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EMCDDA–Europol 2012 Annual Report on the implementation of Council Decision 2005/387/JHA

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EMCDDA–Europol 2012 Annual Report on the implementation of Council Decision 2005/387/JHA

In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

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Overview

This report presents the activities implemented by the EMCDDA and Europol in 2012 in support of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances (hereinafter referred to as the Council Decision) ([1]).

This year was particularly busy for those involved in detecting, monitoring and responding to new psychoactive substances across the European Union (EU) ([2]). The unprecedented growth in the number, type and availability of new drugs over the past few years has also seen the phenomenon take on global significance. The reasons for the growth in this market include the increasing complexity and volatility of the drugs market set against a backdrop of globalisation and technological advancement. The rapid appearance of non-controlled alternatives to controlled drugs underlines the ability of the market to respond to changes in the legal status of psychoactive substances. In addition, an important development has been the growing interaction between the illicit and 'legal highs' markets, whereby some substances are legally sourced and either sold directly on the illicit market or turned into products and sold as 'legal highs'. It is well established that organised crime is involved in some of these activities and continues to exploit the opportunities presented by the market in new drugs.

New psychoactive substances, particularly the so-called 'legal highs', continued to be a high policy priority in the EU and many Member States. This was evidenced by responses at national level including awareness raising, new legislative measures, and the inclusion of new psychoactive substances in general population surveys. As announced in the communication 'Towards a stronger European response to drugs' ([3]), the European Commission is currently preparing and will propose new EU legislation on new psychoactive substances taking into account the rapid developments in this field and scientific evidence on the risks posed by these substances. The EMCDDA participated in many development activities in 2012 in support of the efforts in this field, the most notable of which are described in the body of this report.

Headline activities in 2012

- 73 new psychoactive substances were officially notified for the first time through the EU Early warning system (EWS) in 2012, up from 49 in 2011, 41 in 2010 and 24 in 2009.
- A Joint report was produced and a risk assessment conducted on 4-methylamphetamine (4-MA) after 21 deaths in total were reported by four Member States. The substance will now be subjected to control measures throughout the EU.
- A Joint report was produced on 5-(2-aminopropyl)indole (5-IT) after 21 deaths were reported by three Member States over a short period of time. The substance will be risk-assessed by the Scientific Committee of the EMCDDA in April 2013.
- 693 Internet shops were identified by the EMCDDA selling 'legal highs' to consumers in the EU in 2012. This compares to 314 shops identified in January 2011 and 170 in January 2010.

As highlighted in the first joint EMCDDA and Europol strategic analysis of the drug market in the EU ([4]), 73 new psychoactive substances were officially notified for the first time in 2012 through the EU Early warning system (EWS), the information exchange mechanism that was set up by the Council Decision. This is the largest number of substances ever reported in a single year, considerably up from the 49 substances reported in 2011, 41 in 2010 and

([1]) Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances, OJ L 127, 20.5.2005, p. 32.
([2]) This report uses the terms 'new psychoactive substances' and 'new drugs' interchangeably.
([3]) European Commission (2011), *Communication from the Commission to the European Parliament and the Council, Towards a stronger European response to drugs*, Brussels, 25.10.11, COM(2011) 689/2.
([4]) EMCDDA and Europol (2013), *EU drug markets report: a strategic analysis*, Publications Office of the European Union, Luxembourg.

24 in 2009. The list of new substances notified in 2012 was dominated by 30 synthetic cannabinoids ([5]) and 19 compounds classed as 'others' which do not conform to the main categories currently used by the EMCDDA. Together, these two groups represented about two-thirds of the total number of substances reported in 2012 (Annex 1 and Annex 2). Overall, the number of substances notified in the last two years accounts for more than half of the total number of substances notified under the terms of the Council Decision since May 2005.

In 2012, the EMCDDA and Europol produced two Joint reports on the new psychoactive substances 4-MA and 5-IT, in accordance with Article 5 of the Council Decision. The findings are summarised in this report.

The Joint report on 4-MA ([6]) led to a formal risk assessment that was conducted in November by the extended Scientific Committee of the EMCDDA. The risk assessment report detailed 21 deaths in four Member States (Belgium, Denmark, Netherlands, and the United Kingdom), where 4-MA was detected in post-mortem samples ([7]). These detections were either alone or in combination with other substances, in particular amphetamine. The report also described how 4-MA could have serious adverse effects, such as hyperthermia, hypertension, anorexia, nausea, headache, insomnia, paranoia and anxiety. Fourteen European countries provided data on seizures of the drug where it had been sold as amphetamine and frequently mixed with it. 4-MA has no established medical value or known legitimate purpose, aside from limited use in scientific research and as an analytical reference standard.

The Joint report on 5-IT ([8]) was produced after the substance was considered by the EMCDDA and Europol to be causing significant concern in several EU Member States. It was first detected in Norway in April 2012, and subsequently by authorities in seven countries. It was associated with 21 deaths in three Member States (Hungary, Sweden, and the United Kingdom). As a result of the report, the Council of the European Union requested that the EMCDDA conduct a formal risk assessment on the substance, which is planned for April 2013.

([5]) A more precise term for these compounds is 'synthetic cannabinoid receptor agonists', however, the term 'synthetic cannabinoids' has been widely accepted and is therefore used throughout the report.

([6]) EMCDDA and Europol (2012), *EMCDDA–Europol joint report on a new psychoactive substance, 4-methylamphetamine*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_191982_EN_TDAS12001ENN.PDF

([7]) Council of the European Union (2012), *Risk assessment report on the new psychoactive substance 4-methylamphetamine*, 17275/12 CORDROGUE 98 SAN 320. Available at: http://register.consilium.europa.eu/pdf/en/12/st17/st17275.en12.pdf

([8]) EMCDDA and Europol (2012), *EMCDDA–Europol joint report on a new psychoactive substance, 5-(2-aminopropyl)indole*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-reports/5-IT

1. Introduction and background

As part of the response to new psychoactive substances within the EU, the Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances established a mechanism for the rapid exchange of information on substances that may pose public health and social threats, including the involvement of organised crime (Box 1). This provides a legal basis for EU institutions and Member States to monitor all new narcotic and psychotropic substances that appear on the European drug scene ([9]). Where necessary, the Council Decision also provides for an assessment of the risks associated with these new substances, so that control measures deriving from Member States' obligations to the United Nations international drug control conventions ([10]) can also be applied to new psychoactive substances.

The EMCDDA and Europol, in close collaboration with their respective expert networks, the Reitox national focal points and Europol National Units, are assigned a central role in detecting, notifying and monitoring new psychoactive substances (Article 4 of the Council Decision). Furthermore, where necessary, and in cooperation with the European Medicines Agency (EMA), the two organisations may collect, analyse and present information on a new psychoactive substance in the form of a Joint report (Article 5). The Joint report provides evidence to the Council of the European Union and the European Commission on the need to request a risk assessment on a new psychoactive substance. Such a risk assessment examines the health and social risks posed by: the use of, manufacture of, and, traffic in, a new psychoactive substance; the involvement of organised crime; and, the possible consequences of control measures. In order to conduct the risk assessment, the EMCDDA convenes a special meeting under the auspices of its Scientific Committee, extended with additional experts as necessary (Article 6).

To ensure transparency in the implementation of the Council Decision, Article 10 stipulates that: 'The EMCDDA and Europol shall report annually to the European Parliament, the Council and the Commission on the implementation of this Decision. The report will take into account all aspects required for an assessment of the efficacy and achievements of the system created by this Decision. The report shall, in particular, include experience relating to coordination between the system set out in this Decision and the Pharmacovigilance system'.

In compliance with Article 10, the EMCDDA and Europol herewith present the eighth such Annual Report on the implementation of the Council Decision, covering the period January to December 2012. The report outlines the results of the implementation, describes key issues arising from accumulated experiences, and also serves as a monitoring tool. In order to facilitate the reading of the report, the reader is referred to the full text of the Council Decision (Appendix).

The report is written as a standalone document with annexes kept to a minimum ([11]). Annex 1 provides the list of new psychoactive substances notified in 2012. This includes the systematic chemical name, the reporting country, and date of notification for each substance. Comprehensive information on the new substances described in the report is available from the EMCDDA and Europol. Annex 2 provides a list of those new substances notified in 2012 categorised as 'others'. Annex 3 provides the legal and working definitions used by the EMCDDA to classify and describe new drugs. The reader should note that these definitions were further developed during 2012 to reflect changes in the phenomenon. Finally, Annex 4 provides an overview of the main groups of new psychoactive substances monitored by the EWS and their molecular characteristics.

([9]) See definitions in Annex 3.
([10]) The 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.
([11]) Where possible, the report avoids the use of overly technical discussion and language, however, this is occasionally unavoidable given the nature of the phenomenon.

New drugs in Europe at a glance

The EMCDDA and Europol have played a central role in the detection, monitoring and assessment of new drugs in Europe since 1997. During this time, the new drug phenomenon has evolved to become one of the most important contemporary developments in the drugs field, with the past few years seeing unprecedented growth in their number, type and availability.

- The EU Early warning system (EWS) operated by the EMCDDA and Europol currently monitors more than 280 new psychoactive substances.
- 73 new psychoactive substances were officially notified for the first time in the EU through the EWS in 2012, up from 49 in 2011, 41 in 2010 and 24 in 2009.
- Since 1997, 13 substances have been risk-assessed. Of these, eight (4-MTA, PMMA, 2C-I, 2C-T-2, 2-C-T-7, TMA-2, BZP, mephedrone) are now controlled across the EU and one (GHB) is controlled at international level. 4-Methylamphetamine (4-MA) is in the process of being subjected to control measures across the EU.
- The main groups of substances monitored by the EWS are: phenethylamines (with stimulant, entactogenic or hallucinogenic effects, such as PMMA and 2C-I); tryptamines (which have predominantly hallucinogenic effects, such as AMT and 5-MeO-DALT); piperazines (which exhibit predominantly stimulant effects, such as mCPP and BZP); cathinones (such as mephedrone, methylone and MDPV, which exhibit stimulant effects); synthetic cannabinoids (which can have hallucinogenic and depressant effects); and, a broad group of substances that do not strictly belong to any of the previous groups.
- The Internet appears to be playing a growing role in shaping the market in new drugs. 693 Internet shops selling 'legal highs' to EU consumers were identified by EMCDDA monitoring in 2012. This compares to 314 shops identified in January 2011 and 170 in January 2010.
- A 2011 Eurobarometer survey of young people aged 15–24 from across the EU found that while lifetime use of 'legal highs' in most Member States was 5 % or less, use in the United Kingdom, Latvia, Poland and Ireland was 8 %, 9 %, 9 % and 16 % respectively.

Further information on new drugs can be found at: www.emcdda.europa.eu/activities/action-on-new-drugs

2. Implementation arrangements and cooperation with the EU Pharmacovigilance system

2.1. Specific implementation arrangements

2.1.1. Assistance to national early warning systems

The Action on new drugs team within the EMCDDA regularly provides support to the national early warning systems within the national focal points in order to assist them in the identification of new substances. In addition, other requests for assistance related to the new drug phenomenon are regularly received from the Member States, EU agencies and other institutions, individual experts, third countries and the media. In order to ensure an effective and efficient response to this growing number of requests, the EMCDDA has established a rapid response team.

Building on improvements developed over the past few years, 2012 saw the routine exchange of instrumental analytical data such as GC-MS, FT-IR and NMR ([12]) spectra for the 73 new substances that were notified. These data, along with additional analytical data from substances already reported, were also included in the substance profiles on the European Database on New Drugs (EDND). By providing the data in common formats, laboratories are then able to import them directly into their instruments. In this way, laboratories across Europe can ensure that their analytical libraries are up-to-date, thus improving the capacity and speed in which new substances can be detected. This approach is becoming of growing importance to laboratories as the chemistry of new drugs becomes increasingly complex, and more advanced analytical techniques are often needed to elucidate their molecular structure.

While provision of analytical data plays a key role in identifying new drugs, the EMCDDA has also begun to collect national risk assessments on new psychoactive substances on a routine basis, and has made them available on the EDND in order to help inform policy responses in the Member States.

Also in 2012, the EMCDDA published a compendium providing a comprehensive overview of the 30 national early warning systems that participate in the EWS network ([13]). The publication aims to promote best practice and enhance the exchange of experiences from the national level. Furthermore, the document also serves to assist third parties who may be considering implementing an early warning system — a common enquiry to the EMCDDA from countries outside the EWS network. The document is available on the EMCDDA website ([14]).

The EMCDDA is in the process of preparing to provide assistance in the form of training on the EWS in the context of the project for Pre-Accession Assistance (IPA) beneficiaries ([15]) in Prague in April 2013.

2.1.2. Annual meeting of the Reitox EWS network

The 12th Annual meeting of the Reitox Early warning system network was held in Lisbon on 24–25 May 2012. Participants included representatives from the 27 EU Member States, Croatia, Turkey and Norway. The two candidate countries Serbia and the former Yugoslav Republic of Macedonia and the potential candidate countries Albania and Kosovo ([16]) were also represented. Europol was also represented. Invited expert speakers attended from Finland, the United Kingdom and the United States of America. The meeting was split into the following sessions:

([12]) Gas chromatography–mass spectrometry, Fourier transform-infrared spectrometry and nuclear magnetic resonance spectrometry are some of the typical analytical techniques used to identify new psychoactive substances.
([13]) The 27 EU Member States, Croatia, Turkey and Norway.
([14]) EMCDDA (2012), *Early warning system — national profiles*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/thematic-papers/ews
([15]) Participating countries: Albania, Bosnia and Herzegovina, Serbia, Montenegro, the Former Yugoslav Republic of Macedonia, Kosovo (this designation is without prejudice to positions on status, and is in line with UNSCR 1244 and the ICJ Opinion on the Kosovo declaration of independance), Turkey and Croatia.
([16]) This designation is without prejudice to positions on status, and is in line with UNSCR 1244 and the ICJ Opinion on the Kosovo declaration of independence.

- the implementation of the Council Decision;
- updates from the national EWS correspondents;
- mephedrone, the continuation: promises and pitfalls;
- new approaches for monitoring new drugs and trends in drug use; and,
- controlling new psychoactive substances.

During the sessions, delegates heard about the recent experiences of the Member States and were updated on the developments in the field. Relevant highlights are provided below.

The Belgian national focal point provided an overview of their experience with 4-MA, which was associated with a cluster of deaths that occurred over a short period of time. A formal information request under Article 5.1 of the Council Decision was launched during the meeting in order to provide further information for the Joint report. Details of the Joint report and risk assessment of 4-MA are provided in Sections 3.2.1 and 3.2.2, respectively.

The Hungarian national focal point provided an overview of a two-day workshop on 'Exchange on data collection challenges related to new psychoactive substances use', which took place in Budapest in April 2012. Representatives from 10 Member States and the EMCDDA attended. A summary of the workshop is available on the Hungarian national focal point website ([17]). The national focal point also provided an update on the amendments to Hungarian legislation concerning new psychoactive substances. The amendments introduced a new schedule, which includes a list of named substances and four distinct generic definitions for synthetic cannabinoids, cathinones, tryptamines and phenethylamines.

The EMA provided an update on the cooperation with the EMCDDA, in particular in relation to the EU Pharmacovigilance system.

Experts from the United Kingdom and Finland discussed two novel approaches for monitoring for new psychoactive substances and their metabolites in human waste products. These pioneering methods are being actively supported by the EMCDDA and will be closely monitored and developed in the coming years. More information on this can be found in section 4.3 and on the EMCDDA website ([18]).

A presentation from Cambridge University described how computational methods can be used to predict the potential properties of new substances, including their toxicity and psychoactivity (section 4.4). A guest speaker from the Addiction Research Institute at Austin University, Texas provided an overview of drug trends and use patterns in the United States (US). Of particular note in this presentation was the recent increase in reports of exposure to synthetic cannabinoids and synthetic cathinones to public health agencies.

2.1.3. Structured monitoring of the Internet — online availability of 'legal highs'

Part of the reason for the growth in the availability of new drugs over the past few years is due to the sophisticated ways in which drugs such as the so-called 'legal highs' can now be marketed and distributed. This includes advertising and selling them on an open market, including through online shops and in 'bricks and mortar' head shops. In order to monitor the online market and to get a better understanding of how this affects the availability of new drugs, the EMCDDA has conducted multilingual snapshots since 2006. The snapshots function as a rapid assessment of the market and are undertaken during a limited time window. Information collected in these snapshots can provide insights into the market characteristics, including:

- the number of online shops offering to sell new drugs to consumers in at least one EU Member State and, for these shops:
- the names and prices of the substances and products that are offered for sale;
- the marketing and distribution techniques used;
- the number of businesses in a particular geographical area; and,
- the detection of new drugs that have not yet been identified through chemical analysis of seizures, test purchases or biological samples.

In 2012, a snapshot was conducted in 20 EU languages, as well as Norwegian, Russian and Ukrainian. Along with other key information on this market, the snapshot identified 693 shops selling 'legal high' type products. This compares to 314 shops identified in January 2011 and 170 in January 2010 ([19]). Targeted Internet searches were also conducted

([17]) Hungarian national focal point (2012), *Exchange on data collection challenges related to new psychoactive substances use*, Hungarian national focal point, Budapest. Available at: http://drogfokuszpont.hu/wp-content/uploads/workshop_summary_final.pdf
([18]) http://www.emcdda.europa.eu/wastewater-analysis
([19]) EMCDDA (2011), *Online sales of new psychoactive substances/'legal highs': summary of results from the 2011 multilingual snapshots*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/scientific-studies/2011/snapshot

in English in support of the EMCDDA–Europol Joint reports on 4-MA and 5-IT.

The methodology used for the snapshot series is currently being revised with support from the ICT unit at the EMCDDA. This work will lead to improvements in the scope, coverage and robustness of the methodology. Overall, these revisions will allow the continual monitoring of both the online market in new drugs and the emerging online market in controlled drugs.

2.1.4. Supporting activities

In support of the Council Decision, the EMCDDA regularly organises and participates in events and activities, often in collaboration with partners. These activities are designed to develop the EWS network and provide support to others working in the field of new drugs. These events and activities provide a platform to improve collaboration among EWS partners and promote areas of best practice where possible. Some of the most significant activities carried out in 2012 are described below.

First international conference on novel psychoactive substances

The 'ever-changing world of psychoactive drugs' was the title and focus of the First international conference on novel psychoactive substances. The conference was a joint initiative of the EU-funded Recreational Drugs European Network (ReDNet) project and the EMCDDA, and was held in Budapest in March 2012.

The aim of the conference was the exchange of scientific knowledge on new psychoactive substances and the forensic, clinical and legal challenges faced by practitioners. The programme was based around four key themes: clinical challenges; novel prevention models for novel compounds; legal challenges; and, substance misuse and lifestyle. International experts, including many partners from the EWS network and members of the EMCDDA Action on new drugs team, delivered over 60 presentations.

Building on this, a second conference will be held in Swansea, United Kingdom in September 2013 and will focus on the latest research on the effects of new drugs in humans.

NIDA–EMCDDA second international forum on new drugs

In June 2012, the United States National Institute on Drug Abuse (NIDA) and the EMCDDA co-organised and co-hosted the Second interdisciplinary forum on new and emerging psychoactive substances in Palm Springs, US. The event gathered over 300 participants from 72 countries. Building on the First international multidisciplinary forum on new drugs that was organised by the EMCDDA in Lisbon in May 2011, the event brought together leading US, European and other international experts to examine the issue from a global perspective. The EMCDDA gave one of the keynote presentations as well as six other presentations during the event.

During the event, updates were provided by the EU, Australia, Japan, the US, as well as the United Nations Office on Drugs and Crime (UNODC). These presentations explored the appearance and use of new drugs, as well as how they are detected, monitored, risk-assessed and controlled. The updates revealed important commonalities between countries in the marketing and use of new drugs as well as the responses to this phenomenon.

Importantly, the challenges posed by new psychoactive substances for prevention and treatment were also addressed at the event. Discussions considered individual substances, as well as the broader new drugs phenomenon, the implications for the treatment of acute toxicity and the prevention of use. Presentations included: insights from hospital emergency departments in the United Kingdom; prevention strategies from Poland; and, medical experts from the US who examined synthetic cannabinoids and piperazines.

Europol–EMCDDA law enforcement expert meeting on new psychoactive substances

In September 2012, an expert meeting on new psychoactive substances was held at the headquarters of Europol in the Hague, co-organised and co-chaired by the EMCDDA and Europol. This meeting was foreseen in the EMPACT (European Multidisciplinary Platform Against Criminal Threats) Operational Action Plan (OAP) for 2012 under the priority to 'reduce the production and distribution in the EU of synthetic drugs including new psychoactive substances'. The aim of the meeting was to raise awareness of new psychoactive substances as well as to improve the response by law enforcement, including the information flow to Europol. Representatives from law enforcement from 26 EU Member States and Norway attended.

Europol and the EMCDDA set the scene by presenting the EWS and an overview of the current situation in Europe. The European Commission presented some of the challenges facing EU legislators in terms of tackling the issue. A representative from the Belgian Federal Police provided an overview of the situation in Belgium. This included case

studies demonstrating the scale of the phenomenon as well as the modus operandi of some of the groups involved in making 'legal high' products.

Europol highlighted the global nature of the challenge faced by law enforcement by providing an overview of a multi-national police operation involving 12 EU Member States, Australia, the US and Eurojust (the EU agency responsible for judicial cooperation), which targeted a Chinese supplier involved in trafficking large quantities of new psychoactive substances.

There was an acknowledgement at the meeting that law enforcement has a particularly challenging task when responding to new psychoactive substances and that considerable effort is required to address this. There was, however, an equally strong message that this is an issue that law enforcement is willing to tackle. An area of concern expressed was the requirement for clear definitions for this area of work, which would enable law enforcement officers across Europe to communicate more effectively. It was also identified that customs authorities have a key role to play and therefore close collaboration by all law enforcement agencies is required.

At the conclusion of the meeting it was proposed that:

- There could be a network of law enforcement correspondents who would provide a point of contact for Europol for matters involving new psychoactive substances. In addition, such a network could meet to discuss the issues of new psychoactive substances, perhaps coinciding with the Reitox EWS annual meeting and thus taking the opportunity to develop and enhance the relationship with the national focal points.
- Law enforcement representatives from the Member States who were unaware of their Reitox national focal point were encouraged to make contact with them.
- Law enforcement representatives from the Member States would make efforts to improve information flow to Europol.
- The EMPACT OAP activities for the forthcoming year would be updated to reflect the proposals above.
- A follow-up meeting involving experts from EU law enforcement agencies will be held in 2013 at the EMCDDA in Lisbon.

2.2. Cooperation with the EMA and the Pharmacovigilance system

The EMA is a key partner in the implementation of the system set up by the Council Decision. The EMCDDA and EMA have established protocols for bilateral exchange of information on the basis of data available through the EWS and the EU Pharmacovigilance system. The existing databases of the two agencies, EudraVigilance at the EMA and the European Database on New Drugs (EDND) at the EMCDDA, are used to enable reliable and rapid exchange of information between the two agencies.

On 7 September 2012 in Lisbon, a revised working arrangement was signed by the Directors of the EMCDDA and EMA. The arrangement enhances cooperation between the two agencies, including the exchange of information on the abuse of medicinal products as part of the Pharmacovigilance system ([20]).

As part of the EWS, the two agencies regularly exchange information on new psychoactive substances, as well as ad hoc reports relating to the misuse of medicinal products in order to complement the Pharmacovigilance system ([21]).

In 2012, formal consultations and exchange of information took place between the EMCDDA and EMA regarding 4-MA (section 3.2.1) and 5-IT (section 3.2.3).

([20]) http://www.emcdda.europa.eu/about/partners/ema

([21]) An example of this in 2012 was the exchange of information from EudraVigilance related to the abuse of zopiclone, a medicinal product authorised in some Member States for the treatment of insomnia.

3. Formal activities

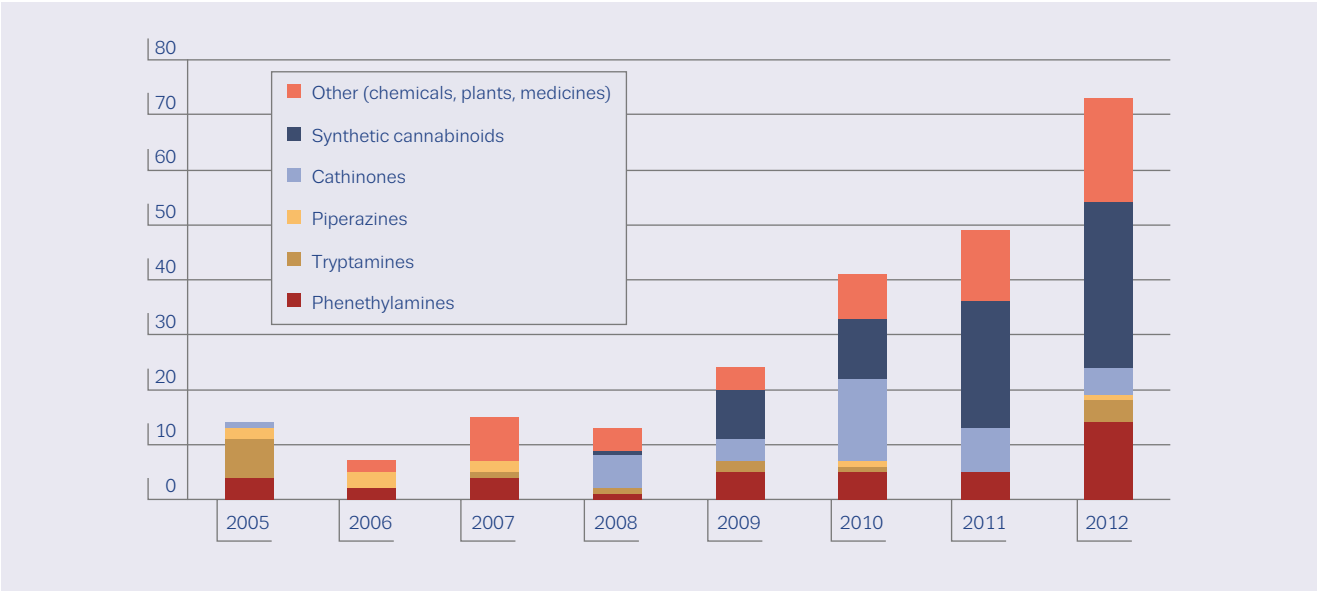
3.1. New psychoactive substances notified in 2012

During 2012, a total of 73 new psychoactive substances were formally notified for the first time through the EWS (Figure 1 and Annex 1). This continues the trend of year-on-year increases that began in 2008. In part this may be due to the increased detection and reporting capacities of Member States, arising from a growing concern about these substances and the need for high quality information by decision-makers in order to inform policy responses. The EMCDDA has supported these developments with the entire EWS network benefiting from the outputs of such national initiatives. These data can then be used by policymakers, government departments and advisory bodies in order to inform policy responses. In addition, such data can serve to provide timely harm reduction messages when appropriately contextualised.

For monitoring purposes, the EMCDDA categorises new psychoactive substances by the chemical family to which they belong. This is the case with phenethylamines, tryptamines, piperazines and cathinones. In the case of the synthetic cannabinoids, these are currently categorised on the basis of their mode of action rather than their chemical family. The remaining substances are categorised as miscellaneous 'others' (Box 2).

In 2012, the list of new substances was dominated by 30 synthetic cannabinoids and 19 miscellaneous 'others'. Together these represented two-thirds of the total number of substances reported in 2012 (Figure 1, Annex 1 and Annex 2).

Figure 1: Number of new psychoactive substances notified for the first time to the EWS since May 2005 ([22])



([22]) In some previous reports, the figure used in graphical representations for the number of new psychoactive substances notified in 2007 was 16. The correct figure, as shown above, is 15, as was reported in the EMCDDA–Europol 2007 Implementation Report. It is thought that this situation may have arisen as 16 new substances appeared in Annex 2 of that report. However, as noted in the report, nimetazepam (Annex 2, substance 12) is controlled under the 1971 United Nations Convention on Psychotropic Substances and is therefore outside of the scope of the Council Decision.

3.1.1. Synthetic cannabinoids

In 2012, 30 new synthetic cannabinoids were formally notified to the EWS. These substances make up the largest group of compounds monitored by the EWS, with 74 notified since 2008. However, this group is based on mode of action rather than chemical family and therefore direct comparisons in terms of numbers should be made with caution.

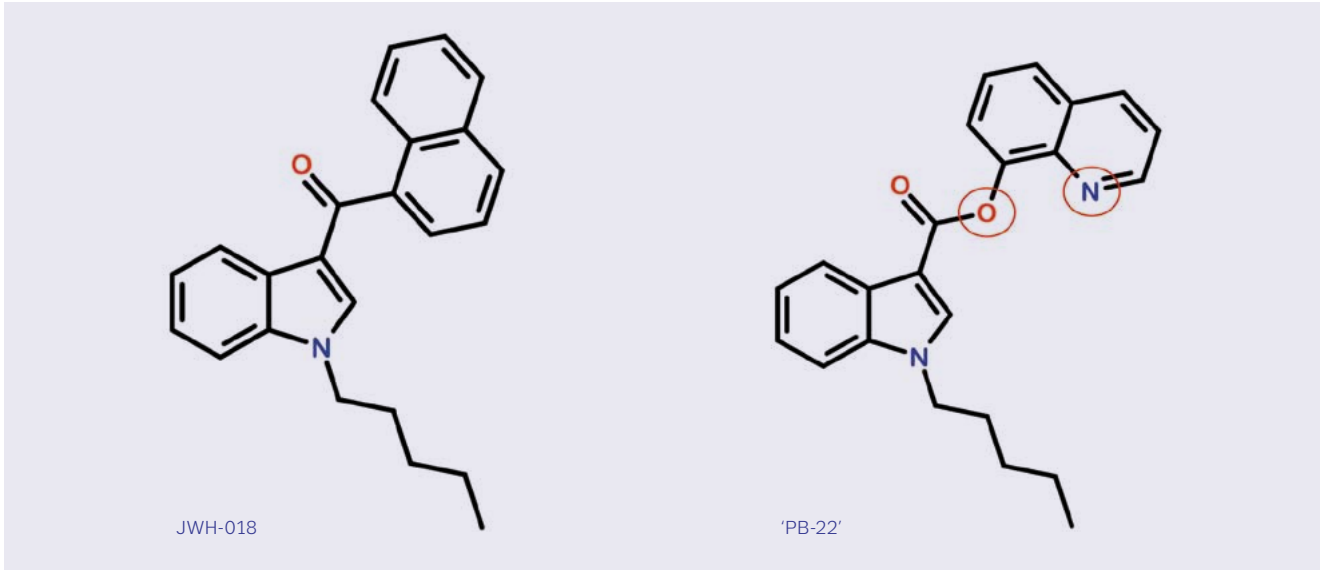
For some of the synthetic cannabinoids that have been notified, there is an existing body of scientific literature about their chemistry, structure-activity relationships, potency and effects. This literature appears to be exploited by those involved in the trade of synthetic cannabinoids leading to the appearance of a growing number of new substances with similar core structures to the studied compounds but with minor chemical modifications. These may be attempts to circumvent drug control laws, however, these new substances may exhibit different chemical and pharmacological properties compared to the synthetic cannabinoids that have been studied. Indeed, frequently in 2012, new synthetic cannabinoids were notified about which little could be found in the scientific literature, perhaps indicating a degree of experimentation on the part of the producer. One such example is JWH-018 carboxylate, quinolinyl derivative (Annex 1, substance 58), which has been offered for sale on the Internet under the name 'PB-22'. This substance is based on JWH-018, a well-studied synthetic cannabinoid named after John W. Huffman, the researcher who first synthesised and characterised the substance. In the case of the 'PB-22', two modifications have been made to the basic molecule to produce a substance with properties that can only be speculated. This substance was notified in December by the Finnish national focal point, which provided details of a case where 54 kilograms were intercepted by customs authorities. The package was sent from China, a common source of the bulk new psychoactive substances, and was en route to Russia.

3.1.2. Phenethylamines

In 2012, 14 new substituted phenethylamines were formally notified to the EWS. This is more than twice the number detected in any previous year and accounts for approximately one-third of all the phenethylamines detected since 2005.

In previous years, the phenethylamines that have emerged on the new drugs market have mainly been limited to those described by Shulgin et al. ([23]). Significantly, six phenethylamine derivatives were notified in 2012 that contain a chemical group called '*N*-2-methoxybenzyl', which is often abbreviated in chemistry as '-NBOMe' ([24]). Studies on some of these compounds have shown that in terms of binding affinity these derivatives are an order of magnitude

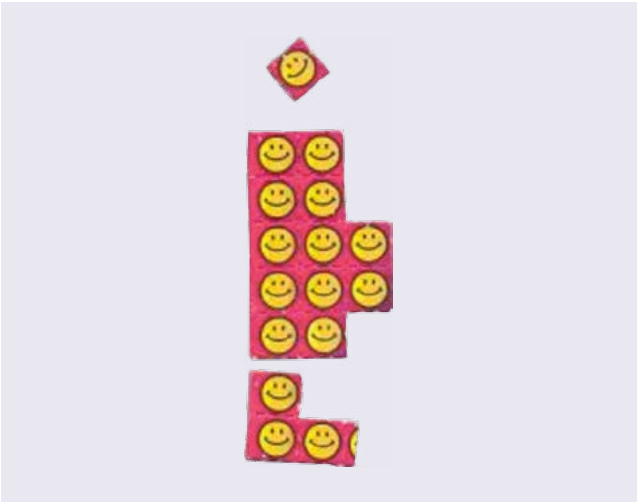
Figure 2: Structure of JWH-018 and 'PB-22'



JWH-018 'PB-22'

([23]) Shulgin, A., et al. (2011), *The Shulgin index volume 1: psychedelic phenethylamines and related compounds*, Transform Press, Berkeley.
([24]) This abbreviation has provided a convenient headline for media reports regarding the dangers of so-called 'N-bomb' drugs.

Figure 3: 25B-NBOMe 'blotters' (Annex 1, Substance 66), Norwegian national focal point



more potent than their parent phenethylamine compounds. This finding is supported by reports to the EWS detailing the seizure of 'blotters' and sugar cube dosage forms, which are typically used to administer drugs that are active in the microgram range (such as LSD).

By the end of 2012, no adverse effects had been reported to the EWS that were associated with these potent phenethylamine substances. However, media reports from the US and Australia suggest that their use has been associated with non-fatal intoxications and deaths. The EWS network is well-informed about the potential dangers posed by '-NBOMe' substances and remains vigilant in light of this new trend. In this respect, at the time of writing this report (March 2013), the first reports of non-fatal intoxications within the EU have been made to the EWS and a public health warning was issued by the EMCDDA.

3.1.3. Tryptamines

In 2012, four new tryptamine derivatives were formally notified to the EWS. Although a small number, it is more than was notified in the previous three years combined.

Three of the new tryptamine substances were detected in powders that were seized by the authorities in 2011. This illustrates that there is often a time lag between when samples are seized or collected and when the notifications are sent to the EMCDDA or Europol.

3.1.4. Cathinones

In 2012, five new synthetic cathinone derivatives were formally notified to the EWS. This compares to eight notified in 2011 and 15 in 2010.

3.1.5. Piperazines

In 2012, one new piperazine was formally notified to the EWS. The substance, 1-(3-methylbenzyl)piperazine, is a derivative of benzylpiperazine (BZP) and a structural isomer of methylbenzylpiperazine (MBZP). This new substance was detected in a urine sample along with the synthetic cathinone derivative MDPV (methylenedioxypyrovalerone), which was first notified to the EMCDDA in 2008. Notably, only two new piperazine derivatives have been notified since 2008.

3.1.6. Miscellaneous 'others' substances

In 2012, 19 new miscellaneous 'other' substances were formally notified to the EWS. This diverse group contains substances that do not fit the established EMCDDA categories described above. They are presented for ease of reference in Annex 2. Of note is the detection of several derivatives of controlled drugs within this category:

- 5-APDB, 6-APDB and 5-APDI (Annex 1, refs. 15, 17 and 54, respectively). These are mono- or di-deoxygenated derivatives of the stimulant drug methylenedioxiamphetamine (MDA);
- thienoamphetamine (Annex 1, ref. 13) a thiophene analogue of amphetamine;
- 3-MeO-PCP, 2-MeO-ketamine and N-ethylnorketamine (Annex 1, refs. 21, 50 and 53, respectively). These are derivatives of the dissociative drug phencyclidine (PCP) and closely related to ketamine; and,
- (iso)butyryl fentanyl (Annex 1, ref. 63) a derivative of the potent synthetic opioid fentanyl.

Furthermore, it is also notable that 5-APDB, 6-APDB and thienoamphetamine contain only minor structural modifications to 5-APB, 6-APB and methylthienylpropamine, respectively, which were notified in 2011 ([25]). These substances are good examples of the rapid chemical evolution seen on the new drugs market.

The miscellaneous 'others' category also contains several substances that are medicinal products or are derivatives thereof:

([25]) EMCDDA and Europol (2012), *EMCDDA–Europol 2011 Annual Report on the implementation of Council Decision 2005/387/JHA*, EMCDDA, Lisbon.

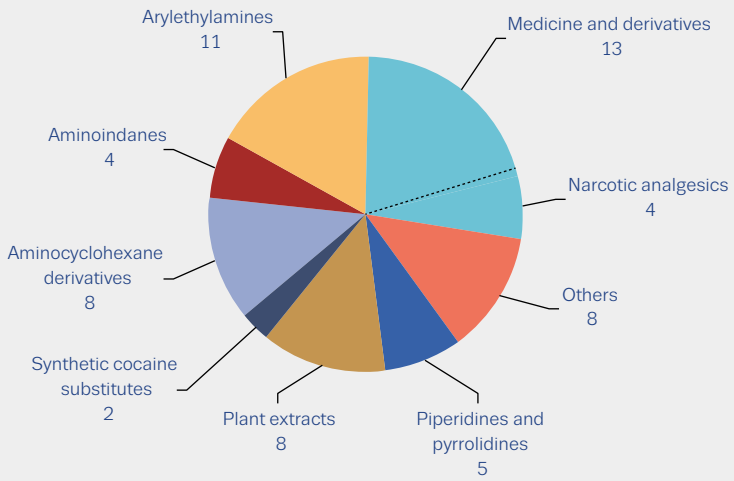
- phenibut: a derivative of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Chemically, it has the parent structure of a phenethylamine. It was discovered and introduced into clinical practice in Russia in the 1960s for its anxiolytic and reported nootropic (cognition enhancing) effects. It is currently being sold both as a 'dietary supplement' and 'research chemical' in a number of EU Member States;
- zopiclone: a non-benzodiazepine hypnotic/sedative that belongs to the group of cyclopyrrolones (one of the so-called 'Z-drugs'). It is authorised as a medicinal product in some Member States for the treatment of insomnia;
- pyrazolam: a benzodiazepine of which apparently little is known. It is similar in chemical structure to alprazolam, which is authorised as a medicinal product in some Member States. However, compared to alprazolam, pyrazolam contains a bromine atom rather than a chlorine atom and contains a pyridinyl group instead of a phenyl group. It currently being sold as a 'research chemical' by Internet retailers;
- 4-fluoroephedrine: a ring-fluorinated derivative of ephedrine. Ephedrine is a sympathomimetic alkaloid of plant origin that increases the activity of noradrenaline on adrenergic receptors. It is used as a stimulant, a bronchodilator and an appetite suppressant. 4-Fluoroephedrine can also be used as a precursor for the manufacture of the new psychoactive substance 4-fluoro-*N*-methylamphetamine (4-FMA). This is directly analogous to the use of ephedrine as a precursor in the manufacture of *N*-methylamphetamine. 4-FMA was first notified to the EWS by Norway in March 2010;
- 4-methylaminorex *p*-methyl derivative: a ring-methylated derivative of 4-methylaminorex ('U4Euh', 'Euphoria'), which has been reported to be a stimulant and possess anorectic effects similar to amphetamine. The parent drug 'aminorex' was once an authorised medicinal product that was used as an anorectic agent. It was withdrawn in 1972 after its use was associated with pulmonary hypertension; and,
- 4-methylphendimetrazine: a ring-substituted derivative of phendimetrazine, which is an appetite suppressant (a

Sub-categorisation within the 'others' group

The EMCDDA has grouped these substances into sub-categories in order to convey the contents of this group in a meaningful, structured way. Some sub-categories are based on chemical family, while others are based on mode of action. Where the substance has a natural origin or is derived from medicines, these are listed separately. This is intended for illustration purposes only and these will not be adopted as official categories in the EWS.

The sub-categories are: aminocyclohexane derivatives; aminoindanes; arylethylamines (not being phenethylamines nor tryptamines); piperidines and pyrrolidines; narcotic analgesics; synthetic substitutes of cocaine; medicines and derivatives of medicines; and, plants, mushrooms and their extracts. The chart below shows the substances notified since 1997 placed into these sub-categories which, despite this exercise, still includes eight substances which do not fit into any other category.

Breakdown of the miscellaneous 'others' category of new psychoactive substances notified between 1997 and 2012



prodrug of phenmetrazine) and a known norepinephrine-dopamine releasing agent (NDRA). Phenmetrazine and phendimetrazine are controlled under the 1971 United Nations Convention on Psychotropic Substances (Schedule II and Schedule IV, respectively).

3.1.7. Information processing and analysis

Following the formal notification of each new substance a profile was created in the EDND. During 2012, 73 new substance profiles were created and more than 200 other substance profiles were updated with new information. These regularly updated profiles are accessed on a daily basis by members of the EWS network. Profiles contain a summary of what is known about the substance including: data on the nature of the substance; alerts and reports associated with it; information from the EMA and other international partners such as the United Nations; legal status; chemistry including molecular information, synthesis, manufacturing and precursor information and analytical data; known uses and risks associated with the substance; published scientific studies; reporting forms from Member States regarding seizures, collected samples and biological samples; and, any other relevant information that is available.

As noted in section 2.1.1, the EDND was expanded in 2012 to include instrumental analytical data such as GC-MS, FT-IR and NMR spectra for the 73 new substances as well as additional analytical data for substances that have been previously notified. A total of 421 reporting forms were received in 2012 ([26]).

In addition to the reporting forms, the EMCDDA also implements longer-term monitoring through the collection of six-monthly EWS reports. Based on the information collected and analysed, the list of all notified substances is reviewed regularly by the EMCDDA and Europol in order to identify those with a potential to trigger a Joint report. In 2012, two substances were considered to merit the production of a Joint report and are discussed below. In addition, a few substances are being actively and continually monitored due to some early indications of harm. Examples of these are given in section 3.3.1.

3.2. Joint reports and risk assessment

In 2012, the EMCDDA and Europol examined the available information on two new psychoactive substances, 4-MA and 5-IT, each through a Joint report 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.

3.2.1. 4-Methylamphetamine (4-MA) — Joint report

At the beginning of 2012, the EMCDDA and Europol agreed that the information collected on 4-MA satisfied all the above criteria. The two organisations concluded that sufficient information had been accumulated to merit the production of a Joint report as stipulated in Article 5.1 of the Council Decision. In compliance with the provisions of the Decision, on 21 May 2012 the EMCDDA and Europol launched a procedure for the collection of information on 4-MA in order to prepare the Joint report.

Key findings of the Joint report

4-MA is a ring-methylated derivative of amphetamine, and belongs to the group of synthetic phenethylamines. It was first detected in Belgium in October 2009, and was notified to the EMCDDA through the EWS on 14 December 2009.

Twelve EU Member States as well as Croatia and Norway reported seizures of 4-MA to the EMCDDA and Europol. These were mostly in powder or paste form, ranging in weight from 0.02 grams up to 147 kilograms. Samples that contained 4-MA typically also contained amphetamine and caffeine in varying ratios.

According to the information provided to Europol, in recent years multiple illicit production sites and/or other indications related to the production of 4-MA have been discovered in the Netherlands. Seizures related to international trafficking of 4-MA were also reported by two Member States, with indications of trafficking from a third Member State. Furthermore, Europol also reported that no distinct difference could be made between 4-MA and amphetamine in terms of the involvement of organised crime groups, production, trade, and/or users. No specific information was reported on money laundering related to the production and/or trafficking of 4-MA and no specific information was received on incidents of violence in

([26]) These include notifications of the first time a new psychoactive substance is identified in a country (including the first report of a new substance identified in the EU) as well as significant new information on a substance (such as non-fatal intoxications, deaths, large or unusual seizures).

connection with the production, wholesale and/or trafficking of 4-MA.

Six Member States and Croatia reported that 4-MA was under drug control or equivalent legislation. Two Member States reported having legislation limiting the unauthorised supply of defined or qualifying psychoactive substances. A further two Member States reported that 4-MA was controlled under medicines legislation. It was also ascertained that 4-MA was not under assessment and had not been under assessment by the United Nations system.

The Joint report also noted that 4-methyl-benzyl methyl ketone (4-methyl-BMK), the precursor known to be used for the manufacture of 4-MA, is not under international control and appeared to be commercially available.

Although some countries noted easy access and availability of 4-MA via the Internet, it was unclear to what extent this substance was advertised and sold online. There was little evidence to suggest a specific demand for 4-MA, however, as noted, the substance was reported to be sold as amphetamine (e.g. as 'speed'). In this respect, the Joint report noted that amphetamine users may be at risk of exposure to 4-MA if the substance became more widely available, given that drug prevalence estimates suggested that about 2 million Europeans had used amphetamines during the past year.

4-MA was found to have no known medical use (human or veterinary) in the EU. There was no marketing authorisation (existing, ongoing or suspended) for 4-MA in the EU or in the Member States which responded to the request from the EMA. There were no indications that 4-MA was used for other purposes other than as an analytical reference standard and in scientific research. Further, there was no information to suggest that 4-MA was used in the manufacture of a medicinal product in the EU.

The Joint report detailed sixteen deaths and nine non-fatal intoxications related to 4-MA, reported by six Member States in a short period of time (from October 2011 to July 2012.

The literature review that was conducted for the Joint report identified a limited number of studies on the chemistry, pharmacology and toxicology of 4-MA. Interestingly, 4-MA underwent human clinical trials as an anorectic agent ('Aptrol') in the 1950s. However, its development and marketing was abandoned for unknown reasons and it was never made commercially available. It was also noted that the Belgian national risk assessment on 4-MA hypothesised that in comparison to amphetamine the more pronounced serotonergic action of 4-MA may diminish the stimulant effects of the substance leading to repeated dosing which may have played a role in some of the deaths ([27]).

The Joint report is available on the EMCDDA website ([28]).

3.2.2. 4-Methylamphetamine (4-MA) — Risk assessment

On the basis of the Joint report, on 24 September 2012, and in accordance with Article 6 of the Council Decision, the Council of the European Union requested a formal risk assessment of the substance.

The extended Scientific Committee of the EMCDDA conducted the risk assessment on 16 November 2012. The Committee considered the following information: the evidence compiled in the Joint report, updated with additional information where available; further detailed information regarding some of the deaths; case reports from Europol of production sites where 4-MA had been detected; details from the findings on the national risk assessments conducted by the Dutch and Belgian authorities; and, expert contributions from members of the Scientific Committee and invited experts.

The risk assessment report is available on the Council of the European Union website ([29]).

On 7 March 2013, after due consideration of the risk assessment report, the Council of the European Union issued a Decision to subject 4-MA to control measures across the EU ([30]).

3.2.3. 5-(2-Aminopropyl)indole (5-IT) — Joint report

At the end of September 2012, the EMCDDA and Europol agreed that the information collected on 5-IT satisfied criteria 1, 4, 5 and 6 above ([31]). The two organisations concluded that sufficient information had been

([27]) Kindly provided by the Belgian national focal point.
([28]) EMCDDA and Europol (2012), *EMCDDA–Europol joint report on a new psychoactive substance, 4-methylamphetamine*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_191982_EN_TDAS12001ENN.PDF
([29]) Council of the European Union (2012), *Risk assessment report on the new psychoactive substance 4-methylamphetamine*, 17275/12 CORDROGUE 98 SAN 320. Available at: http://register.consilium.europa.eu/pdf/en/12/st17/st17275.en12.pdf
([30]) Council Decision of 7 March 2013 on subjecting 4-methylamphetamine to control measures (2013/129/EU), OJ L 72, 15.03.2013, p. 11.
([31]) Specifically: the amount of the material seized; analogy with better-studied compounds; evidence of the potential for further (rapid) spread; and, evidence of cases of serious intoxication or fatalities.

accumulated to merit the production of a Joint report on 5-IT as stipulated by Article 5.1 of the Council Decision. In compliance with the provisions of the Council Decision, on 3 October 2012 the EMCDDA and Europol launched a procedure for the collection of information on 5-IT, in order to prepare the Joint report.

Key findings of the Joint report

5-IT 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-IT also contains the chemical sub-structure of alpha-methylphenethylamine and therefore could be considered to be a substituted phenethylamine, many of which are known to be stimulants. Limited data suggest that 5-IT has stimulant effects.

The first seizure of 5-IT was in Norway on 17 April 2012, and was notified to the EMCDDA through the EWS on 1 June 2012. Several EU Member States reported that forensic and/or toxicological laboratories did not have validated procedures for the confirmation of 5-IT due to the initial lack of certified reference material. This may have led to under-reporting of 5-IT. Seven Member States and Norway reported seizures of 5-IT, mostly as powders ranging in weight from 0.2 grams to 20.5 kilograms, tablets and capsules. It was also detected in tablets resembling 'ecstasy' in one Member State.

The information available for the Joint report suggested that common routes of administration of 5-IT were orally and by insufflation. One Member State reported that injection of the substance may also be occurring.

There was no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for the 5-IT that had been detected on the drug market. One possible route of synthesis was a similar process to the reductive amination used commonly in the manufacture of amphetamines. The reactions were thought to be feasible in an amateur laboratory setting and not to require sophisticated equipment.

According to reports provided to Europol there was no information available to suggest the involvement of organised crime, nor criminal groups, in the production, distribution and trafficking of 5-IT. The substance had been seized at the border of four Member States and Norway. In one case this involved a seizure of 20.5 kilograms of powder.

One Member State reported that 5-IT was controlled under drug control legislation. Two Member States controlled 5-IT under legislation relating to new psychoactive substances. One Member State controlled 5-IT under other legislation. One Member State controlled 5-IT under medicine legislation. It was also ascertained that 5-IT was not under assessment and had not been under assessment by the United Nations system.

No prevalence data were found on the use of 5-IT. In one case, 5-IT had been found in a 'legal high' type products called 'Benzo Fury'. 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. Some Member States reported easy access and availability of 5-IT through Internet retailers. It was noted that the substance was sold as a drug in its own right and in products branded as 'Benzo Fury'. In the latter case, there was also evidence of supply from 'bricks and mortar' head shops.

The Joint report detailed 15 non-fatal intoxications and 21 deaths associated with 5-IT in three Member States (Hungary, Sweden, and the United Kingdom). These were reported to the EMCDDA between July and December 2012. The analysis of biological samples in some of these cases showed that 5-IT may have been used in conjunction with other new psychoactive substances and controlled drugs.

There appeared to be no published studies on the toxicity, tolerance and dependence producing potential of 5-IT. Detailed studies on pharmacology also did not appear to have been published. One available *in vitro* study suggested that 5-IT inhibited monoamine oxidase. The significance of this finding in relation to humans was unclear. In some of the non-fatal intoxications and deaths associated with 5-IT, symptoms typical of monoaminergic toxicity were noted.

5-IT was found to have no known human or veterinary medical use in the EU. There was no marketing authorisation (existing, ongoing or suspended) for 5-IT in the EU or in the Member States which responded to the request from the EMA. There were no indications that 5-IT was used for other purposes other than as an analytical reference material and in scientific research. At the time of writing the report, there was no information that 5-IT was used in the manufacture of a medicinal product in the EU.

The Joint report is available on the EMCDDA website ([32]).

([32]) EMCDDA and Europol (2012), *EMCDDA–Europol joint report on a new psychoactive substance, 5-(2-aminopropyl)indole*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-reports/5-IT

On the basis of the information provided in the Joint report, on the 24 January 2013, the Council of the European Union requested that a formal risk assessment be conducted on the substance. The risk assessment will be conducted by the extended Scientific Committee of the EMCDDA in April 2013.

3.3. Public health alerts

Providing warnings on the adverse health effects of new psychoactive substances through timely and rapid public health alerts is one of the activities of the EWS that provides added value to the Member States ([33]). In addition, the EWS stimulates the exchange of information on emerging trends in new uses of existing psychoactive substances that may pose a potential risk to public health, as well as information on possible public health related measures, in accordance with the mandate and procedures of the EMCDDA.

In 2012, the EWS issued public health alerts to the network concerning noteworthy or unusual hazards related to new psychoactive substances and controlled drugs ([34]).

3.3.1. Alerts related to new psychoactive substances

In 2012, the EMCDDA issued public health alerts concerning adverse health effects related to seven new psychoactive substances and one 'legal high' product.

5-(2-Aminopropyl)indole (5-IT)

Three public health alerts were issued in relation to the substituted indole 5-IT. These alerts were issued in July, September and October 2012 and were triggered by reports of non-fatal intoxications and/or deaths from the Swedish, Hungarian and the United Kingdom national focal points. This information also played a key role in the decision by the EMCDDA and Europol to launch a Joint report on the substance (section 3.2.3). Since the submission of the Joint report to the Council of the European Union, the European Commission and the EMA in December 2012, a further three deaths (two in Hungary and one in Germany) have been reported to the EMCDDA through the EWS.

As noted in section 3.2.3, a formal risk assessment on 5-IT will be conducted on 11 April 2013.

Methylone

In January 2012, an alert was issued after the publication of case report that described the details of a death associated with the synthetic cathinone derivative methylone (3,4-methylenedioxymethcathinone). The death involved a 16-year-old male, and was the first involving methylone to be brought to the attention of the EMCDDA.

Methylone was first notified in 2005 and was one of the first synthetic cathinones to be monitored by the EWS.

Methoxetamine

Methoxetamine is an arylcyclohexylamine and is chemically related to ketamine. The substance was first notified at the end of 2010. An alert was issued in 2011 after publication of a case series of non-fatal intoxications by researchers in the United Kingdom. In 2012, two more alerts were issued in relation to methoxetamine.

The first alert of 2012 was issued in February after the Italian national focal point reported a non-fatal intoxication associated with methoxetamine that involved a 27-year-old male. The report stated that the patient was tachycardic, confused, hallucinating and severely agitated.

The second alert was issued in June after the Swedish national focal point notified the EMCDDA of a death in which methoxetamine, synthetic cannabinoids and THC were detected in post-mortem samples.

Also in 2012, upon request from the United Kingdom national focal point, the EMCDDA launched an informal information request on this substance. The responses were used by the Advisory Council for the Misuse of Drugs in their advice to the government that methoxetamine should be controlled under drugs legislation. The legislation placing methoxetamine into the United Kingdom's drug control law was passed on 26 February 2013.

Alpha-methyltryptamine

Alpha-methyltryptamine (AMT), a substituted tryptamine, was first notified by Finland in 2001 under the 1997 Joint Action ([35]). It was developed in the Soviet Union as an anti-depressant in the 1960s. Over the past few years, it has been widely offered by Internet retailers selling new psychoactive substances.

([33]) Such alerts are not legally binding and therefore Member States are not obliged to act upon them.
([34]) Note that detection of new psychoactive drugs in post-mortem samples does not necessarily imply a causal role in the death.
([35]) Joint Action 97/396/JHA of 16 June 1997 adopted by the Council on the basis of Article K.3 of the Treaty on European Union, concerning the information exchange, risk assessment and the control of new synthetic drugs. OJ L 167, 25.06.1997, p. 1.

Two alerts regarding AMT were issued in 2012 after information was received regarding deaths in the United Kingdom and Norway.

The first of the alerts was issued after the United Kingdom national focal point reported two deaths that occurred in 2011. In one case, AMT was found in two different post-mortem samples. In the other case, MDMA, fluoromethcathinone, AMT, methylone, MDPV, MDAI, methoxetamine and 5-IAI were detected post-mortem. It was reported that this case appeared to involve the use of separate products rather than one product containing all these substances.

The second public health alert was issued after the Norwegian national focal point reported the death of a 19-year-old male whose post-mortem toxicological analysis revealed high concentrations of AMT in the blood. Alcohol and other drugs were not detected.

Para-methyoxyamphetamine (PMA) and para-methoxymethamphetamine (PMMA)

PMA and PMMA are substituted phenethylamine substances which have been associated with serious toxicity including death. PMMA was risk-assessed in 2001 in the framework of the 1997 Joint Action ([36]) and consequently subject to control measures across the EU ([37]).

Alerts were issued on PMMA/PMA in both 2010 and 2011. In 2012, two public heath warnings were issued after serious non-fatal intoxications and deaths were reported from the United Kingdom and Ireland.

The United Kingdom national focal point provided a report of four serious non-fatal intoxications and one death that were believed to be associated with the use of tablets that contained PMA. In a second case, there were a further two fatalities where PMA was detected post-mortem. Further details were not available at the time of the alert. Also at that time, the United Kingdom national focal point reported three further deaths associated with PMA from 2011 that had not been previously reported to the EMCDDA.

A further alert on PMA/PMMA was issued when the Irish national focal point reported two deaths associated with the use of a drug containing PMMA and MDMA. According to the state laboratory, the urines of the decedents contained PMMA, MDMA, an anti-histamine and codeine.

4-Methylamphetamine (4-MA)

Three public health alerts were issued in 2012 in relation to 4-MA, which was the subject of a Joint report and risk assessment (sections 3.2.1 and 3.2.2). These alerts related to reports of deaths in the Netherlands, Belgium and the United Kingdom, and followed the initial alert issued in October 2011 after the Belgian national focal point reported three non-fatal intoxications and three deaths associated with the substance.

Methylthienylpropamine

Methylthienylpropamine (MPA) is the thiophene analogue of *N*-methylamphetamine. It was first notified in January 2011 by Finland. Two separate alerts were issued in 2012 when the United Kingdom national focal point reported three cases involving deaths associated with this substance.

The first alert concerned two cases. The first case involved a 'legal high' product known as 'Blow' that was suspected to have been snorted. Analysis of the product contents found MPA, MDAI (methylenedioxyaminoindane), lignocaine, and caffeine. These drugs were also detected in the post-mortem samples but mainly MPA. In the second case, MPA and methoxetamine were detected. The information from this case suggested that a 'legal high' product called 'China White' had been snorted by the deceased. The deceased had no other significant toxicological findings.

The second alert related to a case where MPA was detected in post-mortem blood along with oxycodone, temazepam, venlafaxine and its metabolite *o*-desmethylvenlafaxine. No other illicit drugs or new psychoactive substances were found.

'Annihilation'

A public health alert was issued on 'Annihilation', which is a 'legal high' product rather than a specific substance. In October 2012, as a result of media reports, the EMCDDA contacted the United Kingdom national focal point regarding a product called 'Annihilation', which was

([36]) EMCDDA (2003), *Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs*, Office for Official Publications of the European Communities, Luxembourg.

([37]) Council Decision of 28 February 2002 concerning control measures and criminal sanctions in respect of the new synthetic drug PMMA (2002/188/JHA). OJ L 63, 06.03.2002, p. 14.

reported to be responsible for a series of non-fatal intoxications in Scotland, United Kingdom. The national focal point reported that analyses of five samples of 'Annihilation' revealed the presence of mixtures of synthetic cannabinoids, and that the contents of different packages of the product were not the same. Furthermore, a search of the EDND revealed that the German national focal point had previously reported a seized sample of 'Annihilation'. The results of these analyses are presented below.

Table 1. Synthetic cannabinoids found in 'Annihilation' 'legal high' products, October 2012

Source of data	UR-144	MAM-2201	AM-2201	JWH-122 pentenyl derivative	AM-1248
UK	✓	✓	—	✓	—
UK	✓	✓	—	—	—
UK	✓	✓	✓	✓	—
UK	✓	—	✓	—	—
UK	✓	✓	—	—	—
Germany	✓	✓	—	—	✓

Of note is that all the samples contained the synthetic cannabinoid UR-144 (first notified to the EMCDDA in February 2012 by the Finnish national focal point). However, it is not known whether this substance caused the effects that were reported to be associated with the consumption of this product. UR-144 is a synthetic cannabinoid that was developed as a selective CB2 receptor ligand with lower affinity for the CB1 receptor (the main endogenous cannabinoid receptor responsible for psychoactive effects) ([38]).

Europol also issued an alert to the network of Europol National Units regarding 'Annihilation' products.

3.3.2. Alerts related to controlled substances

In 2012, public health alerts were also issued in relation to three internationally controlled substances. These were fentanyl, heroin and methamphetamine (*N*-methylamphetamine).

Fentanyl

An alert was issued in March 2012 on the request of the German national focal point due to an observed marked increase in deaths associated with the use of fentanyl. In 2011, 24 % of all drug-related deaths recorded in the Bavaria region were associated with fentanyl use.

A further alert on fentanyl was issued following a media report that highlighted the issue of fentanyl misuse in Estonia.

A Trendspotter meeting was held in Lisbon in October 2012 to examine the use of fentanyl and fentanyl derivatives in Europe (section 4.2).

Anthrax infection associated with heroin use

Several alerts were issued during the course of 2012 regarding outbreaks of anthrax infection in users who injected heroin. The United Kingdom, German, French and Danish national focal points reported confirmed cases of anthrax between the 13 June 2012 and 19 December 2012. There were six cases in the United Kingdom, four in Germany, one in France and one in Denmark. During this period, the EMCDDA worked closely with the relevant authorities in the Member States and with the European Centre for Disease Control (ECDC). A Joint ECDC–EMCDDA rapid risk assessment was conducted in June with relevant advice and public health warnings issued on a rolling basis as updates were received ([39]).

([38]) Poso, A. and Huffman, J. W., (2008), Targeting the cannabinoid CB2 receptor: modelling and structural determinants of CB2 selective ligands, *British Journal of Pharmacology*, 153(2), pp. 335–346.

([39]) ECDC and EMCDDA (2012), *Joint ECDC and EMCDDA rapid risk assessment. Anthrax cases among injecting drug users, Germany*, ECDC, Stockholm.

Methamphetamine (N-methylamphetamine)

Three public health warnings were issued in relation to methamphetamine in 2012.

In early 2012, an alert was issued in response to a report from the Greek national focal point concerning the death of a drug user, thought to be from the use of methamphetamine. This substance has emerged onto the drug scene in Greece and is known locally as 'sisa'. Two seizures of 'sisa' by police in central Athens were found to contain methamphetamine in crystalline form (commonly called 'crystal meth').

A further alert was issued later in the year after an update by the Greek national focal point that concerned further seizures of 'sisa' along with reports of drug users approaching treatment services seeking help in relation to the substance.

The third alert was triggered by the report of a second death in Greece, which involved a female drug user. In this case, methamphetamine, methadone and morphine were confirmed in the post-mortem blood samples.

3.3.3. Emerging trend for future monitoring

The EMCDDA has noted that some of the most potent new psychoactive substances, such as the phenethylamines substituted with the '-NBOMe' group (section 3.1.2) and fentanyls, are being offered for sale online as cyclodextrin complexes.

Cyclodextrin complexes are large synthetic molecules produced from starch. They have many legitimate applications including as potential drug delivery methods. This is because they form so-called 'host-guest complexes', where a drug molecule can be chemically bound to the cyclodextrin but then released on ingestion. Such a mechanism of action could have benefits for producers, distributors and users of particularly potent new psychoactive substances as it would render them easier and safer to handle. On the other hand, the use of cyclodextrin complexes as a vehicle to carry drugs may have implications for the identification of new substances using established detection techniques. Furthermore, it is possible that this mode of delivery may also increase the capacity for further spread of these 'difficult to handle' drugs.

4. Epidemiology and new approaches

4.1. Overview of prevalence data on new psychoactive substances

Data on both the prevalence of use and associated user behaviours are essential components to monitoring, understanding, and, responding to, the phenomenon of new psychoactive substances. Such data are currently limited and may suffer from methodological limitations, including a lack of common definitions. In addition, most users do not know which substances they have actually taken. This may be a particular problem regarding 'legal high' products (such as smoking mixtures that contain synthetic cannabinoids) that are sold using brand names as normally no information is provided about the contents, and, in any case, the contents of a particular product may vary over time. Finally, data are reported with a time delay, which needs to be taken into account considering the highly dynamic and fast-moving market in new psychoactive substances.

Over the past few years some representative general population surveys have been conducted that examine the prevalence of 'legal highs' and new psychoactive substances in school students and/or adults ([40]).

A national survey of Spanish students (aged 14–18) conducted in 2010 found overall lifetime use of 'legal highs' of 0.7 % (0.6 % in the last year and 0.5 % in the last month). While the lifetime use of 'research chemicals' was 0.4 % (0.3 % in the last year, and 0.2 % in the last month), lifetime use of 'Spice' products (which contain synthetic cannabinoids) was 1.1 % (0.8 % in the last year and 0.4 % in the last month), and lifetime use of mephedrone was 0.4 % (0.3 % in the last year and 0.2 % in the last month) ([41]).

The 2010/11 British Crime Survey ([42]) found that among the general population (16–59) in England and Wales, last year use of mephedrone (1.4 %) was at a level similar to that of ecstasy. Among the 16–24 age group, last year prevalence of mephedrone was the same as that of powder cocaine (4.4 %). Most of those who reported using mephedrone in the last year also reported having used another illicit drug (mainly cannabis, cocaine or ecstasy). An important caveat to understanding the significance of these results is that the data collection for the survey covered some time before and after the period when mephedrone was controlled. The 2011/12 survey ([43], [44]) found that last year use of mephedrone among adults aged 16 to 59 was 1.1 %. Mephedrone was found to be the fourth most prevalent drug measured. Among 16- to 24-year-olds, last year use was 3.3 %, the same level as ecstasy, the third most prevalent drug used within this age group. Estimates of use of recently controlled drugs (GBL/GHB, BZP and synthetic cannabinoids) in the last year ranged between 0.1 and 0.2 % for each type of drug.

Mephedrone and 'legal highs' were included for the first time in a joint household survey in Ireland and Northern Ireland (United Kingdom) conducted in 2010/11, after mephedrone was controlled ([45]). The sample included over 7 500 respondents, aged 15–64. In Northern Ireland, lifetime prevalence was estimated at 2 % and last year prevalence at 1 % for both mephedrone and 'legal highs'. Lifetime prevalence levels were higher among those aged 15–24, reaching 6 % for both mephedrone and 'legal highs.

([40]) For some new drugs that are sold directly on the illicit market, the user groups and prevalence may, to some degree, reflect those for established controlled drugs (such as amphetamine and MDMA). A recent example of this was 4-methylamphetamine, which was usually sold as amphetamine (e.g. 'speed'), even though users were mostly unaware of this.

([41]) Clinical Committee of the Government Delegation for the National Plan on Drugs (2011), Emerging drugs. Report 6 of the Clinical Committee, Ministry of Health, Madrid. Available at: http://www.pnsd.msc.es/Categoria2/publica/pdf/DROGAS_EMERGENTES_ingles_WEB.pdf

([42]) Smith, K. and Flatley, J (2011), *Drug Misuse Declared: Findings from the 2010/11 British Crime Survey*, Home Office, London.

([43]) In 2012, the British Crime Survey was renamed the Crime Survey of England and Wales.

([44]) UK Home Office (2012), *Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales,* Home Office, London.

([45]) National Advisory Committee on Drugs (NACD) and Public Health Information and Research Branch (PHIRB) (2011), *Drug use in Ireland and Northern Ireland: first results from the 2010/11 Drug Prevalence Survey. Bulletin 1.* NACD & PHIRB, Dublin.

In Ireland, new psychoactive substances (last year use, 4 %) were the second most frequently reported illicit drugs after cannabis (6 %). The highest levels of last year use of new psychoactive substances were reported by 15- to 24-year-olds (10 %).

In addition, a 2011 Eurobarometer survey of youth attitudes to drugs, which interviewed more than 12 000 young people aged between 15 and 24, estimated that 5 % of young Europeans had used 'legal highs' at some time, with about half of the countries falling in the range 3–5 %. The highest estimates were reported by Ireland (16 %) followed by Latvia, Poland and the United Kingdom (all at nearly 10 %) ([46]).

Surveys have also examined the use, availability and associated user behaviours in targeted populations such as nightclub patrons and dance music fans. The targeted populations tend to include 'early adopters' of new drugs. The findings of these surveys are not generalisable to other groups and populations. Nevertheless, the use of new drugs in these targeted populations can be very high and such studies may provide insights into the harms a drug may have, as well as an indication of substances that may be attractive to other user groups and which could become more widespread.

A survey of individuals attending 'gay friendly' nightclubs in south-east London in 2011 found that, among 313 participants, lifetime use of a 'legal high' was reported by 65.8 %. Lifetime use of mephedrone was reported by 63.8 % of the sample (last month use was 53.2 % and use during the day of the survey was 41 %). In addition, lifetime use of BZP was 9.3 % (1.6 % in the last year); lifetime use of MDAI was 7.7 % (1.3 % in the last year); lifetime use of 'synthetic cocaine' was 9.9 % (3.5 % in the last year); lifetime use of 'Spice/K2' was 9.9 % (2.2 % in the last year); lifetime use of methoxetamine was 6.4 % (1.9 % in the last year); and lifetime use of 'pipradrols' was 1.6 % (1.0 % in the last year) ([47]).

An online survey on 'legal highs' conducted among 860 respondents with experience in 'legal highs' in Germany showed that 'herbal blends' were the most prevalent 'legal high' products, followed by 'research chemicals' and 'bath salts' and similar products. Similarly, a study carried out in nightlife settings in the Czech Republic found that 4.5 % of a sample of 1 091 Internet users aged 15 to 34 reported use of a new psychoactive substance ([48]).

In 2011, the online drug-use survey for the UK clubbing magazine Mixmag and the Guardian newspaper ([49]) which draws on previous Mixmag surveys collected 15 500 responses from around the world, but mostly from the United Kingdom. In 2010/11, reported levels of use of mephedrone in the last year and last month were three times higher among clubbers (30 % and 13 %) than non-clubbers (10 % and 3 %).

4.2. Trendspotter study: fentanyl in Europe

The second EMCDDA Trendspotter study was conducted in October 2012 and examined the availability and use of fentanyl in Europe, including: the extent and patterns of use; illicit production and diversion; harms and deaths; and, responses to the problem. Twelve experts from 10 Member States (Bulgaria, Czech Republic, Germany, Estonia, Greece, Italy, Slovakia, Sweden, Finland, United Kingdom) attended the meeting, presenting their experiences and contributing to an analysis of the topic, providing insights from law enforcement, forensic science, treatment, research and monitoring, and drug user perspectives.

The EMCDDA Trendspotter study methodology incorporates a number of different investigative approaches and data collection from multiple sources. This study included: a review of the international literature; data collection from the 30 national early warning systems; data collection on fentanyl-associated deaths; 12 expert presentations (from 10 countries); an electronic survey of experts attending the meeting; and, three facilitated working groups. Analysis was based on triangulation of the available data, with a view to providing as complete and reliable a picture as possible, with an important caveat being that much of the data are preliminary and many of the results are based on expert opinion and the grey literature.

The report from the meeting is available on the EMCDDA website ([50]).

([46]) Gallup Organization (2011), *Youth attitudes on drugs, Flash Eurobarometer 330*. Available at: http://ec.europa.eu/public_opinion/flash/fl_330_en.pdf
([47]) Wood, D. M., Hunter, L., Measham, F. and Dargan, P.I. (2012), 'Limited use of novel psychoactive substances in South London nightclubs', *Quarterly Journal of Medicine*, 105(10), pp. 959–64.
([48]) EMCDDA (2012), *Annual report 2012: the state of the drug problem in Europe*, Publications Office of the European Union, Luxembourg, p. 92.
([49]) No authors listed (2012), 'Global drug survey', *Mixmag*, 251, pp. 68–73.
([50]) http://www.emcdda.europa.eu/scientific-studies/2012/trendspotters-report

This meeting built upon the success of the first EMCDDA Trendspotter meeting which took place in Lisbon in October 2011, and examined the recent shocks in the European heroin market ([51]).

4.3. Sewage epidemiology

Sewage epidemiology, also known as wastewater analysis, is a rapidly developing scientific discipline. It has been supported by the EMCDDA as it was recognised that this may be a useful epidemiological technique to help support the Agency's work. Monitoring population-level trends in illicit and new drug consumption using this technique is now feasible given the recent advances in analytical chemistry and applied research that allow the identification of illicit and new drugs as well as their main metabolites in wastewater at very low concentrations. This is comparable to taking a much diluted urine sample from an entire community (rather than from an individual user). With certain assumptions, it may be possible to back-calculate from the amount of the metabolite in the wastewater to an estimate of the amount of a drug consumed in a community. Early research focused on identifying cocaine and its metabolites in wastewater, but recent studies have shown that this technique shows promise for monitoring consumption of new psychoactive substances.

Two expert meetings on wastewater analysis were organised by the EMCDDA in 2011. These were followed up with a demonstration project commissioned by the EMCDDA (2012) that aimed to explore the applicability of the technique through the analysis of wastewater in 19 European cities. In December 2012, the EMCDDA hosted a workshop that examined how illicit drug use in populations could be determined through wastewater biomarker analysis. The workshop brought together some of the leading researchers in this field and was an effective platform for the kick-off meeting of the SEWPROF (sewage profiling) project group ([52]).

4.4. Computer-aided prediction of pharmacological properties

The EMCDDA–Europol 2011 Annual Report on the implementation of Council Decision 2005/387/JHA discussed the potential of using computer-based modelling to assist with the monitoring and risk assessment of new psychoactive substances.

This technique is based on the fact that molecules with similar chemical structures may possess similar physicochemical properties and biological activities. The concept of molecular similarity has been exploited in drug discovery, and similarity methods have been used in the prediction of physicochemical properties (solubility, partitioning coefficient), as well as estimating absorption, distribution, metabolism, excretion and toxicity.

This method may be useful, both at an early stage in the process of assessing new psychoactive substances and as a complementary technique during the risk assessment. However, it is not a tool that can be used on its own in the risk assessment process.

Using the computational modelling method, 4-MA was examined and was predicted to have properties similar to other substituted amphetamine stimulants. Other compounds assessed using this technique in 2012 were 5-IT, alpha-PVP and methoxetamine.

5-(2-Aminopropyl)indole (5-IT)

The computational modelling method predicted that the 5-HT_{2C} and 5-HT_{1D} receptors were possible targets of 5-IT. These receptors are known to be involved in the reward circuit of the limbic part of the brain. In addition, the model predicted that 5-IT may cross the blood–brain barrier.

Alpha-PVP

Alpha-PVP belongs to the group of pyrrolidinophenone type drugs, structurally similar to pyrovalerone (4-methyl-α-pyrrolidinovalerophenone) which acts by releasing dopamine and norepinephrine. It was predicted that this compound would affect the dopaminergic and norepinephrinergic systems, in agreement with data from *in vitro* studies. In addition, the model predicted that alpha-PVP may be able to cross the blood–brain barrier.

Methoxetamine

The target prediction algorithm was not able to predict the expected targets for ketamine and methoxetamine. The limitations of the technique at the present time for certain groups of compounds must be acknowledged.

([51]) http://www.emcdda.europa.eu/scientific-studies/2011/trendspotters-report

([52]) SEWPROF is a research project funded by the European Commission, Marie Curie Actions, Seventh Framework Programme and the Initial Training Network to develop interdisciplinary and cross-sectoral research capability for the next generation of scientists working in the newly-emerging field of sewage epidemiology.

5. Production and distribution of new psychoactive substances

5.1. Europol

As a key partner in the system set up under the Council Decision, Europol is at the forefront of monitoring, knowledge sharing and awareness of the regional supply of new psychoactive substances. The role that Europol plays under the Council Decision allows it to have a regional overview and develop expertise concerning the production, trafficking and organised crime involvement in both the 'traditional' synthetic drugs market as well as on new psychoactive substances. Europol has several expert systems which incorporate synthetic drug related data, including new psychoactive substances.

The extensive involvement of organised crime in the production, trafficking and marketing of synthetic drugs is well-known. Further to this, information gathered by Europol shows that organised crime continues to exploit new market opportunities, with production or packaging, mixing and trafficking of new drugs posing an emerging threat to the EU.

Moreover, the Internet has become a major new marketplace for such new psychoactive substances as well as an information hub for sharing knowledge on their synthesis, effects and availability. However, Europol has noted that new psychoactive substances advertised on the Internet as 'legal highs' are not always consistent with the substance sought, and in some cases may actually contain controlled drugs.

The new psychoactive substances seized by European law enforcement agencies are sourced mainly from China and to a lesser extent from India. The illicit production of new drugs inside the EU is rarely reported to Europol by Member States. This may perhaps be due to the requirement for more sophisticated methods of synthesis and equipment required, when compared to the 'traditional' synthetic drugs such as amphetamine and MDMA. In the majority of cases reported by Member States, 'illicit production' of new psychoactive substances in the EU has referred to professional mixing and packaging sites, rather than synthesis of the substances.

During the preparation for the EMCDDA–Europol Joint report on 4-MA, an interesting finding was noted regarding the precursors for new drugs. The Netherlands reported that in recent years multiple illicit production sites and/or incidents related to the production of 4-MA had been discovered (three sites in 2010 and one site in 2011). In each case it was not clear whether the criminals involved in the illicit production were aware that they were producing 4-MA. According to Dutch intelligence, there were suggestions that some producers believed that they were producing amphetamine using the precursor BMK, when they were actually using the precursor 4-methyl-BMK and consequently producing 4-MA.

6. Conclusions

Until about a decade ago, most new psychoactive substances were typically sold directly on the illicit market. They were produced in illicit production facilities and called 'designer drugs' or were sourced from diverted medicines. To some degree, this continues to be the case, with 4-MA being the latest example of a new drug produced in illicit production facilities within the EU. However, the emergence of 'legal highs', beginning with BZP and methylone, and followed by mephedrone, marked a fundamental shift in the drug markets. Now many new psychoactive substances are produced in bulk in China and India and imported into Europe, where they are processed, packaged and sold on the growing 'legal highs' market. These developments have been fuelled by globalisation and technological advancement, which have also allowed a more open market to develop. This includes advertisement and sale through the Internet and 'bricks and mortar' head shops. In addition, for suppliers, the Internet is also facilitating communication as well as providing access to knowledge, expertise and logistics. For users, the Internet has made it easier to learn about 'legal highs', share their experiences of using them and provide advice and support to other users. Overall, these developments have played a role in the dramatic increase in the number, type and availability of new psychoactive substances in Europe. In 2012, 73 new substances were officially notified for the first time in Europe through the EWS, with more than 280 substances now being monitored by the EMCDDA.

The globalised nature of the new drugs phenomenon makes it particularly difficult to control and reduce supply. Differences in drug laws between EU Member States and third countries, such as China and India, where the substances are manufactured, compound the problem. Retailers exploit gaps in existing control and regulatory measures and rapidly adapt to new measures. Insufficient capacity for screening freight and postal packages makes it difficult to prevent new drugs entering the EU. The decentralised and transnational nature of the Internet means that enforcement measures may have a limited impact due to displacement of online shops to countries outside the EU, where legal and regulatory systems may be inadequate to address this phenomenon.

Now, more than ever, the EWS provides added value to the Member States by playing an essential role in ensuring that they have access to the most up-to-date information on new psychoactive substances both from across Europe and beyond. The EWS network continues to grow, as does the amount and quality of the information that it collects. The network now includes not only new forensic science and toxicological laboratories, but also a range of health and law enforcement professionals, as well as many academic researchers. It is clear that the EWS functions efficiently and effectively due to the structure that is underpinned by the Reitox national focal points, the technical expertise that has been built up by members of the network, the clear operating guidelines and the coordination provided by the EMCDDA and Europol.

Further, where necessary, the system allows for the progression through the scientific risk assessment phase to control measures across the EU. In 2012, this sensitive monitoring system provided the EMCDDA and Europol with the signals required to trigger Joint reports for 4-MA and 5-IT. After the risk assessment conducted by the extended Scientific Committee of the EMCDDA, and following opinion of the European Commission, the Council of the European Union decided to control 4-MA across the Union. The risk assessment of 5-IT will be conducted in April 2013.

Sound scientific data are essential to the system set up by the Council Decision. In order to better inform the responses that are likely to be needed to address the new drugs phenomenon, there are some key areas of the EWS that need to be strengthened. These include:

- the data collection and data management infrastructure of the EWS, including the EDND (which was not designed to handle the quantity and range of data that is now generated by the new drugs phenomenon);
- provision of a mechanism to produce and share analytical reference standards across the EU;
- improving the capacity for investigative analysis and applied research at the European level; and,
- epidemiological studies, particularly targeted and general population prevalence surveys.

Finally, advances in the fields of pharmacology and toxicology now allow for the more rapid assessment of the properties of new substances. These data can be used to improve the knowledge and understanding of these substances, including, critically, for the risk assessment process. Such an assessment may include the study of the pharmacological and toxicological properties of new psychoactive substances (such as receptor binding and mode of action studies) that will help provide the evaluation of potential acute and chronic toxicity in humans. While the EMCDDA has applied such techniques on an ad hoc basis in the past, it is clear that such information will be required on a routine, systematic basis in the future.

Annexes

Annex 1. New psychoactive substances notified to the EMCDDA and Europol for the first time in 2012 under the terms of Council Decision 2005/387/JHA

1. **HU-331** ((3*S*,4*R*)-3-hydroxy-2-*p*-mentha-(1,8)-dien-3-yl-5-pentyl-3,4-*p*-benzoquinone) – 12 January 2012 – France
2. **AM-679** ((2-iodophenyl)(1-pentyl-1*H*-indol-3-yl) methanone) – 27 January 2012 – Italy
3. **WIN 55212-2** ((*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-napthalenylmethanone) – 27 January 2012 – Italy
4. **UR-144** ((1-pentyl-1*H*-indol-3-yl)-(2,2,3,3-tetramethyl-cyclopropyl)methanone) – 1 February 2012 – Finland and Poland
5. **JWH-370** ([5-(2-methylphenyl)-1-pentyl-1*H*-pyrrol-3-yl]-1-naphthalenyl-methanone) – 1 February 2012 – Finland
6. ***N*-propylamphetamine** (*N*-(1-phenylpropan-2-yl) propan-1-amine) – 3 February 2012 – Austria
7. **3-(*p*-Methoxybenzoyl)-*N*-methylindole** – 3 February 2012 – Austria
8. **trans-Diastereomer of CP 47,497-C8 homologue** – 3 February 2012 – Austria
9. **1-Cyclohexyl-*x*-methoxybenzene** – 3 February 2012 – Austria
10. **3-Fluoro-isomethcathinone** (1-(3-fluorophenyl)-1-(methylamino)-2-propanone) – 13 February 2012 – Czech Republic
11. **1-(3-Methylbenzyl)piperazine** – 17 February 2012 – Sweden
12. **2-Fluoroamphetamine** (1-(2-fluorophenyl)propan-2-amine) – 21 February 2012 – Sweden
13. **Thienoamphetamine** (1-(thiophen-2-yl)propan-2-amine) – 24 February 2012 – Czech Republic
14. **URB754** (6-methyl-2-[(4-methylphenyl)amino]-1-benzoxazin-4-one) – 27 February 2012 – Bulgaria
15. **5-APDB** (5-(2-aminopropyl)-2,3-dihydrobenzofuran) – 5 March 2012 – Bulgaria
16. **Phenibut** (4-amino-3-phenyl-butyric acid) – 8 March 2012 – Sweden
17. **6-APDB** (6-(2-aminopropyl)-2,3-dihydrobenzofuran) – 8 March 2012 – Spain
18. **2-FMA** (2-fluoro-*N*-methyl-amphetamine) – 12 March 2012 – Finland
19. **ECX** (1-ethynyl-1-cyclohexanol) – 26 March 2012 – United Kingdom
20. **4-Fluoroephedrine** (1-(4-fluorophenyl)-2-(methylamino) propan-1-ol) – 26 March 2012 – United Kingdom
21. **3-MeO-PCP** (1-[1-(3-methoxyphenyl)cyclohexyl] piperidine) – 29 March 2012 – United Kingdom
22. **5FUR-144** ((1-(5-fluoropentyl)-1*H*-indol-3-yl) (2,2,3,3-tetramethylcyclopropyl)methanone) – 30 March 2012 – Latvia
23. **25D-NBOMe** (2-(2,5-dimethoxy-4-methylphenyl)-*N*-(2-methoxybenzyl)ethanamine) – 16 April 2012 – United Kingdom
24. **A-796,260** ([1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone) – 18 April 2012 – Belgium
25. **4-AcO-DALT** (4-acetoxy-*N*,*N*-diallyltryptamine) – 20 April 2012 – Finland
26. **1-Phenyl-2-(piperidin-1-yl)butan-1-one** – 7 May 2012 – Spain

27. **2,4,5-Trimethylmethcathinone / 2,4,5-TMMC** (2-methylamino-1-(2,4,5-trimethylphenyl)propan-1-one)) – 8 May 2012 – Germany

28. **APINACA** (*N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide) – 21 May 2012 – Bulgaria

29. **5-IT** (5-(2-aminopropyl)indole) – 1 June 2012 – Norway

30. **Zopiclone** (6-(5-chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) – 1 June 2012 – United Kingdom

31. **UR-144 (-2H)** ([1-(pent-4-en-1-yl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone) – 14 June 2012 – France

32. **25I-NBOMe** (4-iodo-2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine) – 21 June 2012 – Sweden

33. **4-HO-DPT** (4-hydroxy-*N,N*-dipropyltryptamine) – 21 June 2012 – Sweden

34. **5-MeO-MET** (5-methoxy-*N*-ethyl-*N*-methyl-tryptamine) – 21 June 2012 – Sweden

35. **STS-135** (*N*-(1-adamantyl)-1-(5-fluoropentyl)-1*H*-indole-3-carboxamide) – 26 June 2012 – Hungary

36. **MPHP** (1-(4-methylphenyl)-2-(pyrrolidin-1-yl)-hexan-1-one) – 26 June 2012 – Sweden

37. **APICA** (*N*-(1-adamantyl)-1-pentyl-1*H*-indole-3-carboxamide) – 13 July 2012 – Finland

38. **JWH-018 carboxamide derivative** (1-pentyl-*N*-(naphthalen-1-yl)-1*H*-indole-3-carboxamide) – 16 July 2012 – Finland

39. **MDDM** (3,4-methylenedioxy-*N,N*-dimethylamphetamine) – 17 July 2012 – Austria

40. **MAM-2201 chloropentyl derivative** ([1-(5-chloropentyl)-1*H*-indol-3-yl](4-methyl-1-naphthalenyl)methanone) – 18 July 2012 – United Kingdom

41. **JWH-122 pentenyl 2-methylindole derivative** ((4-methylnaphthalen-1-yl)[2-methyl-1-(pent-4-en-1-yl)-1*H*-indol-3-yl)]methanone) – 18 July 2012 – United Kingdom

42. **JWH-122 pentenyl derivative** ((4-methylnaphthalen-1-yl)(1-(pent-4-en-1-yl)-1*H*-indol-3-yl)methanone) – 18 July 2012 – United Kingdom

43. **AM-694 methyl substituted for iodine** (1-(5-fluoropentyl)-3-(2-methylbenzoyl)indole) – 18 July 2012 – United Kingdom

44. **AM-694 ethyl substituted for iodine** (1-(5-fluoropentyl)-3-(2-ethylbenzoyl)indole) – 18 July 2012 – United Kingdom

45. **JWH-018 *N*-(5-chloropentyl) derivative** ([1-(5-chloropentyl)-1*H*-indol-3-yl](naphthalen-1-yl) methanone) – 31 July 2012 – Germany

46. **JWH-018 *N*-(5-bromopentyl) derivative** ([1-(5-bromopentyl)-1*H*-indol-3-yl](naphthalen-1-yl) methanone) – 31 July 2012 – Germany

47. **AH-7921** (3,4-dichloro-*N*-[[1-(dimethylamino) cyclohexyl]methyl]benzamide) – 2 August 2012 – United Kingdom

48. **4-AcO-DPT** (4-acetoxy-*N,N*-dipropyltryptamine) – 21 August 2012 – Finland

49. **Pyrazolam** (8-bromo-1-methyl-6-phenyl-4*H*- [1,2,4] triazolo[4,3*a*][1,4]benzodiazepine) – 22 August 2012 – Finland

50. **2-MeO-Ketamine** (2-(2-methoxyphenyl)-2-(methylamino)cyclohexanone) – 30 August 2012 – Sweden

51. **Hydroxyamphetamine** (4-(2-aminopropyl)phenol) – 5 September 2012 – Poland

52. **3-Methylmethcathinone / 3-MMC** (1-(3-methylphenyl)-2-(methylamino)propan-1-one) – 5 September 2012 – Sweden

53. **N-Ethylnorketamine** (2-(2-chlorophenyl)-2-(ethylamino) cyclohexanone) – 17 September 2012 – United Kingdom

54. **5-APDI** (1-(2,3-dihydro-1*H*-inden-5-yl)propan-2-amine) – 17 September 2012 – United Kingdom

55. **AM-1248** (1-[(*N*-methylpiperidin-2-yl)methyl]-3-(adamant-1-oyl)indole) – 24 September 2012 – Germany

56. **AKB-48F** (*N*-(1-adamantyl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide) – 27 September 2012 – Latvia

57. **AM-2201 indazolecarboxamide analogue** (*N*-1-naphthalenyl-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide – 30 October 2012 – Finland

58. **JWH-018 carboxylate analogue, quinolinyl derivative** (quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate) – 20 November 2012 – Finland

59. **AB-005** ([1-[(1-methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone) – 20 November 2012 – Germany

60. **AB-005 azepane isomer** ((1-(1-methylazepan-2-yl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone) – 20 November 2012 – Germany

61. **4-HTMPIPO** (4-hydroxy-3,3,4-trimethyl-1-(1-pentyl-1*H*-indol-3-yl)pentan-1-one) – 30 November 2012 – Sweden

62. **(Iso)butyryl-F-fentanyl N-benzyl analogue** (*N*-(1-benzylpiperidin-4-yl)-*N*-(*x*-fluorophenyl)-butanamide) – 4 December 2012 – Finland

63. (**Iso)butyryl fentanyl** (2-methyl-*N*-phenyl-*N*-[1-(1-phenylpropan-2-yl)piperidin-4-yl]propanamide) – 4 December 2012 – Finland

64. **UR-144 N-(5-chloropentyl) analogue** ((1-(5-chloropentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone) – 7 December 2012 – Hungary

65. **4-CA/4-chloroamphetamine** (1-(4-chlorophenyl)propan-2-amine) – 7 December 2012 – Hungary

66. **25B-NBOMe** (2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine) – 6 December 2012 – Sweden

67. **2C-G** (1-(2,5-dimethoxy-3,4-dimethylphenyl)propan-2-amine) – 6 December 2012 – Poland

68. **2C-N** (2,5-dimethoxy-4-nitrophenethylamine) – 6 December 2012 – Poland

69. **25E-NBOMe** (2-(4-ethyl-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine) – 6 December 2012 – Poland

70. **25G-NBOMe** (2-(2,5-dimethoxyphenyl-3,4-dimethyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine) – 6 December 2012 – Poland

71. **25N-NBOMe** (2-(2,5-dimethoxyphenyl-4-nitro)-*N*-[(2-methoxyphenyl)methyl]ethanamine) – 6 December 2012 – Poland

72. **4-Methylaminorex *p*-methyl derivative** – 10 December 2012 – the Netherlands

73. **4-Methylphendimetrazine** – 12 December 2012 – Poland

Annex 2. New psychoactive substances in the category of miscellaneous 'others' that were notified to the EMCDDA and Europol for the first time in 2012 under the terms of Council Decision 2005/387/JHA

Name	Annex 1 ref	Type of substance
3-MeO-PCP 2-MeO-ketamine N-ethylnorketamine	21 50 53	Aminocyclohexanes
Zopilcone Pyrazolam	30 49	Medicinal products
5-APDI	54	Arylethylamine (indenyl derivative of an aminoalkylbenzofuran)
5-APDB 6-APDB	15 17	Arylethylamine (aminoalkylbenzofuran)
4-Methylphendimetrizine	73	Derivative of a medicinal product
ECX	19	Alkynyl cyclohexanol
4-Methylaminorex p-methyl derivative	72	Derivative of a withdrawn medicinal product
Thienoamphetamine	13	Arylethylamine (thiophene derivative of amphetamine)
AH-7921	47	Narcotic analgesic (cyclohexylmethylbenzamide)
Phenibut	16	Derivative of gamma-amino butyric acid
4-Fluoroephedrine	20	Derivative of ephedrine
(Iso)butyryl fentanyl	63	Narcotic analgesic (derivative of fentanyl)
5-IT	29	Substituted indole
1-Cyclohexyl-x-methoxybenzene (Iso)butyryl-F-fentanyl N-benzyl analogue	9 62	Potential intermediates or precursors of other drugs

Annex 3. Legal and working definitions used by the EMCDDA to classify and describe new drugs

The Joint Action 97/396/JHA and the Council Decision 2005/387/JHA provide legally binding definitions of the substances they cover; however, there are a number of other terms in common usage in this area which may cause confusion. For example, at least historically, new psychoactive substances have often been referred to as 'designer drugs' although today the term 'legal highs' is used more often. Much overlap exists between these terms but for practical purposes it is worth delineating the concepts.

The term 'new' in all definitions is not intended to refer exclusively to newly invented or newly synthesised substances, but rather should be understood as 'newly available' or 'newly misused'.

New synthetic drug (Joint Action 97/396/JHA)

The 1997 Joint Action 97/396/JHA ([53]) concerned new synthetic drugs 'which are not currently listed in any of the Schedules to the 1971 United Nations Convention on Psychotropic Substances ([54]), and which pose a comparable serious threat to public health as the substances listed in Schedules I or II thereto and which have a limited therapeutic value' (Article 2).

The Joint Action 'relates to end-products, as distinct from precursors in respect of which Council Regulation (EEC) No 3677/90 of 13 December 1990 laying down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances ([55]) and Council Directive 92/109/EEC of 14 December 1992 on the manufacture and the placing on the market of certain substances used in the illicit manufacture of narcotic drugs and psychotropic substances ([56]) provide for a Community regime' (Article 2).

New psychoactive substance (Council Decision 2005/387/JHA)

Council Decision 2005/387/JHA broadened the scope of, and replaced, the 1997 Joint Action. Like the Joint Action, it takes the United Nations drug control Conventions as a point of reference, both to define the scope of the Council Decision (Article 2) and for the definition of a new psychoactive substance (Article 3).

Council Decision 2005/387/JHA ([57]) defines a new psychoactive substance as 'a new narcotic drug or a new psychotropic drug in pure form or in a preparation, that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV' (new narcotic drug) or 'under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV' (new psychotropic drug). A preparation is defined as 'a mixture containing a new psychoactive substance' (Article 3).

The wording of this definition has a number of implications, for example, substances already listed under the UN Conventions are by definition excluded from the scope of the Council Decision. An important difference to the 1997 Joint Action is the inclusion of narcotic drugs (1961 UN Convention) and psychotropic substances which pose a comparable threat as substances listed in Schedules III or IV of the 1971 UN Convention.

'This Decision relates to end-products, as distinct from precursors in respect of which Council Regulation (EEC) No 3677/90 of 13 December 1990 laying down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances ([58]), and Regulation (EC) No 273/2004 of the

([53]) Joint Action 97/396/JHA of 16 June 1997 adopted by the Council on the basis of Article K.3 of the Treaty on European Union, concerning the information exchange, risk assessment and the control of new synthetic drugs. OJ L 167, 25.06.1997, p. 1.
([54]) 1971 United Nations Convention on Psychotropic Substances.
([55]) Council Regulation (EEC) No 3677/90 of 13 December 1990 laying down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances. OJ L 357, 20.12.1990, p. 1. Regulation as last amended by Commission Regulation (EEC) No 3769/92 (OJ L 383, 29. 12. 1992, p. 17).
([56]) Council Directive 92/109/EEC of 14 December 1992 on the manufacture and the placing on the market of certain substances used in the illicit manufacture of narcotic drugs and psychotropic substances. OJ L 370, 19.12.1992, p. 76. Directive as amended by Directive 93/46/EEC (OJ L 159, 1. 7. 1993, p. 134).
([57]) Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances, OJ L 127, 20.5.2005, p. 32.
([58]) OJ L 357, 20.12.1990, p. 1. Regulation as last amended by Commission Regulation (EC) No 1232/2002 (OJ L 180, 10.7.2002, p. 5).

European Parliament and of the Council of 11 February 2004 on drug precursors ([59]) provide for a Community regime' (Article 2).

'The new psychoactive substances covered by this Decision may include medicinal products as defined in Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products ([60]) and in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use ([61])' (point 5 of the recital to the Council Decision). However, 'substances of established and acknowledged medical value are therefore excluded from control measures based on this Decision' (point 8 of the recital to the Council Decision) as are psychoactive substances used to manufacture a medicinal product (Article 7.3).

New drugs

New psychoactive substances (new drugs) make up a broad range of substances that are not controlled under international drug laws. Often they are intended to mimic the effects of existing controlled drugs. This is reflected in the fact that many are chemically similar to controlled drugs, but, at the same time, sufficiently different that they fall outside of the scope of drug laws. In addition, a growing number of new substances from entirely different chemical families, including stimulants and substances that mimic the effects of cannabis or opioids, have also recently been detected.

The term 'new' refers to the fact that these substances are new to the drug market or newly misused. Many new drugs have previously been described in the scientific and patent literature as part of legitimate research and development. Some have been used in experiments designed to better understand the complex signalling pathways in our bodies, while others have been studied as potential medicines. However, a common feature is that there is usually limited information about the effects of these drugs in humans and the harms that they may cause. Nonetheless, it appears that those involved in supplying new substances are increasingly searching this literature for potential new drugs. Some of these are then sold directly on the illicit market, while others, the so-called 'legal highs', are sold more openly. A further development to this phenomenon is the detection of non-controlled psychoactive medicines on the market. The way in which some of these new drugs are marketed and distributed is also becoming more sophisticated. This includes their advertisement and sale on the open market, such as through the Internet (with delivery via courier and postal services), as well as sale in 'bricks and mortar' head shops.

'Designer drugs'

The way in which new drugs are produced, marketed and supplied can differ significantly. Some are sold directly on the illicit drug market. Here, they may be produced from chemical precursors in illicit production facilities of varying size and sophistication. In the past, these have typically been referred to as 'designer drugs' ([62]) — drugs that are intentionally designed to mimic the effects of controlled drugs but by slightly altering their chemical structure they circumvent existing controls. Examples include PMMA (*para*-methoxyamphetamine) and 2C-I (2,5-dimethoxy-4-iodophenethylamine), which are now controlled across the EU because of the harm they pose. New drugs sold on this market may also be tableted or otherwise packaged from bulk substances that are bought from legitimate sources; these include *m*CPP and BZP.

Both precursors and the substances themselves have been sourced from third countries and from within Europe. This market is dynamic, with source countries changing over time and place. While the source countries for precursors are often unclear, in some cases, the precursor is offered for sale on the Internet by chemical suppliers that appear to be based in China.

Overall, these new drugs are believed to be largely used surreptitiously by producers as replacements for established controlled drugs which may be in short supply, such as MDMA (ecstasy). This supposition is supported by the finding that many of them are found as tablets that use the same logos as ecstasy tablets. In some cases, new drugs may also be found in combination with controlled drugs, possibly in an attempt to 'bulk up' the drug and thereby reduce the amount of controlled drug. An example of both uses is the identification in 2004 of the piperazine

([59]) OJ L 47, 18.2.2004, p. 1.
([60]) OJ L 311, 28.11.2001, p. 1. Directive as last amended by Directive 2004/28/EC (OJ L 136, 30.4.2004, p. 58).
([61]) OJ L 311, 28.11.2001, p. 67. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).
([62]) The term 'designer drugs' emerged in the 1980s in relation to some novel fentanyl compounds and became particularly popular with the emergence of the 'ecstasy' compounds (MDMA, MDA, MDE, etc) on the illicit drug market, although strictly speaking these drugs were around long before the term 'designer drug' became popular.

derivative *m*CPP in tablets sold as ecstasy. One possible reason for the emergence of *m*CPP was the decreased availability of the chemical precursors used in the synthesis of MDMA. This, coupled with the fact that *m*CPP appears to mimic some of the subjective effects of MDMA and that it could be legally sourced in Europe and elsewhere, may have made it an attractive substitute to producers. Similarly, although BZP came to prominence as 'party pills', and was commonly sold on the open 'legal highs' market as such, some of the tablets that were seized on the illicit market were clearly intended to be sold as ecstasy, bearing typical ecstasy logos. It is also important to note that some of these new substances are also sold as drugs in their own right (e.g. 2C-B, also known as 'Nexus', which is now under international control) or as a 'special type' of ecstasy (such as *m*CPP).

'Legal highs'

Another group of new psychoactive substances — the so-called 'legal highs' — are legally sourced and sold as replacements for controlled drugs on the open market by exploiting existing laws. This group includes a wide range of synthetic and plant-derived substances that are often sold as branded products. They are also sometimes sold in combination with other new substances. This may be an attempt to better mimic the effects of controlled drugs, or to achieve novel psychoactive effects, or as a result of accidental contamination or deliberate substitution. These so-called 'legal highs' are usually sold through the Internet and in 'bricks and mortar' head shops. They may also be sold by street-level drug dealers. Mostly, they are advertised with aggressive and innovative marketing strategies. Often, in order to disguise the fact that they are psychoactive drugs, and circumvent 'grey areas' in consumer protection and marketing regulations, they are sold under various product labels, including 'research chemicals', 'bath salts' and 'plant food', and usually with an accompanying disclaimer that they are not intended for human consumption. However, describing these substances as 'legal' may not be strictly correct, as some may be regulated by medicines, food safety or other consumer protection laws; some may even contain controlled drugs.

Information from border seizures and law enforcement investigations in the EU Member States indicate that substances sold as 'legal highs' are typically imported, sometimes in multi-kilogram quantities, from China and, to a lesser degree, India. Moreover, facilities for the processing and packaging of these substances have also been seized within the EU.

As part of the marketing strategy to offer a replacement for controlled drugs, distributors and retailers may use names for 'legal high' products that allude to, or sound like, controlled drugs: 'Snow blow' for cocaine or 'Xtacy' and 'Doves Red' ([63]) for MDMA. Common street names of controlled drugs are also used (e.g. calling products 'Charlie', which is also a street name for cocaine). There have also been attempts to deceive consumers by marketing synthetic drugs as 'natural' herbal products, such as in the case of 'Spice' products that contained synthetic cannabinoids. In the majority of such cases, the substances are not listed on the product packaging. It is also clear that retailers are exploiting the Internet as a vehicle for the marketing and sale of 'legal highs'.

Importantly, some online shops sell not only retail products but also bulk quantities of substances, presumably for resale. In order to raise the profile of their products, Internet retailers use a range of marketing techniques. Many focus around selling the idea that 'legal highs' are good replacements for controlled drugs. Social media are also used a marketing tool. This includes posting videos on YouTube of 'real people' using the drugs and reviewing their effects. Some of these are set at music festivals, where traditionally the use of illicit drugs is common. In some cases, these videos are shot as 'before' and 'after' reviews to emphasise the effects of the drugs.

The 'legal highs' market is characterised by the speed at which suppliers circumvent drug controls by offering new alternatives to restricted products and advertising them with modern marketing strategies.

Finally, the term 'legal highs' is often used to refer to the phenomenon, rather than to a specific substance, similarly to the 'Spice' phenomenon, which is used to describe the marketing and sale of herbal products containing synthetic cannabinoid receptor agonists.

A further dimension of the new drug phenomenon is the growing number of psychoactive medicines that are being misused. Some of these are authorised as medicinal products within the EU (such as pregabalin) and are either diverted from the regulated market or imported from third countries. They may also include substances and products that are not licensed within the EU, such as phenazepam and etizolam (benzodiazepines).

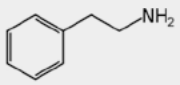
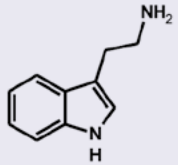
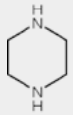
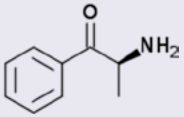
([63]) 'Doves' is a street name for ecstasy.

Annex 4. Main groups of new psychoactive substances monitored by the EU Early warning system

It is scientifically sound practice to categorise new psychoactive substances based on their chemical structure (i.e. by chemical families, see table below). Exceptions to this are the group of synthetic cannabinoids, which are currently categorised based on their mode of action and the group of miscellaneous 'others' (section 3.1.6). Described below are the main families of psychoactive substances notified through the EU Early warning system (EWS) to date. For further details on these categories see the EMCDDA drug profiles ([64]).

- Phenethylamines encompass a wide range of substances that may exhibit stimulant, entactogenic or hallucinogenic effects. Examples include the synthetic substances amphetamine, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine) and mescaline (the latter of which occurs naturally).
- Tryptamines include a number of substances that have predominantly hallucinogenic effects. The main representatives are the naturally occurring compounds dimethyltryptamine (DMT), psilocin and psilocybin (found in hallucinogenic mushrooms) as well as the semi-synthetic lysergic acid diethylamide (LSD).
- Piperazines are represented by *m*CPP (1-(3-chlorophenyl) piperazine) and BZP (1-benzylpiperazine), both of which are stimulants.
- Cathinones have stimulant effects. The main cathinone derivatives are the semi-synthetic methcathinone and the synthetic compounds mephedrone, methylone and MDPV (3,4-methylenedioxypyrovalerone).
- Synthetic cannabinoids share some functional similarities with Δ9-tetrahydrocannabinol (THC), the active principle of cannabis. Like THC, they can have sedative, depressant and hallucinogenic effects. They have been detected in herbal smoking mixtures such as 'Spice' as well as resins that mimic cannabis resin.
- Other substances reported to the EWS include various plant-derived and synthetic psychoactive substances (e.g. indanes, benzodifuranyls, narcotic analgesics, synthetic cocaine derivatives, ketamine and phencyclidine derivatives), which do not strictly belong to any of the previous families. Also included here are a number of medicinal products and derivatives.

([64]) Available at: http://www.emcdda.europa.eu/publications/drug-profiles

Family	Parent compound	Chemical structure of the parent compound	Effects	Representatives	No of substances notified (2005–12)
Phenethylamines	phenethylamine (N)		stimulant and/or hallucinogenic	amphetamine, methamphetamine, MDMA, mescaline (N)	40
Tryptamines	tryptamine (N)		hallucinogenic	psilocin and psilocybin (N), dimethyltryptamine/DMT, lysergide/LSD (S)	16
Piperazines	piperazine		stimulant	mCPP, BZP, TFMPP	9
Cathinones	cathinone (N)		stimulant	cathinone (N), mephedrone, methylone, methcathinone (S)	39
Synthetic cannabinoids	N/A – the category includes a number of chemically unrelated but functionally similar families of cannabinoid receptor agonists that mimic the effects of Δ9 – THC	N/A	depressant, sedative, hallucinogenic	JWH-018, CP 47,497, HU-210	74
Miscellaneous substances	N/A – the category includes new psychoactive plants as well as synthetic psychoactive substances, derivatives of well-established drugs not belonging to any of the families listed above, designer medicines, narcotic analgesics, etc.	N/A	stimulant, hallucinogenic, narcotic analgesic / opiate, depressant, etc.	N/A	58

(N) naturally occurring, (S) semi-synthetic, (N/A) non applicable

Appendix

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances, OJ L 127, 20.5.2005, p. 32.

Available at:

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32005D0387:EN:HTML

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About this report

The unprecedented growth in the number, type and availability of new drugs over the past few years has seen the phenomenon take on global significance. Overall, the number of substances notified in the last two years accounts for more than half of the total number of substances notified to the EU Early warning system since May 2005. Driven by globalisation, technological advancement and the Internet, an open market for new drugs has now developed which presents challenges to public health, law enforcement and policy making. The rapid appearance of non-controlled alternatives to controlled drugs underlines the ability of the market to respond to changes in the legal status of psychoactive substances and has been accompanied, in some cases, by serious adverse health consequences. It is well established that organised crime is involved in some of these activities and continues to exploit the opportunities presented by the market in new drugs. This report presents the key activities performed by the EMCDDA and Europol in 2012 and includes details of all the relevant activities in support of the implementation of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances.

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 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. 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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