molecular structure, formula, weight and monoisotopic mass of 5-(2-aminopropyl)indole. Asterisk indicates chiral centre



Molecular formula: C₁₁H₁₂N₂
 Molecular weight: 174.24
 Monoisotopic mass: 174.1157

Identification and analytical profile

Chemical Abstract Service (CAS) Registry Numbers: 3784-30-3 (racemic base); 96875-04-6 (ethanedioate, 1:1); 1336260-35-5 ((aR)-enantiomer); 1336564-72-7 ((aS)-enantiomer).

Colour screening test (free base): Keller: slightly violet; van Urk: red (Hofmann and Troxler, 1963; Troxler et al., 1968).

High performance liquid chromatography diode array detection (λ_{max} /nm): 218.3 and 272.8 (Elliott et al., 2012).

Melting points: free base 81–83 °C (petroleum ether/benzene); dioxalate salt 199–201 °C (methanol/diethyl ether) (Hofmann and Troxler, 1963; Troxler et al., 1968).

Nuclear Magnetic Resonance spectroscopy (NMR) data of 5-(2-aminopropyl)indole succinate (⁴): ¹H NMR (300 MHz, CD₃OD): δ 7.42 (1H, br d, J = 1.1 Hz, H-4), 7.37 (1H, d, J = 8.3 Hz, H-7), 7.23 (1H, d, J = 3.2 Hz, H-3), 6.98 (1H, dd, J = 8.3 Hz, J = 1.7 Hz, H-6), 6.41 (1H, dd, J = 3.2 Hz, J = 0.8 Hz, H-2), 3.57-3.45 (1H, m (consistent with predicted dqd), α -CH), 3.02 (1H, dd, J_{gem} = 13.8 Hz, ³J = 6.5 Hz, CH_AH_B), 2.86 (1H, dd, J_{gem} = 13.8 Hz, ³J = 8.0 Hz, CH_AH_B), 2.51 (4H, s, succinate), 1.26 (3H, d, ³J = 6.6 Hz, CH₃). ¹³C NMR (75 MHz, CD₃OD): δ 179.4 (succinate), 137.0 (C-7a), 129.9 (C-3a), 127.5 (C-5), 126.3 (C-3), 123.5 (C-6), 121.8 (C-4), 112.6 (C-7), 102.2 (C-2), 50.8 (α -CH), 42.2 (CH₂), 32.9 (CH₂, succinate), 18.5 (CH₃) (Elliott et al., 2012).

Mass spectrometry data: 5-(2-aminopropyl)indole (5-IT) and 3-(2-aminopropyl)indole (AMT) have been found to produce virtually identical mass spectra, especially when applying conventional Electron Impact-Mass Spectrometry (EI-MS) procedures. Thus, all six potential 2-aminopropyl isomers may be expected to yield identical mass spectral data. However, they are easily distinguishable from each other by chromatographic techniques if the reference materials are available for comparison.

⁽⁴⁾ NMR data is provided for 5-(2-aminopropyl)indole succinate as this is the form that has been encountered in collected samples.

Key fragments observed under EI-MS conditions (m/z): 44 (base peak), 131, 130, 77, 103, 117. The M^{*+} (m/z 174) may be detectable at a minor relative abundance but may also be absent. Chemical Ionisation-Mass Spectrometry (CI-MS) (methanol as liquid CI reagent) gave the $[M+H]^+$ at m/z 175 as the base peak and a prominent fragment at m/z 175 following the loss of NH_3 . Positive electrospray tandem mass spectra (m/z): 77, 103, 117, 130, 143, 158 (relative abundance values dependent on collision energy) with some in-source fragmentation of the protonated molecule at m/z 175 (Elliott et al., 2012).

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS Registry Numbers listed above and no information was found.

Physical description

The free base form of 5-(2-aminopropyl)indole has been described to form skewed prisms. The dioxalate salt form has also been documented. It has been reported that some Internet retailers ⁽⁵⁾ have advertised 5-(2-aminopropyl)indole as the succinate salt. NMR data produced as part of the analysis of one of the collected samples of 5-(2-aminopropyl)indole (reported by the United Kingdom) was found to be consistent with the succinate form (see data above). The Internet search conducted by the EMCDDA also noted that 5-(2-aminopropyl)indole hydrochloride was being offered for sale.

Reports from seizures and collected samples have noted the presence of 5-(2-aminopropyl)indole in: brown, pale/light brown or beige powders; beige tablets bearing markings resembling the Lexus logo ⁽⁶⁾; brown glittery tablets; blue/green unmarked tablets; blue unmarked tablets commercially packaged as 'BENZO FURY'; capsules; and, in residues on a spoon and in the liquid recovered from a syringe.

A more detailed description of 5-(2-aminopropyl)indole seizures and collected samples encountered can be found in subsections 3.2.1 and 3.2.2 below.

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

3.2.1 Information provided to Europol

Europol received replies from 22 Member States as well as Norway.

⁽⁵⁾ The term 'Internet retailers' is used in this report to describe Internet shops that offer new psychoactive substances for sale often advertised as 'legal highs' and 'research chemicals'.

⁽⁶⁾ It is common to find markings on tablets sold as 'ecstasy' including those of popular cultural and iconic brands often having an association with quality. Lexus is a luxury Japanese car manufacturer.

The level of production, distribution and trafficking

No reports were received that indicated licit or illicit production of 5-(2-aminopropyl)indole.

Portugal reported that the Drugs Department of the Judicial Police stated that 5-(2-aminopropyl)indole is 'a precursor used to synthesize drugs'. Europol has requested more information and clarification of this statement.

Finland reported that level of distribution of 5-(2-aminopropyl)indole is 'not so high'. No seizures were reported by Finnish authorities. There was, however, an indication that Customs have more information on this phenomenon. Europol requested further clarification of the Finnish report.

Germany reported the seizure of 1.35 grams of 5-(2-aminopropyl)indole and further 0.22 grams of 5-(2-aminopropyl)indole together with traces of MDAI (methylenedioxyaminoindane) on 2 May 2012 in Hanover from an unconscious person (together with other new psychoactive substances) (7). The person subsequently stated that he had bought the substances via the internet from an online shop based in the United Kingdom.

A further seizure was reported by Bavarian police. In this case final forensic examination confirmed the presence of the 5-(2-aminopropyl)indole as main active agent in the tablet, which had round shape, break line, weight 0.15 grams, dimension 0.6 cm and height 0.4 cm.

In addition, checks on the Internet revealed that 5-(2-aminopropyl)indole is known among drug users and is offered as 'legal alternative on the Internet'. The compound is chemically close to phenethylamine derivatives such as 5-APB or 4-APB – this matter together with the fact that so far no adequate reference material is available in Germany impedes the identification of 5-(2-aminopropyl)indole.

Germany also indicated that there is no information on the trafficking of 5-(2-aminopropyl)indole in Germany. However, the Internet 'is full with offers' of 5-(2-aminopropyl)indole and most of the online shops ship the offered substances especially to Europe.

Sweden reported seizures amounting to a total of 30.87 grams of powder and 54 tablets. Europol has requested further information on these seizures.

Denmark reported one seizure that arrived by mail. So far, Danish authorities are only aware of 5-(2-aminopropyl)indole distribution on the Internet. They believe that distribution channels are outside of Denmark, and end users purchase from the Internet with delivery through the mail service.

(7) Reported by the Federal Criminal Police Office (BKA).

3.2.2 Information provided to the EMCDDA

Seven Member States (Denmark, Germany, Finland, Hungary, the Netherlands Sweden and the United Kingdom) and Norway reported detections of 5-(2-aminopropyl)indole ⁽⁸⁾.

It is noteworthy that several Member States have reported that many forensic and/or toxicological laboratories do not currently have validated procedures for the confirmation of 5-(2-aminopropyl)indole in seized, collected and biological samples. Due to the lack of certified reference material (that only became available in August 2012) the laboratories could not distinguish 5-(2-aminopropyl)indole from the related compound AMT (which has also been detected in samples seized on the drug market). Furthermore, in the case of biological samples there is no rapid qualitative screening method for the detection of 5-(2-aminopropyl)indole. Overall, this may lead to under-reporting of 5-(2-aminopropyl)indole.

Seizures

Seven Member States (Denmark, Germany, Finland, Hungary, the Netherlands Sweden and the United Kingdom) and Norway reported seizures of 5-(2-aminopropyl)indole.

5-(2-Aminopropyl)indole has typically been seized in powder form, as well as in tablets and capsules. Where information has been provided, quantities of powder ranged from 0.2 grams (Hungary) to 20.5 kilograms (the Netherlands). Hungary reported a seizure of 7 beige tablets bearing markings resembling the Lexus logo ⁽⁹⁾. This may suggest that 5-(2-aminopropyl)indole is being sold as 'ecstasy', as Europol have reported that tablets containing MDMA and bearing this logo, as well as a tablet punch (for imprinting logos on tablets as part of the manufacturing process) have been seized in the past. In Sweden, blue/green unmarked tablets and brown glittery tablets were also seized. In the United Kingdom, blue unmarked tablets were seized from a head shop and were found in commercial packages marked 'BENZO FURY' that also displayed an image of the chemical structure of 5-APB (5-(2-aminopropyl)benzofuran) ⁽¹⁰⁾. There has been one report of residues found on a spoon and one report where 5-(2-aminopropyl)indole was recovered from the liquid in a syringe (Hungary). This may suggest that 5-(2-aminopropyl)indole is being injected by some users.

Denmark reported one seizure of 5.1 grams of a light brown powder seized on 19 July 2012 by customs (Haderslev). The powder was in a small transparent bag labelled as: '5g 5-IT, Research

⁽⁸⁾ 'Detections' is an all encompassing term, which 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 specimens (tissues, hair, etc.).

⁽⁹⁾ It is common to find markings on tablets sold as 'ecstasy' including those of popular cultural and iconic brands often having an association with quality. Lexus is a Japanese car manufacturer.

⁽¹⁰⁾ Whilst 6-APB was originally marketed as 'Benzo Fury' (or related synonyms such as 'BenzoFury', 'Benzo-fury', 'Benzo', and 'Fury'), the isomer 5-APB has also been confirmed in products sold as 'Benzo Fury'. 'Benzo Fury' products appear to get their name from the benzofuran chemical ring system which is present at the core of the molecule. Other substances have been reported in products sold as 'Benzo Fury' (see section 3.4.2).

Chemical, Not for human consumption'. The bag was inside a 'normal' brown envelope, and without any sender. The post came from the United Kingdom.

Finland reported 11 seizures weighing a total of 26 grams. One of the seizures was 1.1 grams of a light brown powder seized on 1 April 2012 by customs (Helsinki) in the incoming mail.

Germany reported one seizure of 1.35 grams and 0.22 grams together with traces of MDAI (methylenedioxyaminoindane) seized on 2 May 2012 by police (Hanover). These were seized from an unconscious person (together with other new psychoactive substances). The person subsequently stated that he had bought the substances via the internet from an online shop based in the United Kingdom.

Hungary reported 8 seizures, the first of which was in April 2012. One seizure of 2.4 grams of a beige powder in April 2012 was recovered from the scene of a case with two deaths (described in section 3.4.1). 97.3 grams of a brown powder was seized in August 2012 by police along with a set of digital scales which bore traces of 5-(2-aminopropyl)indole. The Hungarian national focal point informed the EMCDDA that the circumstances of the case suggest the distribution of 5-(2-aminopropyl)indole as well as other new psychoactive substances and controlled drugs using the postal system (the business covered the whole of Hungary).

The Netherlands reported one seizure of 20.5 kilograms made by customs. Further details are not available at this time.

Sweden reported 27 seizures. 23 of these were reported by the police and comprised 30.87 grams of powder and 54 tablets. The first seizure was comprised of 13 grams of beige powder and was seized on 16 May 2012. In addition, ethylphenidate was also detected in this powder. This is a potentially significant finding given the detection of ethylphenidate in three non-fatal intoxications in Sweden where 5-(2-aminopropyl)indole was also detected. Customs reported a total of 4 seizures comprised of three seizures of a brown powder weighing a total of 11.07 grams and one seizure of 5 tablets. The three seizures of powder were sent from Spain. The package containing tablets was sent from the United Kingdom.

The United Kingdom reported two seizures. The first seizure was on 9 June 2012 and comprised 116 branded packets marked 'BENZO FURY' that were recovered from a head shop. Each packet contained one blue unmarked tablet. This seizure was made during the police investigation into one of the deaths reported by the United Kingdom where the presence of 5-(2-aminopropyl)indole was confirmed (see section 3.4.1 below). The police were aware that the 'Benzo Fury' product reportedly consumed by the deceased had been purchased at the head shop.

Other items of interest recovered from the head shop were: Yellow capsules labelled 'benzofury' found to contain brown powder containing 5-APB (5-(2-aminopropyl)benzofuran) or 6-APB (6-(2-aminopropyl)benzofuran). 31 grams of brown powder found to contain 5-APB or 6-APB. 174 packages (98 of one type and 76 of a second type) each containing 1 gram of crystalline substance identified as methylthienylpropamine (MPA).

The second seizure was from the British Crown Dependency of the Bailiwick of Guernsey and made by customs on 8 September 2012. The seizure was comprised of seven red and white capsules

with no markings. In addition D2PM (diphenylprolinol) was also detected in these capsules. The capsules were seized along with a number of controlled drugs (Class B) from a person arriving on Guernsey. Further details on this case are not currently available.

Norway reported one seizure of 1 gram in a small bag with zip-lock seized on 17 April 2012 by Customs authorities at Oslo airport. In addition, 6-APB (1000 tablets), and a mixture of AM-2201 and AM-2233 (both synthetic cannabinoids) in green plant material were also seized. The consignment originated from the United Kingdom.

Biological samples

Two Member States (Sweden and the United Kingdom) reported a total of 19 deaths where 5-(2-Aminopropyl)indole was detected (Sweden, 15 deaths; the United Kingdom, 4 deaths). Two deaths were reported by Hungary where 5-(2-aminopropyl)indole was detected in powder found at the scene of the deaths. Due to the similarities between 5-(2-aminopropyl)indole and AMT under certain analytical conditions, the powder was initially thought to contain AMT. AMT was also reported in the post-mortem biological samples. The biological samples from these cases are no longer available for re-analysis. However, the Hungarian national focal point noted that 'based on the active agent identified in the substance found next to the bodies it is assumed that the cause of the deaths was 5-(2-aminopropyl) indole intoxication rather than AMT intoxication' (further details are provided in Annex 3).

Collected samples

One Member State (United Kingdom) reported two collected samples of 5-(2-aminopropyl)indole. In April 2012, a sample was purchased from an Internet retailer (buyresearchchemicals.co.uk). The product was supplied as a brown powder. In May 2012, a further sample was purchased from an Internet retailer (Polatzo head shop). The product was supplied as a pale brown powder and cost GBP22.50 for 500 milligrams ⁽¹¹⁾. Further details of these collected samples, including information on the product labels, are provided in Annex 2.

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

Germany reported that 'no direct hints on any kind of organised crime were identified. However bearing in mind the easy availability of 5-(2-aminopropyl)indole same as a plenty of other new psychoactive substances via internet-shops (e.g. www.benzo-fury.me.uk, www.highstore.net, www.buckledbonzi.co.uk), also in large amounts in and outside of the EU indicate at least a certain degree of organisation.'

Denmark reported that, 'so far we do not believe the distribution of 5-IT in Denmark is organized'.

⁽¹¹⁾ The actual weight supplied was not reported.

Money laundering aspects

No information was received on money laundering related to the production and/or trafficking of 5-(2-aminopropyl)indole.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of 5-(2-aminopropyl)indole.

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

3.4.1 First indication of health risks

Non-fatal intoxications associated with 5-(2-aminopropyl)indole

Two Member States (Sweden and the United Kingdom) reported a total of 15 non-fatal intoxications associated with 5-(2-aminopropyl)indole ⁽¹²⁾.

Sweden reported 13 cases from the Swedish Poisons Information Centre between January and September 2012 where 5-(2-aminopropyl)indole was detected.

Of the 13 cases, 11 were male and 2 were female. Their ages ranged between 17 and 52, however the most common age was 20 to 30 years with 8 of the 13 falling into this bracket. In five cases, the individual stated they had taken '5-IT' (a commonly used abbreviation for 5-(2-aminopropyl)indole), in four cases the stated intake was 'benzofury', whilst three mentioned taking ethylphenidate (one in combination with 'benzofury', one with 5-(2-aminopropyl)indole and one on its own). One person stated they had taken MDPV (methylenedioxypyrovalerone), one said they had been 'drinking only coca cola from an unknown source' and the remaining person stated they had taken 'an unknown substance'. 5-(2-Aminopropyl)indole was analytically confirmed in each case although the concentration was not determined. Other drugs detected in these cases were: ethylphenidate, 4,5- or 6-APB, 4-methylethcathinone, buprenorphine, methylphenidate, methylphenidate metabolites, 4-fluoroamphetamine, oxazepam, temazepam, diazepam metabolites, methylthienylpropamine, methoxetamine, 4-hydroxymidazolam (midazolam metabolite), ketamine, GHB (gamma-hydroxybutyrate), PMMA (*para*-methoxymethamphetamine), amphetamine, *N*-methamphetamine, benzoylecgonine (cocaine metabolite), ethanol and metabolites.

⁽¹²⁾ The German police reported to Europol that the powder seized in Hanover was seized from an unconscious person. It is not known if this is a non-fatal intoxication associated with 5-(2-aminopropyl)indole as further details are not available.

The route of administration of 5-(2-aminopropyl)indole was indicated in one case where the person reported having taken it by nasal insufflation. Three of the 13 individuals reported that they sourced 5-(2-aminopropyl)indole from the Internet (the remaining ten individuals did not report the source of supply).

The reported symptoms included dilated pupils, sweating, restless, disorientated, agitated, anxiety, high heart rate, high blood pressure and high body temperature.

One example of a non-fatal intoxication that was provided was of an eighteen year old female who had taken 1 capsule of 5-(2-aminopropyl)indole of unknown strength. Fifteen hours after administration, the subject was restless, agitated, disorientated, shivering, sweating, with dilated pupils and a heart rate of 160/min. Body temperature rose to 38.6 °C. 'The patient was treated with sedating drugs without sufficient effect. She was sedated and put on respirator. The following day she was full of anxiety but otherwise in a stable condition.'

The United Kingdom reported that there were two non-fatal intoxications associated with the second death detailed below. The two individuals had also reportedly ingested some 'Benzo Fury' from the same source as the deceased. They were also seen at the hospital but neither appeared to have suffered any significant toxic effects. No further information on drug history or the amounts of 'Benzo Fury' taken was available.

Deaths associated with 5-(2-aminopropyl)indole

Three Member States (Sweden, the United Kingdom and Hungary) reported a total of 21 deaths associated with 5-(2-aminopropyl)indole ⁽¹³⁾.

Sweden

Sweden reported that the National Laboratory of Forensic Toxicology (RMV) have observed 5-(2-aminopropyl)indole in 15 post-mortem examinations. These were performed between April 2012 and 30 June 2012. In 14 of the cases the cause of death was considered to be related to 5-(2-aminopropyl)indole. In the remaining case the cause was 'disease'. In 14 cases the 5-(2-aminopropyl)indole concentration in post-mortem blood ranged from 0.7 to 5.2 µg/g blood. In one case the concentration of 5-(2-aminopropyl)indole was 18.6 µg/g femoral blood. All of the deceased were male. 13 were aged between 20 and 30 years, the remaining two were over 30 years old. In two cases 5-(2-aminopropyl)indole was the only substance detected. In the remaining cases, 5-(2-aminopropyl)indole was found in combination with 'pharmaceuticals' or 'other drugs' (not specified).

⁽¹³⁾ In the two deaths reported by Hungary, AMT was reported as being detected in post-mortem biological samples. However, it is assumed that the cause of the deaths was 5-(2-aminopropyl)indole intoxication rather than AMT intoxication. See section 3.2.2, 'Biological samples'.

United Kingdom

The United Kingdom reported four deaths. Details are only provided for two of these cases, both of which occurred in June 2012. The deceased were both male; one was 33 years old, the other was 19 years old.

The cause of death in the first case (33 year old) was 'fatality following the ingestion of 'Benzo Fury'' and certified as '5-(2-aminopropyl)indole (5-API; 5-IT) and Benzofuran toxicity'. The male was treated in hospital prior to death. Analysis of the blood revealed an approximate 5-(2-aminopropyl)indole concentration of 0.379 mg/L in unpreserved post-mortem blood. Other drugs detected in the blood included 5-APB (0.016 mg/L), 6-APB (0.057 mg/L), diazepam (0.037 mg/L), nordiazepam (0.009 mg/L), temazepam (0.001 mg/L) and AMT (less than 0.01 mg/L). Urine analysis detected amphetamine, 5-(2-aminopropyl)indole, 5-APB, 6-APB, AMT and benzodiazepines. In addition, 5-(2-aminopropyl)indole, 5-APB, 6-APB, AMT and diazepam were detected in the stomach contents.

In the second case (19 year old), the toxicological investigation revealed 5-(2-aminopropyl)indole at a concentration of approximately 0.513 mg/L in ante-mortem blood (the deceased was admitted to hospital prior to death) and approximately 0.30 mg/L in unpreserved post-mortem blood. Other drugs detected included MDMA (0.468 mg/L ante-mortem blood, 0.502 mg/L post-mortem blood), MDA (0.036 mg/L ante-mortem blood, 0.046 mg/L post-mortem blood), 6-APB (0.005 mg/L post-mortem blood only), atropine and lignocaine. These drugs were also detected in the urine and stomach contents. It was noted that there was a high concentration of MDMA, which in isolation was considered to be at a fatal level. However, a cumulative/synergistic effect of 5-(2-aminopropyl)indole was not excluded and the cause of death was recorded as 'multidrug toxicity'. This case is linked to the seizure of 116 blue tablets in branded packets labeled as 'BENZO FURY' containing 5-(2-aminopropyl)indole (detailed in section 3.2.2 above).

The remaining two deaths from the United Kingdom were reported in a letter to the British Medical Journal. The letter reports that 5-(2-aminopropyl)indole was detected in the post-mortem blood samples of two young adults. The authors note that 5-(2-aminopropyl)indole was 'found in combination with other drugs in one case. In the other, 5-APB/6-APB' (Seetohul et al., 2012). It was ascertained from the national focal point that these cases were distinct from the other two cases reported by the United Kingdom. However, no further details are available at this time.

Hungary

As noted, the two deaths reported by Hungary were originally thought to be related to AMT which was detected in post-mortem biological samples. The deceased, a 40-year-old male and a 35-year-old female were found together in a flat. The pathological cause of death in each case was 'circulatory failure and respiratory failure, where the direct causes of death... were the results of 5-IT intoxication' and in the case of the female 'the respiration of vomited content of stomach might had a limited impact too'. There were signs of 'prolonged sexual intercourse, extreme hyperthermia and the use of new psychoactive substances'.

The post-mortem concentrations (determined as AMT) were 34 mg/L and 84 mg/L respectively. These figures are provided only to show them relative to each other. The biological samples were no longer available for re-analysis. However, the re-analysis of powders found at the scene identified the presence of 5-(2-aminopropyl)indole and not AMT. The Hungarian national focal point noted that 'based on the active agent identified in the substance found next to the bodies it is assumed that the cause of the deaths was 5-(2-aminopropyl)indole intoxication rather than AMT intoxication.'

Information on toxicity, tolerance and dependence potential

The structured literature search undertaken for the preparation of this report did not find any published information specifically related to toxicity, tolerance nor the dependence producing potential of 5-(2-aminopropyl)indole.

While detailed pharmacological investigations on 5-(2-aminopropyl)indole do not appear to have been published ⁽¹⁴⁾, one study that investigated the ability of 5-(2-aminopropyl)indole and its five isomers to inhibit monoamine oxidase (MAO) was identified. The assay method was based on the ability of guinea pig liver homogenate to absorb oxygen generated from serotonin as the substrate. The activity was expressed as percentage inhibition. The IC₅₀ values for 5-(2-aminopropyl)indole, 6-(2-aminopropyl)indole (6-IT) and 3-(2-aminopropyl)indole (AMT), for example, were 2.2×10^{-5} , 4.6×10^{-6} and 5.8×10^{-5} M, respectively. These data indicate that 6-IT was the most potent inhibitor amongst those three substances. These substances were also evaluated for their ability to antagonise pentylentetrazole/reserpine-induced tonic extensor seizures in mice. 5-(2-Aminopropyl)indole appeared to be less active than 6-IT but more active than AMT with regards to anti-reserpine activity (Cerletti et al., 1968). Overall, the significance of these findings in relation to humans is unclear.

Shulgin and Shulgin (1997) provide some limited data noting that 5-(2-aminopropyl)indole may show long-lasting stimulant properties in humans (for about twelve hours) when 20 mg was given orally. Effects reported were increased heart-rate, anorexia, diuresis, and slight hyperthermia. No information is provided on the methodology of the experiment or the number of volunteers.

In some of the non-fatal intoxications and deaths associated with 5-(2-aminopropyl)indole that were reported, symptoms typical of monoaminergic toxicity have been noted. These include hyperthermia along with dilated pupils, sweating, increased heart rate, high blood pressure, agitation, restlessness, disorientation and anxiety.

Information from Internet drug user discussion forums suggest that the self-reported routes of administration for 5-(2-aminopropyl)indole include oral (such as 'bombing' ⁽¹⁵⁾) and insufflation. Reported doses used include: '20mg' [route of administration not specified], '80 mg orally',

⁽¹⁴⁾ A literature search on 5-(2-aminopropyl)indole revealed a translated article (USSR, Academy of Sciences) on serotonergic properties of several tryptamines. An inspection of the English translation did not appear to yield conclusive data on 5-(2-aminopropyl)indole (Buznikov et al., 1965).

⁽¹⁵⁾ 'Bombing' is where a drug is wrapped in cigarette paper (or similar) prior to swallowing.

'bombed 100 mg', '150Mg swallowed', 'insufflated 65 mg'. There is also one brief user report of what appears to be the intravenous injection of 5-(2-aminopropyl)indole ⁽¹⁶⁾.

Information from the EU pharmacovigilance system

According to information received from the EMA, there are no reports associated with 5-(2-aminopropyl)indole in the EudraVigilance system.

3.4.2 Characteristics of users

Prevalence data on the use of 5-(2-aminopropyl)indole are not available. Information included in this report (including seizures, collected samples, non-fatal intoxications and deaths) provides some information about the characteristics of users and how 5-(2-aminopropyl)indole appears on the market.

Some Internet retailers offer 5-(2-aminopropyl)indole as a drug in its own right. This has been confirmed by collected samples and is supported by discussions on Internet drug user forums. Additionally, the United Kingdom reported that seized samples of branded products labelled as 'BENZO FURY' from a bricks and mortar head shop contained 5-(2-aminopropyl)indole. Information from non-fatal intoxications and deaths reported by Sweden and the United Kingdom suggests that some individuals may have been exposed to 5-(2-aminopropyl)indole as a result of using products labelled as 'Benzo Fury' or '6-APB'. However, the prevalence of 5-(2-aminopropyl)indole in such products relative to other substances is not known.

Hungary reported the seizure of seven tablets that contained both 5-(2-aminopropyl)indole and methylthienylpropamine bearing markings resembling the Lexus logo (see Annex 2). As noted, Europol have reported MDMA tablets and a tablet punch (for stamping logos on tablets) bearing the Lexus logo have been seized in the past. It may be the case that some ecstasy users are at risk of exposure to 5-(2-aminopropyl)indole. However, as noted, the total number of such types of tablets containing 5-(2-aminopropyl)indole that have been reported so far is small and limited to one country.

Hungary reported that 5-(2-aminopropyl)indole has been found in residues on a spoon and in the liquid recovered from a syringe. The assessment of the Hungarian national focal point is that 5-(2-aminopropyl)indole is being injected.

Information suggests that 5-(2-aminopropyl)indole is taken orally, insufflated, and may be injected.

Data from the 2011 Mixmag survey (a non-probabilistic convenience sample Internet survey commissioned by the UK dance music magazine Mixmag, n=2560) found that self-reported lifetime

⁽¹⁶⁾ For example: <http://www.drugs-forum.com/forum/showthread.php?t=140331>, <http://www.drugs-forum.com/forum/showthread.php?t=172223>, <http://www.drugs-forum.com/forum/showthread.php?t=172223#ixzz2Edylffh>, <http://www.drugs-forum.com/forum/showthread.php?t=140331>, <http://www.bluelight.ru/vb/threads/616728-The-Big-amp-Dandy-5-IT-5-API-Thread>

and last year prevalence of use of 'Benzofury' in this group was 2.7 % and 2.3 % respectively. In comparison self-reported lifetime and last year prevalence of MDPV (methylenedioxypropylvalerone) was 4.4 % and 3.0 % respectively; MDAI (5,6-methylenedioxy-2-aminoindane) was 6.7 % and 4.7 % respectively; BZP (1-benzylpiperazine) was 17.2 % and 5.0 % respectively; and, mephedrone (4-methylmethcathinone) was 61.0 % and 51.0 % respectively.

Kelleher et al., (2011), also using a non-probabilistic convenience sample Internet survey of self-reported new psychoactive substance users, the majority of which were from Ireland (n=329), found that of the 159 respondents who reported using 'party pills' and 'liquid highs', 1.3 % (i.e. 2 respondents out of 159) had used a product named 'Benzo Fury'; while none of the respondents reported use of '6-APB'.

Both these surveys predate the detection of 5-(2-aminopropyl)indole. While they provide some indication of the use of 'Benzofury' products the results are not generalisable to other groups and populations.

Information on the composition of 'Benzo Fury' products

Although Internet retailers typically advertise 'Benzo Fury' products as containing 6-APB or 5-APB, a structured search of the information available on the European database on new drugs (EDND) ⁽¹⁷⁾ found that seized and collected samples of 'Benzo Fury' products have contained: 6-APB; 5-APB; D2PM; pentylone with caffeine, lidocaine and procaine; AM-2201 (tentative identification); and, 5-(2-aminopropyl)indole.

Additionally, published studies involving the analysis of collected and biological samples suggest that 'Benzo Fury' products contain: 6-APB; 5-APB; D2PM; and, 1-benzylpiperazine (BZP) with 3-trifluoromethylphenylpiperazine (3-TFMPP) and caffeine (Ayres and Bond, 2012; Baron et al., 2011; Wood et al., 2011; Wood et al., 2012).

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

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971 (hereafter, 'United Nations drug conventions'). On 10 October 2012, the World Health Organization informed the EMCDDA that 5-(2-aminopropyl)indole is currently not under assessment and has not been under assessment by the United Nations system and no such assessment is planned.

⁽¹⁷⁾ Including Reporting Forms, Progress and Annual Reports, and Project Match.

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

The first official EMCDDA–Europol notification of 5-(2-aminopropyl)indole dates from 1 June 2012 from the Norwegian national focal point. The reporting form details a seizure of one zip-lock bag containing one gram of light brown powder intercepted at Oslo Airport, Gardermoen, on 17 April 2012 by the customs authorities. The identification was based on the analytical technique of GC-MS alone.

5-(2-Aminopropyl)indole was added to the list of new psychoactive substances monitored by the EMCDDA and Europol via the European Union early warning system and a profile of the substance was created in the EMCDDA European database on new drugs (EDND). Analytical details and background information have been exchanged on various occasions between EMCDDA, Europol and the Member States. The Commission and the EMA were kept duly informed.

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

One Member State, Denmark, controls 5-(2-aminopropyl)indole under drug control legislation derived from their obligations under the United Nations drug conventions. On the recommendation of the Danish Health and Medicines Authority, the Danish Minister for Health decided to add 5-(2-aminopropyl)indole (1-(1*H*-indol-5-yl)propan-2-amin) to the Danish lists of controlled substances, List B. On 28 September 2012, the Minister signed an Executive Order amending the Executive Order on Euphoriant Substances. This entered into force on 30 September 2012. Subsequently, 5-(2-aminopropyl)indole may only be used for medical or scientific purposes.

Austria, Hungary and Sweden control 5-(2-aminopropyl)indole using other legislative measures. In Austria, 5-(2-aminopropyl)indole is subject to control measures according to the law on new psychoactive substances (NPSG). In Hungary, 5-(2-aminopropyl)indole is controlled as a 'new psychoactive substance' (Government Decree 66/2012) as it is a derivative of 2-phenethylamine (therefore meeting the generic definition of phenethylamine derivatives). In Sweden, with effect from 18 of September 2012, 5-(2-aminopropyl)indole was regulated as a substance hazardous to health under the Act on the Prohibition of certain Goods Dangerous to Health (SFS 1999:42).

In Germany, in accordance with diverse articles of the Medical Products Act (Arzneimittelgesetz, AMG), trafficking of 5-(2-aminopropyl)indole and keeping 5-(2-aminopropyl)indole for sale are forbidden and may be punished ⁽¹⁸⁾.

⁽¹⁸⁾ Spain also noted that 'these types of substances have to be evaluated and authorized by the Spanish Agency of Medicines and Sanitary Products when they are used by humans. This is established by the article 9 of the Law 29/2006, 26th July, regarding guarantees and rational use of medicines and sanitary products.'

The remaining 22 Member States, Croatia, Turkey and Norway have reported that 5-(2-aminopropyl)indole is not under control in their jurisdictions ⁽¹⁹⁾.

3.8 Further information — Article 5.2(h) of the Decision

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

There is no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for the 5-(2-aminopropyl)indole that has been detected on the drug market.

One classic approach for the synthesis of 5-(2-aminopropyl)indole includes a condensation reaction using indole-5-carboxaldehyde ⁽²⁰⁾ and nitroethane ($\text{CH}_3\text{CH}_2\text{NO}_2$). The resulting 5-(2-methyl-2-nitrovinyl)indole can then be reduced with lithium aluminum hydride (LiAlH_4) (Hofmann and Troxler, 1963; Troxler et al., 1968) but other methods and reagents of reduction may equally be employable. This is a similar process to the reductive amination used commonly in the manufacture of amphetamines. The reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment. A further possible route of synthesis that may be applicable to 5-(2-aminopropyl)indole is the 'gramine-nitroalkane' route which can be used to manufacture AMT (Brandt et al., 2004). In this particular case, the starting material would then be 1-(1H-indol-5-yl)-N,N-dimethylmethanamine which, upon reaction with nitroethane, would give the 5-(2-nitropropyl)-1H-indole intermediate. Reduction of the nitro group would then result in the primary amine product, 5-(2-aminopropyl)indole. This particular reaction is not in the published literature. Depending on reaction conditions it may yield dialkylated and other by-products (Brandt et al., 2004). A sub-structure search revealed that 5-(2-aminopropyl)indole exists as a sub-structure of a larger molecule. This means that 5-(2-aminopropyl)indole could serve as a starting material for further modifications. An example was found in the patent literature in the form of 4-((1-(1H-indol-5-yl)propan-2-yl)(propyl)amino)-1-cyclohexylbutan-1-one (Reaxys registry number 15343158) (Duphar International Research, 1988).

⁽¹⁹⁾ Italy also provided further information that in "... September (2012), the Italian Ministry of Health in collaboration with the Department for Antidrug Policies of the Presidency of the Council of Ministers and with the support of the Italian Early Warning System, activated the procedure to include the new psychoactive substance 5-(2-aminopropyl)indole, into the list of controlled substances (Table 1, President of the Republic Decree 309/90). In a few months, the molecule will have the chance to be put under control." Latvia provided information that although 5-IT is not under control at national level, there is a plan to introduce a new generic system. If this system is introduced, "all new psychoactive substances including 5-IT will be under control". Finland provided information that they intend to control 5-IT under existing medicines legislation "...the decision, however, is not in force yet." Bulgaria indicated to Europol that the Customs Agency prepared a proposal to the National Council of Drugs Substances to put under control some new psychoactive substances, including 5-(2-aminopropyl)indole.

⁽²⁰⁾ Indole-5-carboxaldehyde is not under international control and is known to be commercially available. For example Italy reported that it is sold by Sigma for EUR155 for 5 grams (<http://www.sigmaaldrich.com/catalog/product/ALDRICH/513830?lang=it®ion=IT>).

As noted, information provided by the Portuguese Europol National Unit suggested that 5-(2-aminopropyl)indole is 'a precursor used to synthesise drugs'. Europol has requested further information on this issue from the Portuguese Europol National Unit.

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

As noted, 5-(2-aminopropyl)indole has been encountered as powders as well as tablets and capsules. These physical forms suggest that common routes of administration may be orally and by insufflation. Limited information from reports of non-fatal intoxications, deaths and Internet drug user discussion forums appear to support this. The succinate salt of 5-(2-aminopropyl)indole (confirmed in the two collected samples reported by the United Kingdom) may be suitable for injection. Significantly, Hungary has reported that 5-(2-aminopropyl)indole has been found in residues on a spoon and in the liquid recovered from a syringe. The assessment of the Hungarian national focal point is that 5-(2-aminopropyl)indole is being injected. One brief user report of what appears to be the intravenous injection of 5-(2-aminopropyl)indole has been reported on an Internet drug user forum ⁽²¹⁾. The United Kingdom noted that Internet drug user forums suggest that 5-(2-aminopropyl)indole is used at home and in nightclubs.

Several countries have noted that 5-(2-aminopropyl)indole is offered for retail sale as a 'research chemical' on the Internet. Germany reported that 5-(2-aminopropyl)indole is offered for sale alongside other new psychoactive substances (www.benzo-fury.me.uk, www.highstore.net and www.buckledbonzi.co.uk). Italy also reported a similar observation and noted that 5-(2-aminopropyl)indole could be bought for GBP22.50 for 500 milligrams (<http://www.officialbenzofury.com/products/5%252dIT.html>) and GBP9.50 for 100 milligrams (<http://vip-legals.com/buy-5it-powder>; <http://www.lookchem.com/5-2-Aminopropyl-indole/>). The United Kingdom noted that 5-(2-aminopropyl)indole was sold as a 'unique product', structurally 'similar to AMT' with 'euphoric effects similar to 5-APB'. They reported that 5-(2-aminopropyl)indole could be purchased in the form of capsules containing 100 milligrams (e.g. <http://www.wide-mouth-frogs.com/5-it-caps.html>) GBP26.00 for 10 capsules or GBP100.00 for 50 capsules. Powders also appeared to be offered for sale at GBP10.20 for 250 milligrams (discounted from GBP12.00; <http://www.benzofury.me.uk/index/155>) or in bulk powder GBP6000.00 for 1 kilogram (e.g. <http://www.plantfoodpalace.com/5-it/page/2/>). It was offered for sale in combination with AMT by one retailer at a cost of GBP38.00 for 500 milligrams.

In addition to the information given above, the United Kingdom commented that at the time of reporting, 5-(2-aminopropyl)indole is 'not included or has been removed from the stocklist of a number of the more well-known retailers'. They further comment that 'it is unknown whether this is related to lack of availability from wholesalers or importers or due to adverse media attention concerning the drug (e.g. <http://local.stv.tv/glasgow/194611-legal-high-5-it-tablets-recovered-by-police-are-potentially-fatal/>)'.

⁽²¹⁾ <http://www.drugs-forum.com/forum/showthread.php?t=140331>

The Internet search conducted by the EMCDDA found that as of 6 December 2012, '5-IT' is offered for sale by a number of Internet retailers.

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

No information was provided by any Member State that indicated that 5-(2-aminopropyl)indole had any other use apart from legitimate scientific research and as an analytical reference standard.

From the available information it does not appear that 5-(2-aminopropyl)indole is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of an European Union database on the synthetic routes of all medicinal products ⁽²²⁾.

⁽²²⁾ i.e. products that have been granted a marketing authorisation, or where an application for a marketing authorisation has been made, or where the marketing authorisation has been suspended.

4. Information from the EMA as requested by Article 5.3 of the Decision

4.1 Marketing authorisation

The 17 Member States, Iceland and Norway which responded to the EMA's information request (see section 2) reported that the new psychoactive substance 5-(2-aminopropyl)indole has not obtained a marketing authorisation ⁽²³⁾.

4.2 Application for a marketing authorisation

The 17 Member States, Iceland and Norway which responded to the EMA's information request (see section 2) reported that the new psychoactive substance 5-(2-aminopropyl)indole is not the subject of an application for a marketing authorisation.

4.3 Suspended marketing authorisation

The 17 Member States, Iceland and Norway which responded to the EMA's information request (see section 2) reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance 5-(2-aminopropyl)indole.

⁽²³⁾ Belgium, Denmark, Estonia, Ireland, Spain, Sweden and Norway provided responses in relation to both human and veterinary medicinal products. Germany, Hungary, Italy, Malta, Portugal, Romania, Slovenia, Slovakia and the United Kingdom provided responses in relation to human medicinal products. Latvia and Poland provided responses in relation to veterinary medicinal products.

5. Summary of findings

- 5.1. 5-(2-Aminopropyl)indole is a synthetic derivative of indole substituted at the phenyl side of the indole ring system (position 5). It is a positional isomer of alpha-methyltryptamine (AMT) which belongs to the chemical family of tryptamines, many of which are hallucinogenic. However, 5-(2-aminopropyl)indole also contains the sub-structure of alpha-methylphenethylamine and therefore could be considered to be a substituted phenethylamine, many of which are stimulants. Limited data suggests that 5-(2-aminopropyl)indole has stimulant effects.
- 5.2. The first seizure of 5-(2-aminopropyl)indole was in Norway on 17 April 2012. It was notified to the EMCDDA through the EU early warning system on 1 June 2012.
- 5.3. Several Member States reported that forensic and/or toxicological laboratories do not currently have validated procedures for the confirmation of 5-(2-aminopropyl)indole. This was due to the initial lack of certified reference material. This may have led to under-reporting of 5-(2-aminopropyl)indole detections.
- 5.4. Seven Member States and Norway have reported seizures of 5-(2-aminopropyl)indole. These were mostly as powders (ranging from 0.2 grams to 20.5 kilograms), tablets and capsules. It has also been detected in tablets resembling 'ecstasy'.
- 5.5. The information available suggests that common routes of administration of 5-(2-aminopropyl)indole may be orally and by insufflation. One Member State reported that injection may also occur.
- 5.6. There is no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for the 5-(2-aminopropyl)indole that has been detected on the drug market. One possible route of synthesis is a similar process to the reductive amination used commonly in the manufacture of amphetamines. The reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment.
- 5.7. According to reports provided to Europol there is no information available to suggest the involvement of organised crime, or criminal groups, in the production, distribution and trafficking of 5-(2-aminopropyl)indole. The substance has been seized at the border of four Member States and Norway. In one case this involved a seizure of 20.5 kilograms.
- 5.8. One Member State controls 5-(2-aminopropyl)indole under drug control legislation. Two Member States control 5-(2-aminopropyl)indole under legislation relating to new psychoactive substances. One Member State controls 5-(2-aminopropyl)indole under other legislation. One Member State controls 5-(2-aminopropyl)indole under medicine legislation.
- 5.9. 5-(2-Aminopropyl)indole is currently not under assessment and has not been under assessment by the United Nations system.

- 5.10. There are no prevalence data on the use of 5-(2-aminopropyl)indole. In some cases 5-(2-aminopropyl)indole has been found in 'Benzo Fury' products. A non-representative Internet survey of readers of a dance music magazine found that 2.3 % of respondents reported use of 'Benzo Fury' in the last year.
- 5.11. Some Member States reported easy access and availability of 5-(2-aminopropyl)indole through Internet retailers. It is sold as a drug in its own right and in branded products sold as 'Benzo Fury'. In the latter case there is also evidence of supply from bricks and mortar head shops.
- 5.12. There have been 15 non-fatal intoxications and 21 deaths associated with 5-(2-aminopropyl)indole in three Member States. These have been reported to the EMCDDA from the 6 July 2012 to the time of writing the report. The analysis of biological samples shows that 5-(2-aminopropyl)indole may be used in conjunction with controlled drugs and new psychoactive substances.
- 5.13. There appear to be no published studies on the toxicity, tolerance and dependence producing potential of 5-(2-aminopropyl)indole. Detailed studies on pharmacology also do not appear to have been published. One available study suggests that 5-(2-aminopropyl)indole inhibits monoamine oxidase. The significance of this finding in relation to humans is unclear. In some of the non-fatal intoxications and deaths associated with 5-(2-aminopropyl)indole symptoms typical of monoaminergic toxicity have been noted.
- 5.14. 5-(2-Aminopropyl)indole has no known human or veterinary medical use in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for 5-(2-aminopropyl)indole in the European Union or in the Member States which responded to the EMA.
- 5.15. There are no indications that 5-(2-aminopropyl)indole is used for other purposes other than as an analytical reference material and in scientific research. At the time of writing the report, there is no information that 5-(2-aminopropyl)indole is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of an European Union database on the synthetic routes of all medicinal products.

6. Conclusions

The health and social risks caused by the manufacture, trafficking and use of 5-(2-aminopropyl) indole, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

Annexes

Annex 1 — Main information sources

General

1. EMCDDA and its network of Reitox national focal points — standard reporting and replies to Joint Report questionnaire.
2. Europol and its network of Europol National Units — standard reporting and replies to Joint Report questionnaire.
3. EMA and its network of Member States' national competent authorities responsible for human and veterinary medicinal products — replies to Joint Report questionnaire.
4. Scientific articles published in peer reviewed journals.
5. Grey literature.
6. Internet sites and drug user discussion forums (including media articles).
7. Personal communications with experts.

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Annex 2 — Details of seizures and collected samples of 5-(2-aminopropyl)indole (5-IT) reported to the EMCDDA

Date of seizure or collection	Amount and physical form	Seizing or collecting authority	Place of seizure or collection	Notes	Images
Denmark					
19/07/2012	One seizure of 5.1 g light brown powder	Customs	Haderslev	Powder was found in a small transparent bag and with a sticker: '5g 5-IT, Research Chemical, Not for human consumption'. The bag was inside a 'normal' brown envelope, and without any sender. The post came from United Kingdom. Identification based on GC-MS, UPLC-TOF, H-NMR.	
Finland					
01/04/2012	One seizure of 1.1 g of a light brown powder	Customs	Helsinki	Seized in incoming mail. Identification based on NMR.	
Germany					
02/05/2012	1.35 g and a further 0.22 g together with traces of MDAI (together with other new psychoactive substances)	Police	Hannover	The accused stated that he has bought the substances via the internet from an online shop in the United Kingdom.	
Hungary*					
04/2012	2.4 g of a beige powder	Police	Tapolca	Confirmed as 5-(2-aminopropyl)indole	
04/2012	Residues on paper, liquid in syringe (0.75 ml)	Police	Debrecen	Confirmed as 5-(2-aminopropyl)indole	
04/2012	2.2 g of a brown powder	Police	Szombathely	Confirmed as 5-(2-aminopropyl)indole	
05/2012	Residues on spoon	Police	Szentes	Confirmed as 5-(2-aminopropyl)indole	
05/2012	10.2 g of a brown powder	Police	Tata	Confirmed as 5-(2-aminopropyl)indole	

Date of seizure or collection	Amount and physical form	Seizing or collecting authority	Place of seizure or collection	Notes	Images
06/2012	0.2 g of a light-brown powder	Police	Szigetvár	Confirmed as 5-(2-aminopropyl)indole	
06/2012	7 beige tablets with 'Lexus' logo, also containing, methylthienylpropamine and caffeine	Police	Kiskőrös	Confirmed as 5-(2-aminopropyl)indole. Weight of tablets: 0.285 g, diameter: 8.10 mm, thickness: 5.8 mm. The identification was carried out by TLC and GC/MS based on the laboratory's 'own' reference materials (their structure was confirmed by NMR).	
08/2012	97.3 g of a brown powder, residues on digital scale	Police	Szigetvár	In this case the investigation confirmed the fact of dealing both new psychoactive substances (according to schedule "C" Gov. Decree 66/2012) and illicit drugs (covered by the illicit drugs definition of the Penal Code). Mail delivery and selling from the flat was also confirmed. The business covered the whole country did not concentrate on the area of Szigetvár.	
Netherlands					
Not available	20.5 kg	Customs		Not available	
Sweden					
	23 seizures incorporating 30.87 g powder and 54 tablets.	Police		The first seizure comprising 13 g beige powder was seized by the police 16/05/2012 in Örnsköldsvik city with identification based on GC-MS, GC-IRD and NMR. Examples of seized tablets: One type of tablet in 6 materials: These are blue, green melange; round and curved with border; diameter 9.0 mm, width 4.0 mm, weight 0.25 g. Another type of tablet that occurred only in one material: brown, glittery tablet; round and flat and scored; diameter 6.0 mm, width 2.9 mm, weight 0.10 g.	

Date of seizure or collection	Amount and physical form	Seizing or collecting authority	Place of seizure or collection	Notes	Images
	Four seizures in total, comprising: three seizures of a brown powder weight a total of 11.07 g. One seizure of 5 tablets	Customs	Arlanda Airport, Sweden.	The three packages containing powder were from Spain. The package containing tablets were sent from United Kingdom.	
United Kingdom					
April 2012	500 mg brown powder	State's Analyst Guernsey	Purchased from the Internet	Confirmed as 5-IT succinate by NMR.	
May 2012	Pale brown powder containing succinate salt	TicTac Ltd.	Purchased from Internet £22.50 for 500 mg	Product label stated '5-IT' '500mg' 'NOT FOR HUMAN CONSUMPTION'. Analysis by GCMS. Molecular formula confirmed by High Res MS. Confirmed as 5-IT succinate by proton NMR.	

Date of seizure or collection	Amount and physical form	Seizing or collecting authority	Place of seizure or collection	Notes	Images
09/06/2012	One seizure of 116 packets. Blue unmarked tablet in packet	Police	Edinburgh, Scotland	<p>During the police investigation of one of the fatal cases from the United Kingdom where the presence of 5-IT was confirmed, the police were informed that the product consumed by the deceased had been purchased at a 'headshop' in Edinburgh. Police executed a search warrant at the Edinburgh premises and recovered a large quantity of items (160 productions) including bulk quantities of powders, herbal material and packaged products.</p> <p>One of the items submitted to the Forensic Science Laboratory contained 116 yellow packages labelled 'Benzofury' with a graphic displaying the structure of 5-APB. Four of these packages, selected at random, were examined and each found to contain a single blue unmarked biconvex tablet which were each analysed and found to contain 5-IT.</p> <p>Other items of interest recovered from the 'headshop' were: Yellow capsules labelled 'benzofury' found to contain brown powder containing 5/6-APB. 31 g of brown powder found to contain 5/6-APB. 174 packages (98 of one type and 76 of a second type) each containing 1 g of crystalline substance identified as methylthienylpropamine (MPA).</p>	
08/09/2012	One seizure of seven red and white gelatine capsules with no markings on them. Also contained diphenyl prolinol (D2PM).	Customs	Guernsey	The Guernsey Border Agency seized the capsules along with a number of Class B substances from a person arriving on the Island. Analysis was carried out by the Guernsey States Analyst.	
Norway					
17/04/2012	One seizure of 1 g in a small bag with zip-lock	Customs	Gardermoen, Oslo Airport	Identified with MS only.	

* The Forensic Institute of the National Tax and Customs Administration of Hungary reported 0 seizures of 5-IT.

Annex 3 — Deaths associated with 5-(2-aminopropyl)indole (5-IT) reported to the EMCDDA

Country	Date of death	5-(2-aminopropyl)indole (mg/L) in blood	Other substances present	Notes
Hungary	12 April 2012	Not determined 34 microg/ml (blood) (the toxicological examination identified it as AMT based on GC-MS, while the substance found next to the bodies was finally confirmed to be 5-(2-aminopropyl)indole by FTIR and NMR)	Not specified	40 year old male found dead in his flat beside his companion. No signs of forcible entry in the room or external injuries on the body. Signs of long sexual intercourse, extreme hyperthermia and the use of psychoactive substances. Cause of death 'Circulatory failure and respiratory failure were the direct causes of death that were the results of 5-IT intoxication.'
Hungary	12 April 2012	Not determined 84 mikrog/ml (blood) (the toxicological examination identified it as AMT based on GC-MS, while the substance found next to the bodies was finally confirmed to be 5-(2-aminopropyl)indole by FTIR and NMR)	Not specified	35 year old female found dead in her flat beside her companion. No signs of forcible entry in the room. Some external injuries (due to faint/fall) but no sign of violence. Signs of long sexual intercourse, extreme hyperthermia and the use of psychoactive substances. Cause of death 'Circulatory failure and respiratory failure were the direct causes of death that were the results of 5-IT intoxication.'
Sweden 15 deaths	April – June 2012	0.7 to 5.2 microg/mL blood In one case 18.6 microg/mL blood	In two cases, 5-(2-aminopropyl)indole was the only substance found and in the other cases, it was found in combination with pharmaceuticals or other drugs (not specified)	All of the deceased were men, 13 of whom were aged 20-30 years, the remaining two were over 30. In 14 of the cases the cause of death is considered to be related to 5-(2-aminopropyl)indole and in the remaining case the cause was disease.

Country	Date of death	5-(2-aminopropyl)indole (mg/L) in blood	Other substances present	Notes
United Kingdom	June 2012	0.379 mg/L	5-APB (0.016 mg/L), 6-APB (0.057 mg/L), diazepam (0.037 mg/L), nordiazepam (0.009 mg/L), temazepam (0.001 mg/L) and AMT (less than 0.01 mg/L). Urine analysis detected amphetamine, 5-(2-aminopropyl)indole, 5-APB, 6-APB, AMT and benzodiazepines. In addition, 5-(2-aminopropyl)indole, 5-APB, 6-APB, AMT and diazepam were detected in the stomach contents.	Cause of death was 'fatality following the ingestion of 'Benzo Fury'' and certified as '5-(2-aminopropyl)indole (5-API; 5-IT) and Benzofuran toxicity'
United Kingdom	June 2012	0.300 mg/L in post-mortem blood and approximately 0.513 mg/L in ante-mortem blood	MDMA (0.468 mg/L ante-mortem blood, 0.502 mg/L post-mortem blood), MDA (0.036 mg/L ante-mortem blood, 0.046 mg/L post-mortem blood), 6-APB (0.005 mg/L post-mortem blood only), atropine and lignocaine.	It was noted that there was a high concentration of MDMA, which in isolation was considered to be at a fatal level however, a cumulative/synergistic effect of 5-(2-aminopropyl)indole was not excluded and the cause of death was recorded as 'multidrug toxicity'.
United Kingdom 2 deaths	Not known	Not specified	5-/6-APB in one case and other drugs (not specified)	In a letter to the British Medical Journal the authors from Centre for Forensic and Legal Medicine, University of Dundee, United Kingdom 'identified 5-IT in postmortem blood samples of two young adults.' Further details were not available.

Cataloguing data

European Monitoring Centre for Drugs and Drug Addiction
Europol

EMCDDA–Europol Joint Reports

EMCDDA–Europol Joint Report on a new psychoactive substance: 5-(2-aminopropyl)indole

Luxembourg: Publications Office of the European Union

2013 – 36 pp. – 21 x 29.7 cm

ISBN: 978-92-9168-596-7

DOI: 10.2810/85464

EMCDDA–Europol Joint Reports

In the European Union, Council Decision 2005/387/JHA provides a legal mechanism for the information exchange (the early warning system), risk assessment and control of new psychoactive substances. When a new substance is detected in a Member State, information on its manufacture, traffic and use is transmitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Police Office (Europol) via the Reitox national focal points and Europol national units. The data are also submitted for information to the European Commission and the European Medicines Agency. Under Article 5.1 of the Council Decision where the EMCDDA and Europol, or the Council of the European Union, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information is collated and presented by Europol and the EMCDDA in the form of a Joint Report. This EMCDDA-Europol Joint Report forms the basis on which a decision may be taken by the Council of the European Union on whether or not to launch a risk assessment of the substance.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the hub of drug-related information in Europe. Its mission is to provide the EU and its Member States with 'factual, objective, reliable and comparable information' on drugs, drug addiction and their consequences. Established in 1993, it opened its doors in Lisbon in 1995 and is one of the EU's decentralised agencies. With a 100-strong multidisciplinary team, the agency offers policymakers the evidence base they need for drawing up drug laws and strategies. It also helps professionals and researchers pinpoint best practice and new areas for analysis. As well as gathering information on the demand and reduction of the demand for drugs, the agency in recent years has extended its monitoring and reporting on drug supply, supply reduction and illicit drug markets.

www.emcdda.europa.eu

About Europol

Europol is the European Union's law enforcement agency handling criminal intelligence. Its aim is to improve the effectiveness of, and cooperation between, the competent authorities in the EU Member States in preventing and combating serious international organised crime and terrorism. Operational since 1999 and based in The Hague, the organisation employs some 600 staff to support national law enforcement agencies in their everyday work, including efforts to tackle illicit drug trafficking, money laundering, cyber crime and terrorism. Europol comes into play when an organised criminal structure is involved and two or more EU Member States are affected. Among others, it facilitates cross-country information exchange and provides analysis of operations.

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Publications Office

ISBN 978-92-9168-596-7



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