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The challenge of new psychoactive substances

Global SMART Programme

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The challenge of new psychoactive substances

A Report from the Global SMART Programme
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The Global SMART Programme

UNODC launched the Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) Programme in September 2008. The Programme seeks to enhance the capacity of Member States and authorities in priority regions, to generate, manage, analyse and report synthetic drug information, and to apply this scientific evidence-based knowledge to design the policies and programmes. The Global SMART Programme is being implemented in a gradual phased manner, with East Asia being the first focus priority region. Operations in Latin America started in 2011.

This report is the first global situation assessment on new psychoactive substances put forward under the Global SMART Programme and pursuant to Commission on Narcotic Drugs Resolution 55/1 on "Promoting international cooperation in responding to the challenges posed by new psychoactive substances", which requested the United Nations Office on Drugs and Crime to provide an update to its 2011 report entitled "Synthetic cannabinoids in herbal products", addressing a wider range of new psychoactive substances, in addition to synthetic cannabinoids, and to take into consideration the creation of a compilation of new psychoactive substances encountered by Member States, to serve as an early warning advisory.

It constitutes the first step in providing consolidated up to-date analysis, based primarily on the information shared by Member States and the International Collaborative Exercise network of drug analysis laboratories. It is hoped that the information on new psychoactive substances presented in this report will make a practical contribution to addressing the significant threat posed by the manufacture, trafficking and use of these substances throughout the world, and place policymakers in a better position to evaluate the drug situation, and to make informed decisions on intervention and prevention strategies.

This report provides an overview of the situation throughout the world. It outlines the emergence of different groups of new psychoactive substances in the regions and highlights several key issues associated with these substances, including reported adverse effects associated with their use, the challenges for the identification of these substances and their subsequent control through legislation. While the information presented points towards increasing efforts by the countries to address the NPS problem, it also highlights the need for continued and joint efforts, both at the national as well as regional levels. It is hoped that this report will contribute to a better understanding of the NPS problem and in developing effective strategies to address it.

Abbreviations

2-AI	2-Aminoindane
3-MeO-PCE	3-Methoxyeticyclidine
4-AcO-DiPT	4-Acetoxy-*N*,*N*-diisopropyltryptamine
4-AcO-DMT	4-Acetoxy-*N*,*N*-dimethyltryptamine
4-FA	4-Fluoroamphetamine
4-FMA	4-Fluoromethamphetamine
4-MeO-PCP	4-methoxyphencyclidine
5-APB	5-(2-Aminopropyl)benzofuran
5-HTP	5-Hydroxytryptophan
5-IAI	5-Iodo-2-aminoindane
5-MeO-DALT	5-Methoxy-*N*,*N*-diallyltryptamine
5-MeO-DMT	5-Methoxy-*N*,*N*-dimethyltryptamine
5-MeO-DPT	5-Methoxy-*N*,*N*-dipropyltryptamine
6-APB	6-(2-Aminopropyl)benzofuran
α-PPP	α-Pyrrolidinopropiophenone
α-PVP	α-Pyrrolidinopentiophenone
ARQ	UNODC Annual Reports Questionnaire
ATS	Amphetamine-type stimulants
BCS	British Crime Survey (UK)
BZP	Benzylpiperazine
'CP' compounds	cyclohexylphenols or 3-arylcyclohexanols
CSA	Controlled Substances Act (USA)
DAINAP	Drug Abuse Information Network for Asia and the Pacific
DEA	Drug Enforcement Administration (USA)
DET	3-[2-(diethylamino)ethyl]indole
DOB	Brolamphetamine
DOC	2,5-dimethoxy-4-chloroamphetamine
DOI	2,5-dimethoxy-4-iodoamphetamine
DOM / STP	2,5-dimethoxy-*alpha*,4-dimethylphenethylamine
EACD	Expert Advisory Committee on Drugs (New Zealand)
EDND	European database on new drugs
EDRS	Ecstasy and Related Drugs Reporting System (Australia)
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMEA	European Agency for the Evaluation of Medicinal Products
ETAI	*N*-Ethyl-5-trifluoromethyl-2-aminoindane
EU	European Union
EUROPOL	European Police Office
FTIR	Fourier transform infrared spectroscopy
GC-MS	Gas chromatography - mass spectrometry
GHB	Gamma-hydroxybutyrate
HPLC	High performance liquid chromatography
ICE	International Collaborative Exercises
INCB	International Narcotics Control Board
LC–MS	Liquid chromatography–mass spectrometry
LSD	d-lysergic acid
MBZP	1-Benzyl-4-methylpiperazine

*m*CPP	1-(3-Chlorophenyl)piperazine
MDA	3,4-methylenedioxyamphetamine
MDAI	5,6-Methylenedioxy-2-aminoindane
MDBP	Methylenedioxybenzylpiperazines
MDE	*N*-ethyl-α-methyl-3,4-(methylenedioxy)phenethylamine
MDMA	3,4-methylenedioxymethamphetamine
MDMAI	5,6-Methylenedioxy-*N*-methyl-2-aminoindane
MDPV	3,4-Methylenedioxypyrovalerone
Mephedrone (4-MMC)	4-methylmethcathinone
MMAI	5-Methoxy-6-methyl-2-aminoindane
NFLIS	National Forensic Laboratory Information System
NMR	Nuclear magnetic resonance
NPS	New Psychoactive Substances
np-SAD	National Programme on Substance Abuse Deaths (UK)
NTA	National Treatment Agency for Substances Misuse (UK)
PCE	Eticyclidine
PCP	Phencyclidine
pFPP	1-(4-Fluorophenyl)piperazine
PHP/PCPY	Rolicyclidine
PMA	*p*-methoxy-alpha-methylphenethylamine
PMMA	1-(4-methoxyphenyl)-2-methylaminopropane
SMART	Global Synthetics Monitoring: Analyses, Reporting and Trends
TAI	5-trifluoromethyl-2-aminoindane
TCP	Tenocyclidine
TFMPP	1-(3-Trifluoromethylphenyl)piperazine
THC	Δ^9-tetrahydrocannabinol
UK	United Kingdom
US	United States of America
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization
YSS	Youth Smoking Survey (Canada)

Weights and measurements

kg	Kilogram
mt	Metric tons

Notes to the reader

This report has not been formally edited.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Countries and areas are referred to by the names that were in official use at the time the relevant data were collected.

The following notes describe certain terms, regional designations, data sources and timeframes used throughout this document.

NPS – New psychoactive substances are substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat. In this context, the term 'new' does not necessarily refer to new inventions but to substances that have been recently become available.

Data sources – Unless indicated specifically, data contained in this report draws upon official sources as reported in the UNODC questionnaire on new psychoactive substances by Member States and by the International Collaborative Exercise network of drug analysis laboratories, data reported in the UNODC Annual Reports Questionnaire (ARQ) by Member States, annual and technical reports of official government and inter-governmental entities (e.g. Europol, EMCDDA, World Health Organization, UNODC reports) and scientific literature.

Annexes – Any compound or substance reported through the UNODC questionnaire on new psychoactive substances under control in the international drug control conventions or whose name was not provided in full or only as an analogue without further indication was excluded from the annexes to this report. Individual reports on active ingredients of plant-based substances were merged with the corresponding plant/herb. Substances with several positional isomers in which the specific isomer was not indicated were merged into the generic compound.

Data time frame – The statistical data contained in this report cover the 2009-2012 period, except in instances where a longer historical frame is necessary to provide a clear explanation of emergence and use of new psychoactive substances. Data for 2012 should be considered preliminary as the UNODC questionnaire on NPS was circulated in July 2012. Data are subject to change for a variety of reasons, such as new or late data being added or revisions in data already provided by Member States. Thus, some figure may differ from previously published figures. All data reported herein reflect the most up-to-date and precise information available at the time of publication.

Symbols – In the tables throughout this report arrows indicate an increase or decrease in the trend of use or availability of a specified new psychoactive substance during the previous year - (↑) an increase, (↓) a decrease, (↔) a stable and (-) indicates that the information is not available, not known, or was not reported.

Terms – Since there is some scientific and legal ambiguity about the distinctions between drug 'use', 'misuse' and 'abuse', this report uses the neutral terms, drug 'use' or 'consumption'.

Country names and geographical names – In various sections, this report uses a number of regional designations. These are not official designations. They are defined as follows:

Africa

Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Democratic Republic of Congo, Côte d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Togo, Tunisia Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

Americas

Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bermuda, Bolivia (Plurinational State of), Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador,

Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States of America, Uruguay and Venezuela (Bolivarian Republic of).

Asia

Afghanistan, Armenia, Azerbaijan, Bahrain, Bangladesh, Bhutan, Brunei Darussalam, Cambodia, China, Democratic People's Republic of Korea, Georgia, India, Indonesia, Iran (Islamic Republic of), Iraq, Israel, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Malaysia, Maldives, Mongolia, Myanmar, Nepal, Oman, Pakistan, Philippines, Qatar, Republic of Korea, Saudi Arabia, Singapore, Sri Lanka, Syrian Arab Republic, Tajikistan, Thailand, Timor-Leste, Turkmenistan, the United Arab Emirates, Uzbekistan, Viet Nam and Yemen

Europe

Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the former Yugoslav Republic of Macedonia, Turkey, Ukraine and United Kingdom of Great Britain and Northern Ireland.

Oceania

Australia, Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, New Zealand, Palau, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu and Vanuatu.

Background

The amphetamine-type stimulants (ATS) market has always been characterized by a large variety of substances. However, in recent years, new psychoactive substances (NPS) have rapidly emerged in this market purportedly as "legal" alternatives to internationally controlled drugs, causing similar effects to the latter, with the potential to pose serious risks to public health and safety. The fast-paced nature of this market, the increased availability of these substances and the reports of increased and emerging use of and trade in such substances have drawn concerns among the international community as there is the potential for transnational organized criminal groups to exploit the market for these substances.

As a response, the Commission on Narcotic Drugs, recalling its resolution 48/1 of 11 March 2005 on promoting the sharing of information on emerging trends in the abuse of and trafficking in substances not controlled under the international drug control conventions, and noting the increasing number of reports about the production of synthetic cannabinoids in herbal products, adopted resolution 53/11 of 12 March 2010, on promoting the sharing of information on the potential abuse of and trafficking in synthetic cannabinoid receptor agonists. In that resolution, the Commission requested the United Nations Office on Drugs and Crime to "share information on the issue of cannabinoid receptor agonists with the Expert Committee on Drug Dependence of the World Health Organization to increase its understanding and awareness of the issue". Pursuant to this resolution, UNODC prepared the 2011 report "Synthetic cannabinoids in herbal products".[1]

The continued high number and wide range of new psychoactive substances of diverse origin, effect and risk profile, identified as posing serious risks to public health, as well as the challenges that identification and control of such substances pose to effective health and law enforcement regulation, resulted in Commission on Narcotic Drugs resolution 55/1, which in paragraph 13 requests UNODC "to provide an update to its 2011 report entitled 'Synthetic cannabinoids in herbal products', addressing a wider range of new psychoactive substances, in addition to synthetic cannabinoids, and to take into consideration the creation of a compilation of new psychoactive substances encountered by Member States, to serve as an early warning advisory".

This report was prepared pursuant to resolution 55/1. Its aim is to provide an overview of the main groups of new psychoactive substances present in illicit ATS markets, their chemistry, mode of use and reported adverse effects associated with their use. It reflects the situation as of February 2013 and provides information about the emergence of NPS, the prevalence of use, the origins of these substances and the different approaches in regulation that have been taken by some Governments. It finally suggests ways that could be potentially used to detect, identify and monitor NPS, in order to facilitate States making effective evidence-based decisions to counteract the challenges posed by such substances.

Methodology

The information and data presented in this report were obtained primarily through an electronic questionnaire on NPS, which was sent to all Member States as well as to the drug analysis laboratories that participate in the UNODC International Collaborative Exercises (ICE) in July 2012. The questionnaire covered a wide spectrum of issues related to NPS, *inter alia*, legislation, seizures of NPS, substances detected and analyzed, identification of NPS, sources, trafficking, distribution and the use of NPS. Additional information was obtained from Government reports, scientific literature and data extracted from the UNODC ICE Portal.

[1] United Nations Office on Drugs and Crime, 'Synthetic cannabinoids in herbal products', Vienna, 2011

1. INTRODUCTION

1.1 Emergence of new psychoactive substances

New psychoactive substances that fall outside international drug control conventions are not a novel phenomenon. Many of these substances were synthesized and patented in the early 1970s or even earlier, but only recently their chemistry or process of synthesis have been slightly modified to produce effects similar to known illicit substances.

NPS have been known in the market by terms such as 'designer drugs', 'legal highs', 'herbal highs', 'bath salts'. The term 'designer drugs' had been traditionally used to identify synthetic substances but has recently been broadened to include other psychoactive substances that mimic the effects of illicit drugs and are produced by introducing slight modifications to the chemical structure of controlled substances to circumvent drug controls. 'Legal highs', 'herbal highs', 'research chemicals' and 'bath salts' are also common names used to refer to NPS offered as a legal alternative to controlled drugs. These substances are frequently labelled as 'not for human consumption'.

Over the last decade these substances have been introduced in ATS markets through various modes of distribution, including the Internet, 'head' or 'smart shops' which sell drug paraphernalia, or street-level drug traffickers as legal alternatives to illicit drugs, accounting for an increasingly significant share of illicit drug markets in some countries and becoming a matter of great concern and a threat to public health.

Ketamine is one of the oldest NPS. Its abuse was recognized in the United States since the beginning of the 1980s and started to be noticed in Europe in the 1990s.[2] Other NPS such as those belonging to the family of phenethylamines and piperazines appeared in the market through the 1990s and at the beginning of the 2000s respectively.[3] From 2004 onwards synthetic cannabinoids such as 'spice', started to be seen in the market, followed by synthetic cathinones and other emerging groups of NPS, as identified in this report.

1.2 Definition and categories of new psychoactive substances

For the purposes of this document, NPS are defined as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat". In this context, the term 'new' does not necessarily refer to new inventions but to substances that have recently become available.

The information and analysis of NPS presented throughout this report is based on the identification of six main groups of substances present in this market, i.e. synthetic cannabinoids, synthetic cathinones, ketamine, phenethylamines, piperazines, plant-based substances, and a seventh group of miscellaneous substances that contain recently identified NPS which do not fit into the aforementioned groups.

Given the almost infinite possibilities of altering struc-

[2] European Monitoring Center for Drugs and Drug Addiction, 'Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs', Belgium, 2002

[3] For instance, Benzylpiperazine (BZP) was first sold commercially as an alternative and a legal drug in New Zealand around the year 2000. Bassindale, T., 'Benzylpiperazine: the New Zealand legal perspective', Drug Testing and Analysis, 2011, 3, 428-429; BZP was first noted in Europe around 2004

tures of chemicals, the list of substances mentioned in each of the NPS groups is not exhaustive but offers some guidance on the most common substances as reported by respondents to the UNODC questionnaire on NPS.

Substances that are not covered in this report include substances that are subject to international control under the 1961 Convention on Narcotic Drugs or under the 1971 Convention. Benzodiazepines, for instance, or any other prescription drugs that are prone to abuse, such as opioids, central nervous system depressants and stimulants are not the subject of this report.

2. MAIN NEW PSYCHOACTIVE SUBSTANCES ENCOUNTERED IN ILLICIT ATS MARKETS AND THEIR EFFECTS

Many of the substances that are available on the market for NPS contain unfamiliar molecules that may or may not share similar risk effects and profiles to the illicit substances they are designed to mimic. As a result, they may pose serious challenges to researchers and policy-makers that try to assess the risk of harm and to take appropriate measures to control them.

Research on most NPS is very limited. There are no comprehensive scientific studies on their toxicity and most studies are based on work in animals, fatal poisonings in humans or clinical observations in intoxicated patients. Toxicity, abuse liability and risks associated with long-term use in particular remain unknown. Most NPS have little or no history of medical use.

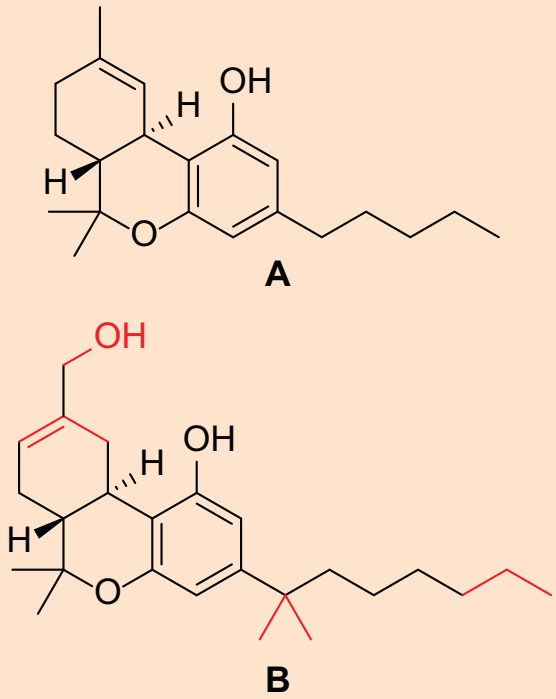
2.1. Synthetic cannabinoids

Background

The appearance of 'herbal highs' in the market is not a new phenomenon. Such products usually consisted of plant mixtures with little psychoactive effects. Since 2004, however, the composition of these herbal products seems to have substantially changed to include potent new psychoactive compounds known as synthetic cannabinoids.

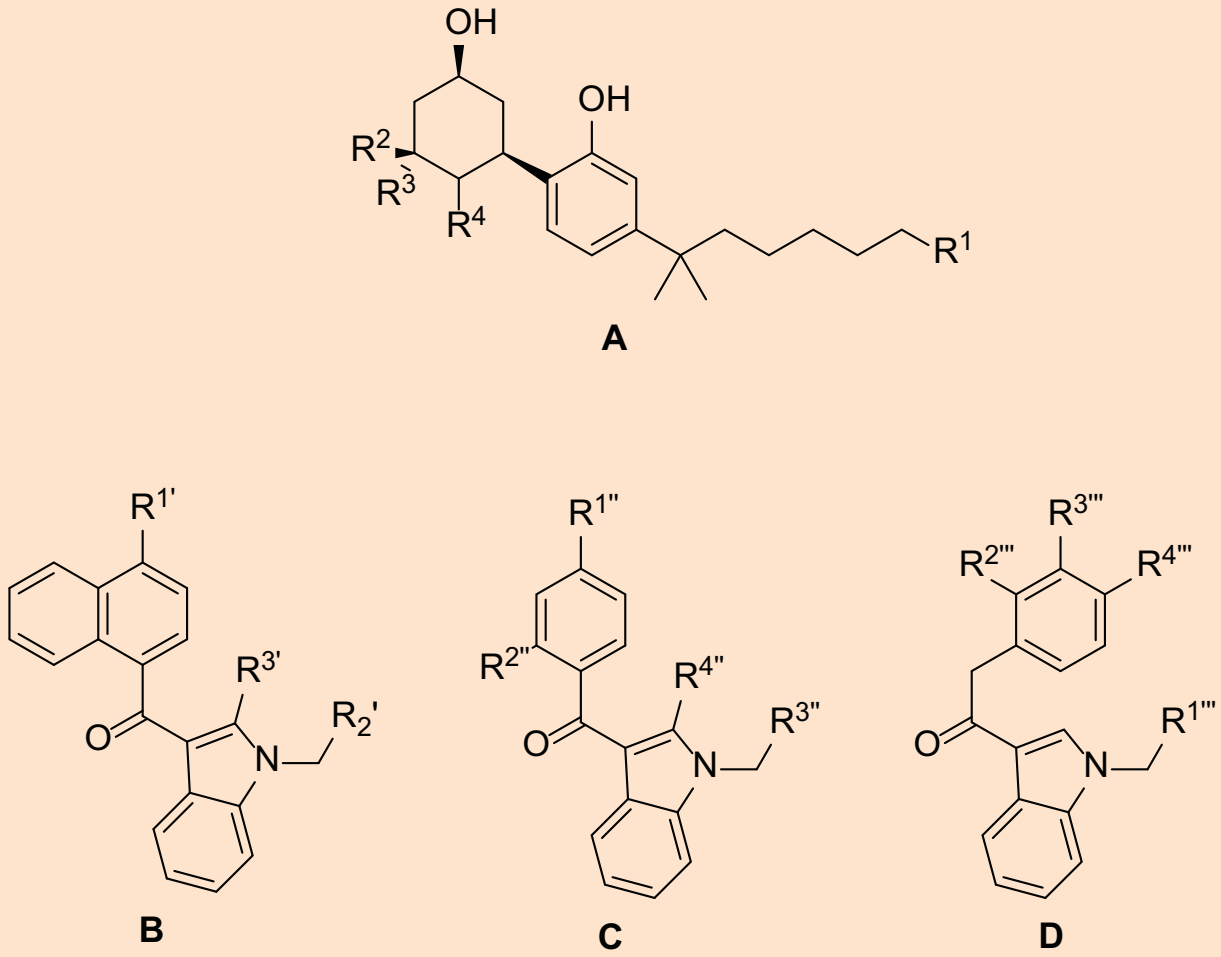
Research on the mechanism of cannabis activity dates back several decades when molecules with similar behaviour to Δ^9-tetrahydrocannabinol (THC) were first examined. A synthetic analogue of THC , 'HU-210', was first synthesized in Israel in 1988[4] and is considered to have a potency of at least 100 times more than THC. Due to its similar chemical structure to THC, 'HU-210' is regarded as a 'classical cannabinoid' and has been found in synthetic cannabinoids sold in the United States and other countries.

Non-classical cannabinoids include cyclohexylphenols or 3-arylcyclohexanols ('CP'compounds). 'CP' compounds were developed as potential analgesics by a pharmaceutical company in the 1980s. Respondents to the UNODC questionnaire on NPS have reported



Chemical structure of classical cannabinoids: Δ9-tetrahydrocannabinol (A), and of the synthetic cannabinoid HU-210 (B). The differences between the synthetic cannabinoid and the controlled substance tetrahydrocannabinol are highlighted in red.

[4] Mechoulam, R., Lander, N., Breuer, A., Zahalka, J., 'Synthesis of the individual, pharmacologically distinct, enantiomers of a tetrahydrocannabinol derivative', Tetrahedron: Asymetry, 1990, 1 (5), 315-18



Generic chemical structure of non-classical cannabinoids and aminoalkylindoles: generic chemical structure of synthetic non-classical cannabinoids (A), and three groups of aminoalkylindoles, i.e. naphthoylindoles (B), phenacetylindoles (C), and benzoylindoles (D). Many cannabinoid derivatives and analogues could be synthesized by the addition of a halogen, alkyl, alkoxy or other substituent to one of the aromatic ring systems. Other small changes, such as variations of the length and configuration of the alkyl chain, can also be made to synthesize other compounds.

the emergence of CP-47,497 and CP-47,497-C8 in numerous countries in all regions except Africa since 2009.

Other structurally dissimilar varieties of synthetic cannabinoids unrelated to THC have also emerged on the market. These include aminoalkylindoles, such as naphtoylindoles (e.g. JWH-018), phenylacetylindoles (e.g. JWH-250), and benzoylindoles (e.g. AM-2233).[5] JWH-018, arguably the best known synthetic cannabinoid, belongs to the group of aminoalkylindoles and is considered to be three times as potent as THC. The JWH-compounds had been previously developed as test compounds in the research of receptor-drug interactions by Professor John William Huffman[6] and his team in the United States.

While cannabis and THC are controlled under the international drug control treaties, none of the synthetic cannabinoids are under international control. However, several have been subject to control measures at the national level. Respondents to the 2012 UNODC survey on NPS identified JWH-018 as the most widespread synthetic cannabinoid, followed by JWH-073, JWH-250 and JWH-081, all of which are aminoalkylindoles.

[5] United Nations Office on Drugs and Crime, 'Synthetic cannabinoids in herbal products', Vienna, 2011, 5; see also Hudson, S., Ramsey, J., 'The emergence and analysis of synthetic cannabinoids', Drug Testing and Analysis, 2011, 3, 466–478

[6] John W. Huffman is a US chemist and a retired professor of organic chemistry at Clemson University in the United States, whose research led to the synthesis of non-cannabinoid cannabimimetrics in the 1990s. Dr Huffman's research group focuses on the synthesis of analogues and metabolites of THC with the aim to develop new pharmaceutical products for medical treatment. 'John Huffman', Clemson University (http://www.clemson.edu/chemistry/people/huffman.html; accessed in: October 2012)

Description

Most synthetic cannabinoids are functionally similar to THC. Synthetic cannabinoids are usually available in powder form and are sold as *'Spice Gold'*, *'Spice Silver'*, *'Spice Diamond'*, *'K2'*, *'Bliss'*, *'Black Mamba'*, *'Bombay Blue'*, *'Blaze'*, *'Genie'*, *'Zohai'*, *'JWH -018, -073, -250'*, *'Kronic'*, *'Yucatan Fire'*, *'Skunk'*, *'Moon Rocks'*, *'Mr. Smiley'*. They are usually smoked, but oral use has also been reported. Labels on packages and actual constituents of the product are often mismatched.

Reported adverse effects

While side effects of cannabis are well documented,[7] data on human toxicity related to the use of synthetic cannabinoids remains limited. As with other NPS, products sold as synthetic cannabinoids often contain several chemicals in different concentrations, making it very difficult to determine substance-specific effects. Available knowledge on the toxicity of these compounds comes from scientific reports and clinical observations.

Health-related problems associated with the use of synthetic cannabinoids include cardiovascular problems and psychological disorders,[8] and it appears that there may be carcinogenic potential with some of the metabolites of the substances contained in these products.[9]

A study published in 2011 on the severe toxicity following synthetic cannabinoid ingestion suggested that JWH-018 could lead to seizures and tachyarrhythmia (irregular heartbeat).[10] In a recent review of clinical reports, addiction and withdrawal symptoms similar to those seen with cannabis abuse were also linked to the use of synthetic cannabinoids.[11] An analysis of synthetic cannabinoids in 'spice-like' herbal blends highlighted the increasing number of reports on suicides associated with preceding use of these products.[12]

2.2. Synthetic cathinones

Background

Cathinone and its derivatives are closely related to the phenethylamine family (which includes amphetamine and methamphetamine), but with a lower potency than the latter.[13] They are characterised by the presence of a β-keto group on the side chain of the phenethylamines. Cathinone, the principal active ingredient in the leaves of the khat plant *(catha edulis)*, can be considered as the prototype from which a range of synthetic cathinones have been developed.

Synthetic cathinones appeared in drug markets in the mid 2000s. In 2005, methylone, an analogue of MDMA, was the first synthetic cathinone reported to the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA). In 2007, reports of 4-methylmethcathinone (mephedrone) use emerged, first in Israel and then in other countries and regions, including Australia, Scandinavia, Ireland and the United Kingdom.[14] Mephedrone was reportedly first synthesized in 1929.[15]

Typically, synthetic cathinones have an amphetamine-type analogue, *i.e.* cathinone, ephedrone, and methylone are structurally related to amphetamine, methamphetamine and MDMA respectively. However, little is known about the mechanism of action and the potential harms of mephedrone, but it has been suggested that mephedrone is likely to act in a similar way to other stimulants (e.g. cocaine, amphetamine and

7 For example in Hall, W., Solowij, N., 'Adverse effects of cannabis', The Lancet, 1998, 352, 1611-6; Ashton, C. H., 'Adverse effects of cannabis and cannabinoids', British Journal of Anaesthesia, 1999, 83 (4), 637-49

8 Müller, H., Huttner, H.B., Köhrmann, M., Wielopolski, J.E., Kornhuber, J. and Sperling, W., 'Panic attack after spice abusein patient with ADHD', Pharmacopsychiatry, 2010, 43, 4, 152-153; Mir, A., Obafemi, A., Young, A. and Kane, C., 'Myocardial infarction associated with use of the synthetic cannabinoid K2', Jounal of Pediatrics, 2011, 128, 6, 1622-1627; Every-Palmer, S., 'Synthetic cannabinoid JWH-018 and psychosis: an explorative sudy', Drug and Alcohol Dependence, 2011, 117 (2-3), 152-157

9 Lin, C.Y., Wheelock, A.M., Morin, D., Baldwin, R.M., Lee, M.G., Taff, A., Plopper, C., Buckpitt, A., and Rohde, A, 'Toxicity and metabolism of methylnaphthalenes: comparison with naphthalene and 1- Nitronaphthalene', Toxicology, 2009, 260, 16-27

10 Lapoint, J., James, L.P., Moran, C.L., Nelson, L.S., Hoffman, R.S., & Moran, J.H., 'Severe toxicity following synthetic cannabinoid ingestion', Clinical Toxicology (Philadelphia), 2011, 49, 760-64

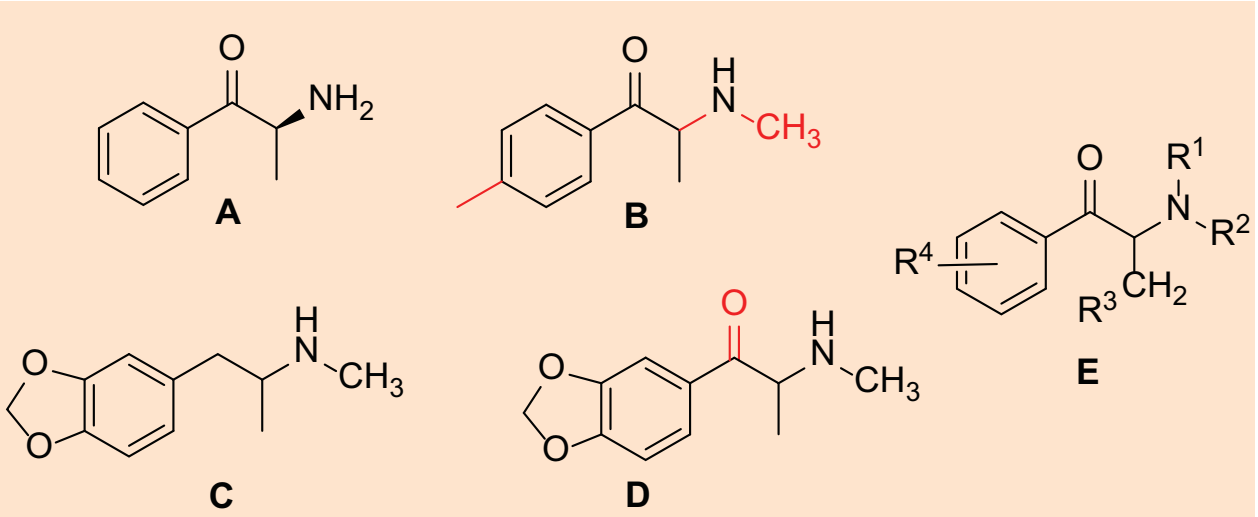
11 Vardakou, I., Pistos, C., Spiliopoulou, C.H., 'Spice drugs as a new trend: mode of action, identification and legislation', Toxicology Letter, 2010, 197, 157-162

12 Ludger, E., Krueger, K., Lindigkeit, R., Schiebel, HM., Beuerle, T., 'Synthetic cannabinoids in "spice-like" herbal blends: first appearance of JWH-307 and recurrence of JWH-018 on the German market', Forensic Science International, 2012, 222 (1), 216-222

13 European Monitoring Centre for Drugs and Drug Addiction, 'Synthetic cathinones', Drug Profiles (www.emcdda.europa.eu)

14 Kelly, J.P., 'Cathinone derivatives: A review of their chemistry, pharmacology and toxicology', Drug Testing and Analysis, 2011, 3, 439-453

15 Saem de Burnaga Sanchez, J., 'Sur un homologue de l'ephedrine', Bulletin de la Société Chimique de France, 1929, 45, 284-86.



Chemical structures of cathinone (A), mephedrone (B), MDMA (C) and methylone (D). Differences between controlled substances (i.e. cathinone and MDMA) and synthetic derivatives of cathinones (i.e. mephedrone and methylone) are highlighted in red. The molecular structure of generic cathinone derivatives is represented in structure (E). The 'R' groups indicate locations of the molecule where modifications can occur to produce a wide range of cathinone derivatives.

MDMA).[16] Up to 2010, methylone and mephedrone (4-methylmethcathinone) were identified as the most common substances of use in this group in Europe.[17]

Other synthetic cathinones recently identified in the drug market are analogues of pyrovalerone (3,4-methylenedioxypyrovalerone and naphyrone). For instance, 3,4-methylenedioxypyrovalerone (MDPV), first synthesized in 1969,[18] emerged in 2007 as a new psychoactive substance in Germany.[19] In 2008, it was first reported to the European Early Warning System by the United Kingdom and by Finland, after being associated with adverse health effects.[20] Initially unregulated, many countries, including countries of the European Union as well as Australia, Israel and the United States have introduced control measures over the substance. Other synthetic cathinones, *inter alia*, flephedrone and naphyrone also became available in the drug market as NPS from 2008 onwards.[21]

Responses to the UNODC questionnaire on NPS indicated that other synthetic cathinones, including methylone, butylone, 4-methylethcathinone, 4-fluoromethcathinone, naphyrone, 3-fluoromethcathinone, methedrone, and, to a lesser extent, 3,4-dimethyl-methcathinone, α-pyrrolidinopentiophenone (α-PVP), buphedrone, pentedrone and α-pyrrolidinopropiophenone (α-PPP), have increasingly been used as NPS from 2010 onwards.

While some synthetic cathinones such as methylone had been patented as antidepressant and antiparkinsonian agents,[22] very few have been exploited clinically predominantly on account of their abuse and dependence potential. For instance, whereas diethylcathinone (amfepramone) is used as an appetite suppressant, pyrovalerone, first synthesized in 1964 and marketed for use as an appetite suppressant and in the treatment of chronic fatigue, was later withdrawn due to abuse and dependency in users.[23] Apart from cathinone, the only

16 European Monitoring Centre for Drugs and Drug Addiction, 'Risk assessment report of a new psychoactive substance: 4-methylmethcathinone (mephedrone)', 2010

17 European Monitoring Centre for Drugs and Drug Addiction, 'Synthetic cathinones', Drug Profiles (www.emcdda.europa.eu)

18 'Boehringer Ingelheim Patent for MDPV' (http://catbull.com/alamut/Bibliothek/Boehringer_MDPV _Patent.htm)

19 In 2007, MDPV was first identified in a seizure in Germany. Westphal, F., Junge, T., Rosner, P., Sonnichsen, F., Schuster, F., 'Mass and NMR spectroscopic characterization of 3,4-methylenedioxypyrolvalerone: a designer drug with apyrrolidinophenone structure', Forensic Science International, 2009, 190, 1-8

20 European Monitoring Centre for Drugs and Drug Addiction and European Police Office, 'EMCDDA–Europol 2010 Annual report on the implementation of Council Decision 2005/387/JHA', Lisbon, 2011

21 Kelly, J.P., 'Cathinone derivatives: A review of their chemistry, pharmacology and toxicology', Drug Testing and Analysis, 2011, 3, 439-453

22 Jacob, P., Shulgin, A.T., Patent WO9639133 1996, 19. CA 126: 117961, Neurobiological Technologies Inc, USA

23 Meltzer, P., Butler, D., Deschamps, J.R., Madras, B.K., '(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors', Journal of Medicinal Chemistry, 2006, 49, 1420-32; other cathinone derivatives, such as amfepramone and bupropion are or have also been used as active pharmaceutical ingredients.

cathinone derivatives under international drug control are amfepramone, methcathinone and pyrovalerone.[24]

Description

Synthetic cathinones are frequently found in products sold as 'research chemicals', 'plant food', 'bath salts' or 'glass cleaner' and are usually sold in powder, pill or capsule form. Mephedrone (*'m-cat'*, *'meph'*, *'drone'* or *'miaow'*) and methylone (*'explosion'* or *'top cat'*) are usually available as white or brown powders or in the form of pills that are often sold as 'ecstasy'. Most synthetic derivatives are ingested but may be injected. Mephedrone is commonly nasally insufflated, injected, ingested by swallowing a powder wrapped in paper ('bombing'), or mixed in a drink.

Reported adverse effects

Few reports on the toxicity of synthetic cathinones exist to date. Much of the current knowledge on health-related effects comes from user reports and clinical observations. Further research is needed to provide evidence of short and long-term health risks and the addiction potential associated with the use of these substances.

Whereas cardiac, psychiatric, and neurological signs are some of the adverse effects reported by synthetic cathinone users, agitation, ranging from mild agitation to severe psychosis, is the most common symptom identified from medical observations.[25] Studies of patients under the apparent influence of mephedrone have also shown that synthetic cathinones present similar sympathomimetic effects (including tachycardia and hypertension as well as psychoactive effects) to similar amphetamine derivatives.[26] In a student survey, more than half of those who had taken mephedrone reported adverse effects associated with the central nervous system, nasal/respiratory system and cardiovascular system.[27] The first fatality related to the sole use of mephedrone, confirmed by toxicological analysis, was reported in Sweden in 2008.[28] Most fatalities associated with the use of mephedrone involved the use of other substances.[29] Deaths associated with the use of other synthetic cathinones include two deaths related to methedrone[30] and two other deaths related to butylone.[31]

The Finnish Poisons Information Centre reported 33 calls regarding exposures to MDPV during the period of January 2008 to October 2009. Post mortem toxicological analysis confirmed 6 deaths related to MDPV between 2009 and 2010, although in most of the cases the presence of other drugs was also detected.[32] A report from the United States provided details on the case of 35 patients who visited an Emergency Department over a 3-month-period after ingesting, inhaling or injecting substances sold as 'bath salts' and asserted that these products could contain stimulant compounds such as MDPV or mephedrone. One person was dead upon arrival at the emergency department. The toxicological analysis revealed a high level of MDPV, along with cannabis and prescription drugs, but the autopsy results revealed MDPV toxicity to be the primary factor contributing to death.[33]

24 Cathinone and methcathinone are listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances. Amfepramone and pyrovalerone are listed in Schedule IV of the same Convention.

25 Prosser, J.M. and Nelson, L.S., 'The toxicology of bath salts: a review of synthetic cathinones', The Journal of Medical Toxicology, 2012, 8 (1), 33-42

26 European Monitoring Centre for Drugs and Drug Addiction, 'Synthetic cathinones', Drug Profiles (www.emcdda.europa.eu); The term sympathomimetic refers to a pharmacologic agent that mimics the effects of stimulation of organs and structures by the sympathetic nervous system. It functions by occupying adrenergic receptor sites and acting as an agonist or by increasing the release of the neurotransmitter norepinephrine at postganglionic nerve endings.

27 Dargan, P.I., Albert, S., Wood, D.M., 'Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change', Oxford Journal of Medicine, 2010, 103 (10), 875-9

28 Gustavsson, D., Escher, C., 'Mephedrone – internet drug which seems to have come and stay. Fatal cases in Sweden have drawn attention to previously unknown substance', Lakartidningen, 2009, 106 (43), 2769-71

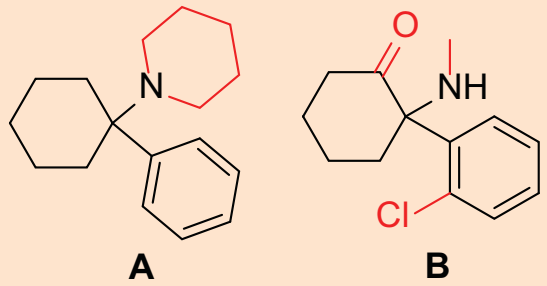
29 The death of a 46-year old man in the UK was caused by a combination of mephedrone and heroin. Other cases reported from Scotland revealed the presence of other substances along with mephedrone. See Dickson, A.J., Vorce, S.P., Levine, B., Past M.R., 'Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin', Journal of Analytical Toxicology, 2010, 34 (3), 162-8; Torrance, H., Cooper, G., 'The detection of mephedrone (4-methylmethcathinone) in 4 fatalities in Scotland', Forensic Science International, 2010, 202 (1-3), 62-3

30 Wikström, M., Thelander, G., Nyström, I. and Kronstrand, R, 'Two fatal Intoxications with the New Designer Drug Methedrone (4-Methoxymethcathinone)', Journal of Analytical Toxicology, 2010, 34, 594-98

31 Carter, N., Rutty, G., N., Milroy, C. M., Forrest, A. R. W, 'Deaths associated with MBDB misuse', Journal of Legal Medicine, 2000, 113, 168–70

32 Finland, National Institute for Health and Welfare, 'MDPV in Finland', 2010 (http://ewsd.wiv-isp.be/Publications%20on%20new%20psychoactive%20substances/MDPV/MDPV%20facts%20from%20Finland.pdf)

33 United States, Centers for Disease Control and Prevention, Atlanta, 'Emergency Department visits after use of a drug sold as "bath salts"--- Michigan, November 13, 2010--March 31, 2011' (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a6.htm)



Chemical structures of phencyclidine (A) (controlled substance) and ketamine (B). A significant portion of the molecule is common to both compounds (the phenylcyclohexyl), while the differences between them are highlighted in red.

2.3. Ketamine

Background

Ketamine is closely related to the internationally controlled drug phencyclidine (also known as PCP or 'angel dust') which is listed in Schedule II of the 1971 Convention (see section 2.7.2).

Phencyclidine was investigated as an intravenous anaesthetic in the 1950s but was later withdrawn due to undesired hallucinogenic and delirium effects.[34] Following the withdrawal of phencyclidine, ketamine was synthesized as an anaesthetic in 1962, patented in 1963 in Belgium and three years later in the United States. In the early 1970s, ketamine was marketed as a medical alternative to phencyclidine.

The use of ketamine as a new psychoactive substance dates back to the 1980s and 1990s. At the international level, ketamine was subject to a series of risk assessments. The Expert Committee on Drug Dependence of the WHO pre-reviewed ketamine in 2003 and conducted critical review in 2006. After reviewing the information contained before it, the Committee concluded that "this information was not sufficient to warrant scheduling".[35] It also requested an updated version of the critical review to be presented at the next meeting of the Committee which was held in 2012. At that meeting, the Committee decided that "bringing ketamine under international control is not appropriate."[36] At the level of European Union, in 2000, growing concern over the use of ketamine as a NPS prompted a risk assessment in the framework of the joint action on new synthetic drugs.[37] The European Commission concluded that it was not appropriate to introduce control measures and recommended further monitoring of the use of ketamine.

Description

Ketamine and phencyclidine have similar modes of action, affecting a range of central neurotransmitters. Ketamine is frequently sold as 'ecstasy' in illicit ATS markets. Street names for ketamine include *'K'*, *'special K'*, *'kit kat'*, *'tac'*, *'tic'*, *'cat valium'*, *'cat tranquilizer'*, *'vitamin K'*, *'ket'*, *'super K'*.[38]

Pharmaceutical preparations of ketamine are usually found in liquid form, but powder and capsules are also available. The powder prepared by evaporation of the original solution is often nasally insufflated ('bumping'), smoked or swallowed.

Reported adverse effects

Ketamine appears to stimulate the cardiovascular system, producing changes in the heart rate and blood pressure. As such, tachycardia is one of the most common symptoms identified in recreational users.

Findings of neurotoxicity in animal studies have raised concerns on the consumption of ketamine by recreational users, for a number of reasons: unlike when it is clinically administered, substance users will not take ketamine in combination with protective agents. Moreover, substances which may increase the neurotoxic potency of ketamine might be co-administered (including PCP, tiletamine as well as alcohol). Furthermore, recreational use usually implies repeated exposure, whereas clinical use is mostly incidental.[39]

34 European Monitoring Center for Drugs and Drug Addiction, 'Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs', Belgium, 2002

35 World Health Organization, 'WHO Expert Committee on Drug Dependence. Thirty-fourth Report', Geneva, 2006

36 World Health Organization, 'WHO Expert Committee on Drug Dependence. Thirty-fifth Report', Geneva, 2012

37 European Monitoring Center for Drugs and Drug Addiction, 'Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs', Belgium, 2002

38 European Monitoring Center for Drugs and Drug Addiction, 'Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs', Belgium, 2002

39 Jansen, K.L., 'Ketamine - Can chronic use impair memory?', International Journal of the Addictions, 1990, 25, 133-139, in World Health Organization, 'WHO Expert Committee on Drug Dependence. Thirty-fifth Meeting', 2012

Side effects related to the use of ketamine in conjunction with other drugs include hypertension and pulmonary oedema. Psychological dependence in some users has also been identified. Adverse effects in long-term users of ketamine have been reported albeit scarce. These included persistent impairment of attention and recall, and a subtle visual anomaly. Other reported effects include anxiety, changes of perception, an impairment of motor function and rhabdomyolysis.

Between 1987 and 2000, 12 fatal cases in which ketamine was identified were reported, but only three of them involved ketamine alone. Chronic ketamine use has been reported to result in potential lasting memory and cognitive dysfunction.[40]

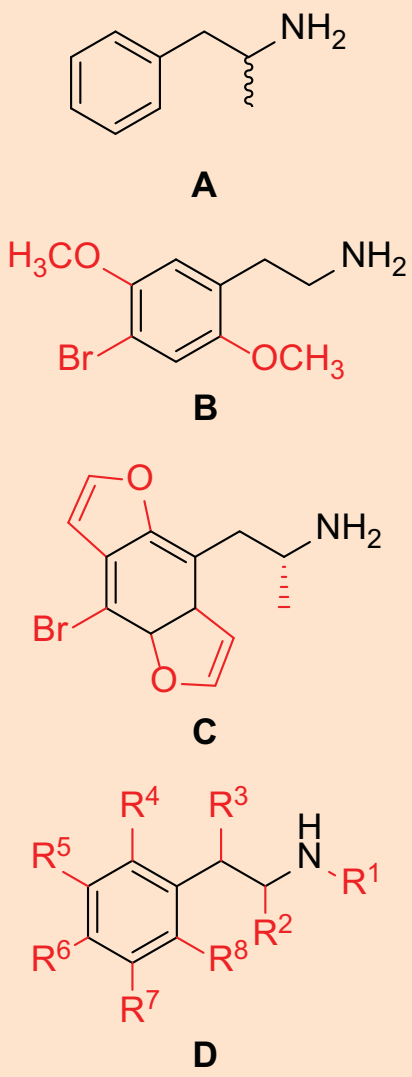
2.4. Phenethylamines

Background

Phenethylamines refer to a class of substances with documented psychoactive and stimulant effects and include amphetamine, methamphetamine and MDMA, all of which are controlled under the 1971 Convention.[41] The phenethylamines also include ring-substituted substances such as the '2C series', ring-substituted amphetamines such as the 'D series' (e.g. DOI, DOC), benzodifurans (e.g. Bromo-Dragonfly, 2C-B-Fly) and others (e.g. *p*-methoxymethamphetamine (PMMA)).

Seizures of phenethylamines were first reported from the United States and European countries and since 2009 substances such as 2C-E, 2C-I, 4-FA and PMMA have been commonly reported by several countries in different regions. Other phenethylamines increasingly reported in the UNODC questionnaire on NPS since 2011 include 4-FMA, 5-APB, 6-APB and 2C-C-NBOMe.

A number of studies have reported the synthesis of some phenethylamines and amphetamine substitutes. In the 1980s and 1990s, Alexander Shulgin, a biochemist and pharmacologist, reported the synthesis of numerous new psychoactive compounds.[42] This included the 'D series' (e.g. DOC, DOI) and the '2C series' (e.g. 2C-T-7, 2C-T-2) of phenethylamines.



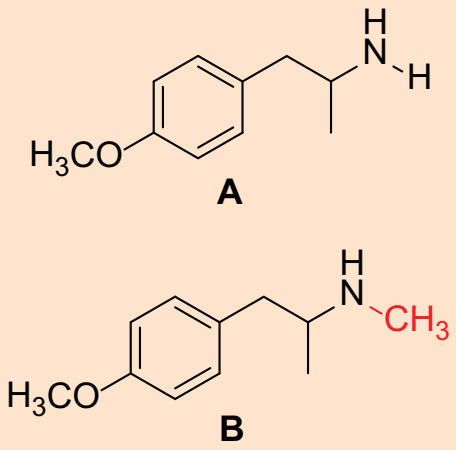
Chemical structure of amphetamine (A), two substituted phenethylamines: 2C-B (B) and Bromo-Dragonfly (C), and the generic structure of phenethylamines (D). The differences between amphetamine and two of the phenethylamine derivatives (i.e. 2C-B (internationally controlled substance) and Bromo-Dragonfly) are highlighted in red. The eight positions of the phenethylamine core that can be modified to generate a wide range of substituted phenethylamine derivatives are also highlighted in structure (D).

Simple variations on the mescaline molecule (a natural phenylethylamine) led to the synthesis of powerful hallucinogenic substances, e.g. 4-bromo-2,5-dimethoxyphenethylamine (2C-B), synthesized by Shulgin in 1974. The '2C' series differs from the 'D' series only by a slight modification in the chemical structure, and their psychoactive effects have been reported to be dose dependant, ranging from mere stimulant

40 Okon, T., a case based review 'Ketamine: an introduction for the pain and palliative medicine physician', Pain Physician, 2007, 10, 493-500

41 Hill, SL., Thomas, S.H., 'Clinical toxicology of newer recreational drugs', Journal: Clinical Toxicology, 2011, 49(8), 705-19

42 Alexander Shulgin research institute, 'Alexander 'Sasha' Shulgin' (http://www.shulginresearch.org/home/about/alexander-sasha-shulgin/)



Chemical structures of other synthetic phenethylamines: PMA (A) and PMMA (B). Structure (B) shows how the derivative PMMA is produced by introducing a small modification in the structure of PMA (internationally controlled substance).[43]

effect at lower doses, with hallucinogenic and entactogenic effects at higher doses.[44]

Over two decades later, a new generation of phenethylamines was researched by Professor David Nichols and his research team at Purdue University in the United States. The team found the potency of synthetic analogues of mescaline such as 2C-B and DOB, to exceed that of many naturally occurring hallucinogens.[45] Several substances were synthesized, including a wide range of benzodifuranyl substances, later known as the 'FLY'.[46] Benzodifurans, such as 'FLY' (tetrahydrobenzodifuranyl) and 'Dragonfly' (benzodifuranyl aminoalkanes) are potent hallucinogens. Bromo-Dragonfly is the most common and potent substance in this sub-group.

Other phenethylamines such as PMMA, first synthesized in 1938,[47] are also sold in the drug market as a substitute for 'ecstasy'. PMMA, in combination with PMA (a substance listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances), has been frequently found in tablets that carry a similar logo to 'ecstasy'.[48]

Whereas some phenethylamines such as 2C-B, brolamphetamine (DOB), STP/DOM, MDE, 4-MTA, are listed in Schedules I and II of the 1971 Convention, most of the new substances such as the 2C series, the D-Series and 'others' such as PMMA are not under international control. Some phenethylamine derivatives are controlled in some countries.

Description

Street names for some phenethylamines include *'Europa'* for 2C-E; *'4-FMP'*, *'para-fluoroamphetamine'*, *'RDJ'* for 4-FA; and *'4-MMA'*, *'Methyl-MA'* for PMMA. Phenethylamines are usually available in form of pills, but FLY compounds are commonly sold in powder form, while oral doses (on a slip of blotter paper) are usually available for 'D substances'. Ingestion is the most common route of administration of phenethylamines.

Reported adverse effects

Phenethylamines included in the 'D series' are described to be longer lasting, more potent and reportedly more liable to induce vasoconstriction than other members of the phenethylamine family.[49]

Reported adverse effects associated with the use of the 'D series' derivatives include agitation, tachycardia, mydriasis, hallucinations, severe limb ischemia, seizures, liver and renal failure.[50] Bromo-Dragonfly has also been associated with a number of deaths in Scandinavia.[51] A

43 *p*-methoxy-alpha-methylphenethylamine (PMA) is controlled in Schedule I of the 1971 United Nations Convention on Psychotropic Substances

44 Huang, H.H. and Bai, Y.M. 'Persistent psychosis after ingestion of a single tablet of ' 2C-B ", Journal: Progress in Neuro-Psychopharmacology & Biological Psychiatryis, 2010, 35 (1), 293-4

45 Monte, A.P., Waldman, S.R.., Marona-Lewicka, D., Wainscott, D.B., Nelson, D.L., Sanders-Bush, E., Nichols, D.E., 'Dihydrobenzofuran analogues of hallucinogens. 4. Mescaline derivatives', Journal of Medicinal Chemistry, 1997, 40 (19), 2997–3008

46 Collins, M., 'Some new psychoactive substances: precursor chemicals and synthesis-driven end-products', Drug Testing and Analysis, 2011, 3 (7-8), 404-16

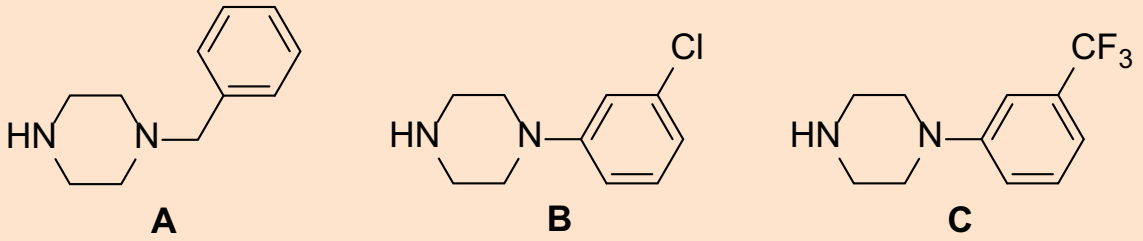
47 Glennon, R. A., Ismaiel, A. E. M., Martin, B., Poff, D. and Sutton, M., 'A preliminary behavioral investigation of PMMA, the 4-methoxy analog of methamphetamine', Pharmacology Biochemistry and Behavior, 1988, 31 (1), 9-13

48 European Monitoring Centre for Drugs and Drug Addiction, 'Report on the risk assessment of PMMA in the framework of the joint action on new synthetic drugs', 2003, 56

49 Hill, S. and Thomas S. H., 'Clinical toxicology of newer recreational drugs', Clinical Toxicology, 2011, 49, 705-19

50 King's College London. Institute of psychiatry, Psychonaut Web Mapping Research Group, 'Bromo-Dragonfly report', London UK, 2009, (http://194.83.136.209/documents/reports/Bromodragonfly.pdf; accessed in: September 2012); Wood, D.M., Looker, J.J., Shaikh, L., Button, J., Puchnarewicz, M., Davies, S., Lidder, S., Ramseyd, J., Holt, D.W., Dargan, P.I., 'Delayed onset of seizures and toxicity associated with recreational use of Bromo-dragonFLY', Journal of Medical Toxicology, 2009, 5, 226

51 Andreasen, M.F., Telving, R., Birkler, R., Schumacher, B. and Johannsen, M., 'A fatal poisoning involving Bromo-Dragonfly', Annales de Toxicologie Analitique, 20 (1), 1-55; Personne, M., Hulten, P., 'Bromo-Dragonfly, a life threatening designer drug', Journal: Clinical Toxicology, 2008, 46, 379-80



Chemical structures of BZP (A), *m*CPP (B) and TFMPP (C).

case of acute psychosis after ingestion of 2C-T-4 was reported in Japan.[52] Three fatal cases associated with the use of 2C-T-7 have been identified, two of which involved poly-drug use.[53]

PMA, PMMA and 4-methylthioamfetamine have been more often associated with incidental deaths than other phenethylamines. PMA and PMMA are known to have a particularly high toxicity but there is no data available on fatalities associated with their use. Clinical observations have reported severe hyperthermia following the use of these substances.[54] Studies in animals have suggested that some metabolites may be exposed to increased toxicity from 4-MTA.

2.5. Piperazines

Background

Piperazines have been described as 'failed pharmaceuticals', as some had been evaluated as potential therapeutic agents by pharmaceutical companies but never brought to the market.[55] While the best known piperazine that has been used as a new psychoactive substance is 1-benzylpiperazine (BZP), during the last decade other compounds such as 1-(3-chlorophenyl) piperazine (*m*CPP), 1-(3-trifluoromethylphenyl) piperazine (TFMPP) and, to a lesser extent, 1-Benzyl-4-methyl-piperazine (MBZP) and 1-(4-Fluorophenyl)piperazine (*p*FPP) have been identified on the market.[56]

BZP was initially developed as a potential antidepressant drug, but was found to have similar properties to amphetamine and therefore liable to abuse. In the 1980s, it was used in Hungary to manufacture piberaline, a substance marketed as an antidepressant, but later withdrawn.[57] In the late 1990s, BZP emerged in New Zealand as a 'legal alternative' for MDMA and methamphetamine.[58] In Europe, its use was first reported in Sweden in 1999, but it only became widespread as a NPS from 2004 onwards until controls over the substance were introduced in 2008, in the European Union.[59]

*M*CPP, reportedly more widespread than BZP in some regions of the world,[60] was developed during the late

52 Miyajima, M., Matsumoto, T and Ito, S., '2C-T-4 intoxication: acute psychosis caused by a designer drug', Journal: Psychiatry and Clinical Neurosciences, 2008, 62, 243

53 Curtis, B., Kemp, P., Harty, L., Choi, C. and Christensen, D., 'Postmortem identification and quantitation of 2,5-dimethoxy-4-n-propylthiophenethylamine using GC-MSD and GC-NPD', Journal of Analytical Toxicology, 2003, 27, 493-98

54 Ling, L.H., Marchant, C., Buckley, N. A., Prior, M., Irvine, R.J., 'Poisoning with the recreational drug paramethoxyamphetamine (' death ')', Medical Journal of Australia, 2001, 174, 453-55; De Letter, E.A., Coopman, V.A., Cordonnier, J.A. and Piette, M.H., 'One fatal and seven non-fatal cases of 4-methylthioamphetamine (4-MTA) intoxication: clinico-pathological findings', International Journal of Legal Medicine, 2001, 114, 352-56; Elliot, S.P., 'Fatal poisoning with a new phenethylamine: 4-methylthioamphetamine (4-MTA)', Journal of Analytical Toxicology, 2000, 24, 85-9; Felgate, H.E., Felgate, P.D., James, R.A., Sims, D.N. and Vozzo, D.C., 'Recent paramethoxyamphetamine deaths', Journal of Analytical Toxicology, 1998, 22, 169-72; Lamberth, P.G., Ding, G.K., Nurmi, L.A., 'Fatal paramethoxy-amphetamine (PMA) poisoning in the Australian Capital Territory', Medical Journal of Australia, 2008, 188, 426

55 Drug Testing and Analysis [Editorial], 'A brief history of 'new psychoactive substances'', 2011, 3, 401-403

56 United Nations Office on Drugs and Crime, 'UNODC questionnaire on NPS', submitted by Member States and a network of drug analysis laboratories in 2012.

57 European Monitoring Centre for Drugs and Drug Addiction, 'Report on the risk assessment of BZP in the framework of the Council decision on new psychoactive substances', Risk Assessments Issue 8, Lisbon, 2009, 23

58 "Approximately 1.5 to 2 million tablets had been manufactured by Vitafit Nutrition Ltd. for Stargate International (one of the major distributors in New Zealand) since 2001" New Zealand, Expert Advisory Committee on Drugs (EACD), 'Advice to the Minister on: Benzylpiperazine (BZP)', 2004; Industry figures pointed out that 26 million doses were sold over an 8-year period. Stargate International, 'Party pills: successful safety record', 2008, (http://www.stargateinternational.org/press_07_08/Party%20Pills-%20Successful%20Safety%20Record.doc.pdf; accessed in: September 2012)

59 European Monitoring Centre for Drugs and Drug Addiction, 'Report on the risk assessment of BZP in the framework of the Council decision on new psychoactive substances', Risk Assessments Issue 8, Lisbon, 2009, 23

60 By 2006, it was estimated that almost 10% of illicit tablets sold in the EU, as part of the illicit ecstasy market, contained *m*CPP, percentage that increased up to 50% in some Member States at the end of 2008 and beginning of 2009. European Monitoring Centre for Drugs and Drug Addiction, 'BZP and other piperazines', Drug Profiles (www.emcdda.europa.eu; accessed in: September 2012)

1970s and is used as an intermediate in the manufacture of several antidepressants, e.g. trazodone and nefazodone.[61] TFMPP is almost always seen in combination with BZP to produce the entactogenic[62] effects of MDMA.[63]

Neither BZP nor any other piperazines are under international control, although several (BZP, TFMPP, *m*CPP, MDBP) were pre-reviewed by the WHO Expert Committee on Drug Dependence in 2012. Several countries have introduced national control measures over piperazines.

Description

Piperazines are frequently sold as 'ecstasy'. Some of the generic names for these substances include, 'pep pills', 'social tonics' or simply 'party pills'. The latter term was used to commercialize BZP in New Zealand.[64] Other street names include *Jax*, *A2*, *Benny Bear*, *Flying Angel*, *Legal E* or *Legal X*, and *Pep X*, *Pep Love* or *Nemesis*.[65] *M*CPP is known as *3CPP*, *3C1-PP* or *CPP*.

Piperazines are usually available in the form of pills (regularly pressed with logos similar to ecstasy pills), capsules or loose powders, and are mainly consumed by ingestion. Liquid forms are rarely seen, but injection, smoking and snorting is also possible.

Reported adverse effects

Information on the toxicological aspects of many piperazines listed in this group remain limited. Further research is required to provide evidence on short and long term health-effects associated with the use of these substances. Current knowledge comes from user reports, studies in animals, limited human studies, and clinical observations.

Piperazines have been found to act as stimulants as a result of dopaminergic, noradrenergic, and predominantly serotoninergic effects produced in the brain. BZP produces toxic effects similar to amphetamine and other sympathomimetics, although, according to animal studies, its effects are less potent than amphetamine, methamphetamine and MDMA.[66] TFMPP, used in conjunction with BZP, has been reported to produce some of the effects of MDMA, but with a lower potency,[67] while *m*CPP has been indicated to produce similar stimulant and hallucinogenic effects as MDMA.[68]

In New Zealand, toxic seizures and respiratory acidosis after the use of BZP alone or in conjunction with other drugs were reported from three patients.[69] Another study of 61 patients reported toxic effects of BZP, with two cases presenting life-threatening toxicity.[70] Hyper-

61 Fong, M.H., Garattini, S., Caccia, S., '1-m-Chlorophenylpiperazine is an active metabolite common to the psychotropic drugs trazodone, etoperidone and mepiprazole', Journal of Pharmacy and Pharmacology, 1982, 34, 674-5

62 "Entactogens evoke mainly pleasant emotional effects of relaxation, feelings of happiness, increased empathy, and closeness to others". (Downing, J., 'The psychological and physiological effects of MDMA on normal volunteers', Journal Psychoactive Drugs, 1986, 18, 335-40; Greer, G.R., Tolbert, R., 'Subjective reports of the effects of MDMA in a clinical setting', Journal Psychoactive Drugs, 1986, 18, 319-27; Liester, M.B., Grob, C.S., Bravo, G.L., Walsh, R.N., 'Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine', Journal of Nervous and Mental Disease, 1992, 180, 345-52; Hermle, L., Spitzer, M., Borchardt, D., Kovar, K-A., Gouzoulis, E., 'Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents?', Neuropsychopharmacology, 1993, 8, 171-76; Cohen, R.S., 'Subjective reports on the effects of the MDMA ("Ecstasy") experience in humans', Progress in *Neuro-Psychopharmacology* & Biological Psychiatryis, 1995, 19, 1137-45; Vollenweider, F.X., Gamma, A., Liechti, M., Huber,T., 'Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers', Neuropsychopharmacology, 1998, 19, 241-51) as cited in Gouzoulis-Mayfrank, E., 'Differential actions of an entactogen compared to a stimulant and a hallucinogen in healthy humans', The Heffter Review of Psychedelic Research, 2001, 2, 64-72

63 Wilkins, C., Girling, M., Sweetsur, P., Huckle, T., Haukau, J., 'Legal Party Pill use in New Zealand: Prevalence of Use, Availability, Health Harms and 'Gateway Effects' of Benzylpiperazine (BZP) and Trifluorophenylmethylpiperazine (TFMPP)', National Household Survey, Centre for Social and Health Outcomes Research and Evaluation (SHORE), Massey University, New Zealand, 2006

64 Stargate International, 'Party pills: successful safety record' (http://www.scoop.co.nz/stories/PO0803/ S00129.htm)

65 United States, Drug Enforcement Administration, 'N-Benzylpiperazine. (street Names: BZP, A2, Legal E or Legal X)', 2012; European Monitoring Centre for Drugs and Drug Addiction, 'Report on the risk assessment of BZP in the framework of the Council decision on new psychoactive substances', Risk Assessments Issue 8, Lisbon, 2009; World Health Organization, 'N-benzylpiperazine (BZP) pre-review report. Expert Committee on Drug Dependence. Thirty-fifth Meeting', 2012

66 Elliott, S., 'Current awareness of piperazines: pharmacology and toxicology', Drug Testing and Analysis 2011, 3, 430-38

67 Baumann, M., Clark, R.D., Budzynski, A.G., Partilla, J.S., Blough, B.E., Rothman R.B., 'Effects of 'Legal X' piperazine analogs on dopamine and serotonin release in rat brain', Annals of the New York Academy of Sciences, 2004, 1025, 189-97; Baumann, M., Clark, R.D., Budzynski, A.G., Partilla, J.S., Blough, B.E., Rothman R.B., 'N-Substituted piperazines abused by humans mimic the molecular mechanism of 3,4- methylenedioxymethamphetamine (MDMA, or 'Ecstasy')', Neuropsychopharmacology, 2005, 30 (3), 550-60

68 Tancer, M.E., Johanson, C.E., 'The subjective effects of MDMA and *m*CPP in moderate MDMA users', Drug and Alcohol Dependence, 2001, 65, 97, (cited in Elliott, S., 'Current awareness of piperazines: pharmacology and toxicology', Drug Testing and Analysis, 2011, 3, 430-8)

69 Gee, P., Richardson, S., Woltersdorf, W. and Moore, G., 'Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand', New Zealand Medical Journal, 2005, 118, U1784

70 Gee, P., Richardson, S., Woltersdorf, W. and Moore, G., 'Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand', New Zealand Medical Journal, 2005, 118, U1784

thermia, rhabdomyolysis and renal failure associated with BZP ingestion have also been reported.[71] In the United Kingdom, self-terminating grand mal seizures[72] after the use of BZP have also been reported.[73]

Between 2004 and 2008, six fatal cases involving piperazines use were reported in Europe. Two of the cases involved the use of BZP in conjunction with TFMPP and none referred to the use of piperazines alone.[74] BZP and TFMPP were also associated with 19 fatalities between 2007 and 2010.[75] While reported effects of *m*CPP include the serotonin syndrome, no fatal poisonings from *m*CPP have been reported so far.[76] Similarly, toxic effects from the use of TFMPP alone have not been documented.[77]

2.6. Plant-based substances

2.6.1. Khat

Background

The khat shrub (*Catha edulis*) of the celastraceae family is a plant native to the horn of Africa and the Arabian peninsula. Khat chewing is a social custom in the communities living in these areas. The psychoactive effects resulting from the release of cathinone and cathine alkaloids after chewing of khat are well-documented.[78] The khat shrub became known to Europeans in the late 18th century and in the 19th century, and the active constituents of the plant were isolated in the 19th and 20th century. A 'katin' alkaloid was identified first in 1887, 'cathine' in 1930 and 'cathinone' in 1975.[79]

In Europe and North America, khat was considered to be traditionally used by migrant communities from Ethiopia, Kenya, Somalia and Yemen, but in recent years its use has spread beyond these communities. Respondents to the UNODC questionnaire on NPS from Bahrain, Canada, Finland, Ireland, Italy, New Zealand, Norway, Oman, United States and Hong Kong (China) reported that khat emerged on their markets in 2009, and was the second most popular plant based substance, after *salvia divinorum*, reported by Member States from 2009 to 2012.

Catha edulis is not under international drug control, but cathinone and cathine are listed in Schedules I and III, respectively, of the 1971 Convention. Khat is under national control in several countries.

Description

Street names for khat include *'qat'*, *'gat'*, *'chat'*, *'miraa'*, *'murungu'* and *'Arabian* or *Abyssinian tea'*. Due to the degradation of cathinone, khat leaves need to be consumed soon after harvesting and therefore fresh leaves of khat are the preferred form of use, but dried leaves (*'graba'*) are also available. Khat is usually consumed by chewing the leaves and shoots of the plant, but infusions are also possible. Recently, alcoholic extracts of khat sold as 'herbal highs' have been reported.[80]

Reported adverse effects

It has been estimated that a typical chewing session of khat results in the absorption of its active constituents with an activity equivalent to that of approximately 5 mg of amphetamine.[81] The pharmacological effects of

71 Gee, P., Jerram, T., Bowie, D., 'Multiorgan failure from 1-benzylpiperazine ingestion–legal high or lethal high?', Clinical Toxicology (Philadelphia), 2010, 48, 230-3

72 "A generalized tonic-clonic seizure is a seizure involving the entire body. It is also called a grand mal seizure. The terms "seizure," convulsion," or "epilepsy" are most often associated with generalized tonic-clonic seizures". United States, National Library of Medicine (http://www.nlm.nih.gov/medlineplus/ency/article/000695.htm)

73 Wood, D.M., Button, J., Lidder, S., Ramsey, J., Holt, D.W., Dargan, P.I., 'Dissociative and sympathomimetic toxicity associated with recreational use of 1-(3-trifluoromethylphenyl) piperazine (TFMPP) and 1-benzylpiperzine (BZP)', Journal of Medical Toxicology, 2008, 4, 254-7

74 Elliott, S., Smith, C., 'Investigation of the first deaths in the UK involving the detection and quantitation of the piperazines BZP and 3-TFMPP', Journal of Analytical Toxicology, 2008, 32, 172; Wikstrom, M., Holmgren, P., Ahlner, J., 'A2 (N-Benzylpiperazine) a new drug of abuse in Sweden', Journal of Analytical Toxicology, 2004, 28, 67; Balmelli, C., Kupferschmidt, H., Rentsch, K. and Schneemann M., 'Fatal brain edema after ingestion of ecstasy and benzylpiperazine', Deutsche Medizinische Wochenschrift, 2001, 126, 809-11

75 Elliott, S., 'Current awareness of piperazines: pharmacology and toxicology', Drug Testing and Analysis, 2011, 3, 430-8; A detailed description of fatal and non-fatal cases related to the use of BZP is available in World Health Organization, 'N-benzylpiperazine (BZP) pre-review report. Expert Committee on Drug Dependence. Thirty-fifth Meeting', 2012

76 European Monitoring Centre for Drugs and Drug Addiction, 'BZP and other piperazines', Drug Profiles (www.emcdda.europa.eu)

77 Elliott, S., 'Current awareness of piperazines: pharmacology and toxicology', Drug Testing and Analysis, 2011, 3, 430-8

78 Sawair, F.A., Al-Mutwakel, A., Al-Eryani, K., Al-Surhy, A., Maruyama, S., Cheng, J., Al-Sharabi, A. and Saku, T., 'High relative frequency of oral squamous cell carcinoma in Yemen: qat and tobacco chewing as-its aetiological background', International Journal of Environmental Health Research, 2007, 17, 185-95

79 See Szendrei, K., 'The chemistry of khat', Bulletin on Narcotics, 1980, 32, 3, 5-35 for further information.

80 European Monitoring Centre for Drugs and Drug Addiction, 'khat', Drug Profiles (www.emcdda.europa.eu)

81 Dhaifalah I. and Santavy J., 'Khat habit and its health effect. A natural amphetamine', Biomedical Papers, 2004, 148, 11-5

khat resemble those of amphetamine use, and includes increased alertness, euphoria, hyperthermia, anorexia, increased respiration rate, heart rate and blood pressure.[82]

Fatalities associated with the sole consumption of khat have not yet been reported. However, prolonged use of khat has been linked to adverse effects that range from psychiatric disturbances (from psychosis to depression) to damage of major organs of the body, as well as to similar neurological disorders to those associated with amphetamine and cocaine use.[83]

2.6.2. Kratom

Background

Mitragyna speciosa Korth (of the *Rubiaceae* family) is a large tree found in tropical and sub-tropical regions of South-East Asia. In Thailand, the tree known as 'Kratom' is found throughout the country but predominantly in the southern region, although the growing and harvesting is prohibited.

Kratom contains many alkaloids including mitragynine, mitraphylline, and 7-hydroxymitragynine. Traditionally, kratom had been used in Malaysia and Thailand by labourers and farmers to enhance productivity, but also as a substitute to opium and in traditional medicine, allegedly due to its morphine-like pharmacological effects. However, its use as a new psychoactive substance in the global market has been recently reported.

In the early 2000s, products labelled as *'kratom acetate'* or *'mitragynine acetate'* became available in Europe, although it was found that neither of them contained mitragynine. Caffeine and synthetic O-desmethyltramadol (an active metabolite of tramadol) were found in products under the name *'krypton'*.[84] More recently, products containing kratom have been sold as *'incense'* for their psychoactive effects, but concentrations of the active components mitragynine and 7-hydroxymitragynine in these products differ depending on the variety of the plant used, the environment and the time of harvesting.

Internet surveys conducted by the EMCDDA in 2008 and 2011 revealed that kratom is one of the most widely offered NPS.[85] Respondents to the UNODC questionnaire on NPS reported kratom among the top three plant-based substances, along with khat and *salvia divinorum*.[86] As kratom is often not monitored in national drug abuse surveys, there is little information on prevalence of its use.

Neither kratom nor any of its active alkaloids are listed under the 1961 and 1971 Conventions, but several countries have adopted control measures on kratom, mitragynine and 7-hydroxymitragynine.

Description

Street names for kratom include *'thang'*, *'kakuam'*, *'thom'*, *'ketum'* and *'biak'*. Kratom leaves are usually consumed fresh, although dried leaves in powder form are also available. The fresh leaves are chewed while the powder form is often either swallowed or brewed into tea. Dried leaves are rarely smoked.

Reported adverse effects

In spite of the increasing use of this substance, scientific literature about the effects and toxicity of kratom alone remains very scarce.

Kratom is a central nervous system stimulant, from which over 40 alkaloids have been isolated. In low doses it is reported to have stimulant effects (used to combat fatigue during long hours of work), while at high doses, it can have sedative-narcotic effects.[87] In 1921, the major alkaloid found in this plant, 'Mitragynine', was first isolated. Mitragynine has an opioid agonistic activity and its derivative 7-hydroxymitragynine (7-OH-mitragynine) is reported to be more potent than mitragynine or morphine.[88]

82 Kelly, J.P., 'Cathinone derivatives: a review of their chemistry, pharmacology and toxicology', Drug Testing and Analysis, 2011, 3, 439-53

83 Hoffman, R. and Al'absi, M., 'Khat use and neurobehavioural functions: suggestions for future studies', Journal of Ethnopharmacology, 2010, 132, 554; Morrish, P.K., Nicolaou, N., Brakkenberg, P. and Smith, P.E., 'Leukoencephalopathy associated with khat misuse', Journal of Neurology, Neurosurgery, and Psychiatry, 1999, 67, 556; Odenwald, M., 'Chronic khat use and psychotic disorders: a review of the literature and future prospects', Sucht, 2007, 53, 9-22

84 European Monitoring Centre for Drugs and Drug Addiction, 'kratom', Drug Profiles (www.emcdda.europa.eu)

85 European Monitoring Centre for Drugs and Drug Addiction, 'kratom', Drug Profiles (www.emcdda.europa.eu)

86 United Nations Office on Drugs and Crime, 'UNODC questionnaire on new psychoactive substances', submitted by Member States and a network of drug analysis laboratories in 2012.

87 European Monitoring Centre for Drugs and Drug Addiction, 'kratom', Drug Profiles (www.emcdda.europa.eu)

88 Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H. and Goda, Y., 'Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant "kratom" (*Mitragyna speciosa*) by LC-ESI-MS', Forensic Toxicology, 2009, 27 (2), 67-74

Nine fatal cases of intoxication associated with the use of *'krypton'*, a mixture of mitragynine and O-desmethyltramadol, have been described in scientific literature. However, these fatalities have been attributed to the addition of O-desmethyltramadol to the dried kratom leaves.[89]

2.6.3. *Salvia divinorum*

Background

Salvia divinorum (of the mint family Lamiaceae), is a psychoactive plant indigenous to forest areas in Oxaca, Mexico. It was traditionally used by the Mazatec Indians for religious practices and medical purposes, although there is no approved medicinal use for *salvia divinorum* or its active ingredient salvinorin A. The use of *salvia divinorum* as a new psychoactive substance dates back to the 1990s but respondents to the UNODC questionnaire on NPS identified this plant as the most common plant-based substance in 2009, and the third, after khat and kratom, in 2012.

Neoclerodane diterpene (i.e. salvinorin A) is the active component responsible for the psychoactive effects of the plant in the 1980s. The concentration of salvinorin A in *salvia divinorum* leaves varies and depends on the stage of development of the plant and the type of preparation.

Neither *salvia divinorum* nor salvinorin A are under international control. However, due to the increasing use of this plant as a new psychoactive substance, the plant and its active constituent salvinorin A are increasingly controlled in several countries under different regulatory frameworks.

Description

Street names for *salvia divinorum* include *'Maria Pastora'*, *'Sage of the Seers'*, *'Diviner's Sage'*, *'Salvia'*, *'Sally-D'*, *'Magic Mint'*, *'Purple Sticky'*, *'Shepherdess's Herb'*.[90]

Salvia divinorum is usually sold as seeds or leaves, but a liquid extract purported to contain salvinorin A and a combination of dried leaves and extracts of salvinorin A (known as *'the fresh-man selection'* or the *'starter pack'*) are also available on the market.[91] Recent studies of products containing *salvia divinorum* have shown a mismatch between the label and the actual constituent of the products. Vitamin E and caffeine have also been reported as adulterants.

Salvia divinorum is traditionally consumed by sucking and chewing the fresh leaves from a cigar-like roll or alternatively the fresh leaves are crashed to make a drinkable infusion. Many users reportedly inhale vaporized salvinorin A extract, or smoke the dried leaves of the plant. Smoking of the dry leaves is reported to produce short but intense hallucinations, and the effects of salvinorin A have been compared to those of LSD or DOB.[92]

Reported adverse effects

Animal studies have shown low toxicity and low addictive potential for *salvia divinorum*.[93] Like other plant-based substances, there are limited scientific studies in humans that report acute or chronic toxicity associated with its use, but clinical observations have indicated lasting psychosis in vulnerable individuals. Thus far, there are no reports on fatalities from use of *salvia divinorum*. However, toxicological analyses have proved difficult as salvinorin A and other diterpenoids of the plant are not detected by conventional drug screening methods.[94]

2.7. Miscellaneous substances

2.7.1. Aminoindanes

Background

In the 1970s, aminoindanes were reported to possess significant bronchodilating and analgesic properties, but recent research has indicated that they also have potent effects on serotonin release and re-uptake.[95] These sub-

89 Kronstrand, R., Roman, M., Thelander, G. and Eriksson, A., 'Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend krypton', Journal of Analytical Toxicology, 2011, 35 (4), 242-7

90 United States, Drug Enforcement Administration, *'Salvia divinorum* and salvinorin A', 2012 (http://www.deadiversion.usdoj.gov/drugs_concern/salvia_d.pdf); European Monitoring Centre for Drugs and Drug Addiction, *'Salvia divinorum'*, Drug Profiles (www.emcdda.europa.eu)

91 Babu, K.M., McCurdy, C.R. and Boyer, E.W., 'Opioid receptors and legal highs: *Salvia divinorum* and Kratom', Clinical Toxicology (Philadelphia), 2008, 46 (2), 146-52

92 European Monitoring Centre for Drugs and Drug Addiction, *'Salvia divinorum'*, Drug Profiles (www.emcdda.europa.eu)

93 Mowry, M., Mosher, M., and Briner, W., 'Acute physiologic and chronic histologic changes in rats and mice exposed to the unique hallucinogen salvinorin A', Journal of Psychoactive Drugs, 2003, 35, 379-82

94 European Monitoring Centre for Drugs and Drug Addiction, *'Salvia divinorum'*, Drug Profiles (www.emcdda.europa.eu)

95 Solomons, E. and Sam, J, '2-aminoindans of pharmacological interest', Journal of Medicinal Chemistry, 1973, 16 (12), 1330-33; Johnson, M.P., Frescas, S.P., et al., 'Synthesis and pharmacological examination of 1-(3-methoxy-4-methylphenyl)-2-aminopropane and 5-methoxy-6-methyl-2-aminoindan: similarities to 3,4-(methylenedioxy)methamphetamine (MDMA)', Journal of Medicinal Chemistry, 1991, 34, 1662-8

stances have been sold as NPS for their ability to produce empathogenic and entactogenic effects of serotonin releasing drugs, such as MDMA.[96]

2-Aminoindane (2-AI) is a rigid analogue of amphetamine. Its basic ring structure can be modified to produce diverse chemical substances such as 5-Iodo-2-aminoindane (5-IAI) and 5,6-methylenedioxy-2-aminoindane (MDAI). Analogues of aminoindanes are prepared using indanone, indene or after intramolecular cyclization of the acyl chloride derivative of 3-phenyl-2-propanoic acid.[97] Other aminoindanes sold as NPS include ETAI (N-Ethyl-5-trifluoromethyl-2-aminoindane) and TAI (5-trifluoromethyl-2-aminoindane)[98] which are analogues of fenfluramine and norfenfluramine, substances used as appetite suppressants.[99]

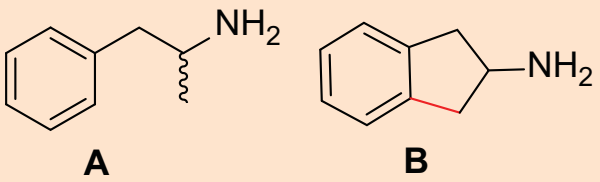
MDAI, 5-IAI and 2-AI were reported by respondents to the UNODC questionnaire on NPS as the most common substances within this group. None of the aminoindanes are under international control.

Description

Street names of MDAI include '*MDAI gold*', while 2-AI has been found in party pills known as '*Pink Champagnes*'.[100] Aminoindanes are commonly found in powder form and crystals and are usually ingested, but snorting is also possible.

Reported adverse effects

Research conducted in animals and in *in vitro* cell cultures indicates that aminoindanes are relatively benign at recreational doses; however, the effects on humans have not yet been reported.[101] MDAI and 5-IAI are reported to be highly potent selective serotonin releasing agents. Animal studies have shown that these analogues did not present any long-term neurotoxicity at the levels administered,[102] but slight neurotoxicity on rodents was shown after administration of very high doses of 5-IAI.[103]



Chemical structures of Amphetamine (A) and 2-AI (B). The differences between amphetamine (internationally controlled substance) and 2-AI are highlighted in red.

2.7.2. Phencyclidine-type substances

Background

Another group of NPS that has recently appeared in the market include phencyclidine-type substances. Phencyclidine (PCP) and ketamine (see section 2.3) show structural similarity and are classified as arylcycloalkylamines.[104]

PCP was first synthesized in the 1950s and sold until 1967 as an injectable anaesthetic in the United States under the trade names Sernyl and Sernylan. It was withdrawn from the market due to intensely negative psychological effects, such as dysphoria, confusion,

96 Monte, A.P., Maronalewicka, D., et al., 'Synthesis and pharmacological examination of benzofuran, indan, and tetralin analogs of 3,4-(methylenedioxy)amphetamine', Journal of Medicinal Chemistry, 1993, 36, 3700-6

97 Sainsbury, P.D., Kicman, A.T., et al., 'Aminoindanes - the next wave of 'legal highs'?', Drug Testing and Analysis, 2011, 3, 479-82

98 Ibid

99 Fenfluramine (Pondimin™) and (+)-fenfluramine (Redux™) were approved for the treatment of obesity by the United States Food and Drug Administration in 1973 and 1996, respectively. Both fenfluramines were withdrawn from the market in 1997 because valvular heart disease (VHD) was discovered in some patients receiving these drugs. Connolly, H.M., Crary, J.L., McGoon, M.D., Hensrud, D.D., Edwards, B.S. and Schaff, H.V., 'Valvular heart disease associated with fenfluramine-phentermine', New England Journal of Medicine, 1997, 337 (9), 581-8; Connolly, H.M. and McGoon, M.D., 'Obesity drugs and the heart', Current Problems in Cardiology, 1999, 24, 745-92; Weissman, N. J., 'Appetite suppressants and valvular heart disease', The American Journal of the Medical Sciences, 2001, 321 (4), 285-91

100 Kavanagh, P.V., Sharma, J., et al., 'Head shop "legal highs" active constituents. Identification chart (May 2010, pre-ban)', Department of Pharmacology and Therapeutics, School of Medicine, Trinity Centre for Health Sciences, St James's Hospital, Dublin

101 Sainsbury, P.D., Kicman, A.T., et al., 'Aminoindanes - the next wave of 'legal highs'?', Drug Testing and Analysis, 2011, 3, 479-82

102 Johnson, M.P., Frescas, S.P., et al., 'Synthesis and pharmacological examination of 1-(3-methoxy-4-methylphenyl)-2-aminopropane and 5-methoxy-6-methyl-2-aminoindan: similarities to 3,4-(methylenedioxy)methamphetamine (MDMA)', Journal of Medicinal Chemistry, 1991, 34, 1662; Monte A.P., Maronalewicka, D., et al., 'Synthesis and pharmacological examination of benzofuran, indan, and tetralin analogs of 3,4-(methylenedioxy)amphetamine', Journal of Medicinal Chemistry, 1993, 36, 3700; Marona-Lewicka, D., Rhee, G.S., et al., 'Reinforcing effects of certain serotonin-releasing amphetamine derivatives', Pharmacology Biochemistry and Behavior, 1996, 53, 99-105

103 Nichols, D., Johnson, M. P. and Oberlender, R., '5-iodo-2-aminoindan, a nonneurotoxic analog of para-iodoamphetamine', Pharmacology Biochemistry & Behavior, 1991, 38, 135-39

104 Baldridge, E.B., Bessen, H.A., 'Phencyclidine', Emergency Medicine Clinics of North America, 1990, 8 (3), 541-50; Balster, R.L., 'The behavioral pharmacology of phencyclidine', in H.Y. Meltzer (Eds.), Psychopharmacology: The third generation of progress, New York, 1987, 1573–9; The structure-activity relationships among arylcycloalkylamines can be further consulted in Manallack, D.T., Davies, J.W., Beart, P.M., Saunders, M.R. and Livingstone, D.J., 'Analysis of the biological and molecular properties of phencyclidine-like compounds by chemometrics', Arzneimittelforschung, 1993, 43 (10), 1029-32

delirium, and psychosis.[105] Its use as a recreational drug started in the mid-1960s, but its unpredictable dysphoric reactions made the drug infamous.

PCP-type substances appeared for the first time in Europe as 'research chemicals' in 2010, when the United Kingdom reported 3-methoxyeticyclidine (3-MeO-PCE) to the European Early Warning System.[106] In 2011, 4-methoxyphencyclidine (4-MeO-PCP) was identified in Norway, Russian Federation and the United Kingdom.[107] Respondents to the UNODC questionnaire on NPS reported 4-MeO-PCP as the most common PCP-type substance.

PCP and phenylcyclohexyl analogues, including eticyclidine (PCE), rolicyclidine (PHP, PCPY), tenocyclidine (TCP) are controlled in Schedule I of the 1971 Convention but derivatives such as 3-MeO-PCE and 4-MeO-PCP are not under international control.

Description

3-MeO-PCE and 4-MeO-PCP are frequently sold as research chemicals and usually in powder form.

Reported adverse effects

There is very limited information on the PCP analogues. Acute PCP intoxication results in a wide range of behavioural/psychological effects, from mild neurologic and physiologic abnormalities, stupor or light coma to deep coma. Manifestations of behavioural toxicity resemble psychiatric syndromes. PCP has also been claimed to cause violent behaviour.[108]

105 Pearlson, G.D., 'Psychiatric and medical syndromes associated with phencyclidine (PCP) abuse', Johns Hopkins medical journal, 1981, 148, 25-33; Smith, J.B., 'Situational specificity of tolerance to effects of phencyclidine on responding of rats under fixed-ratio and spaced-responding schedules', Psychopharmacology, 1991, 103, 121-8

106 European Monitoring Centre for Drugs and Drug Addiction and European Police Office, 'EMCDDA–Europol 2010 Annual report on the implementation of Council Decision 2005/387/JHA. Annex 2 — New psychoactive substances reported to the EMCDDA and Europol for the first time in 2010 under the terms of Council Decision 2005/387/JHA', Lisbon, 2011

107 United Nations Office on Drugs and Crime, 'UNODC questionnaire on new psychoactive substances', submitted by Member States and a network of drug analysis laboratories in 2012

108 Gorelick, D.A. and Balster, R.L., 'Phencyclidine (PCP)', in F.E. Bloom & R.L. Kupfer (Eds.), Psychopharmacology: The fourth generation of progress, New York, 1995, 1767-76; Brecher, M., Wang B.W., Wong, H. and Morgan, J.P., 'Phencyclidine and violence: clinical and legal issues', Journal of Clinical Psychopharmacology, 1988, 8 (6), 397-401; Daghestani, A.N. and Schnoll, S.H., 'Phencyclidine abuse and dependence', Treatments of Psychiatric Disorders: A task force report of the American Psychiatric Association, American Psychiatric Association, Washington D.C., 1989, 1209-18

2.7.3. Tryptamines

Background

Tryptamine, the prototype of the tryptamines group, is a primary amine alkaloid. Some tryptamines are natural neurotransmitters while most are psychoactive hallucinogens found in plants, fungi and animals.[109] Natural tryptamines include serotonin, melatonin, bufotenin,[110] 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) and dimethyltryptamine (DMT). Other tryptamines have been synthesized for pharmaceutical purposes to combat medical conditions (e.g. sumatriptan and zolmitriptan to treat migraine), but they have also been used as NPS.

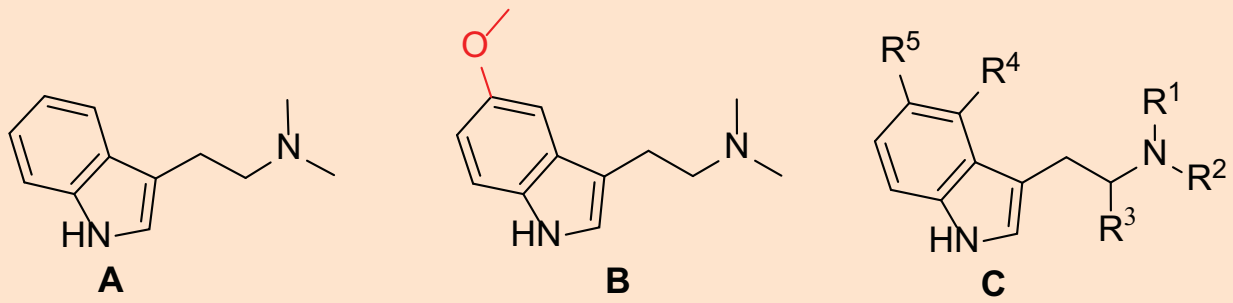
The use of psilocybin,[111] a natural hallucinogen found in certain species of mushrooms that contain the tryptamine structure, became widespread in the late 1950s in the United States, but synthetic tryptamines appeared on illicit drug markets only throughout the 1990s. The use of tryptamines remains limited but appears to have increased over the past five years. For example, the Drug Enforcement Administration of the United States reported that the estimated number of tryptamine reports to State and local laboratories in the United States rose from 42 reports in 2006 to 474 reports in 2010. Respondents to the UNODC questionnaire on NPS reported the incidence of both natural and synthetic tryptamines including, 5-MeO-DMT, 5-MeO-DPT, AMT, 4-AcO-DMT, 4-AcO-DiPT, and 5-HTP.

Psilocin, psilocybin, DET, DMT, and etryptamine are the only tryptamines under international control (listed in Schedule I of the 1971 Convention). Some others are restricted at the national level in several countries.

109 Collins, M., 'Some new psychoactive substances: precursor chemicals and synthesis-driven end-products', Drug Testing and Analysis, 2011, 3 (7-8), 404-16

110 Bufotenin (a tryptamine closely related to serotonin) was originally found by Wieland in the 1930s. Wieland, H., Konz, W. and Mittash, H., 'Die Konstitution von Bufotenin und Bufotenidin. Über Kröten-Giftstoffe VII', Justus Liebigs Annalen der Chemie, 1934, 513 (1), 1-25

111 The structures of psilocin and psilocybin were confirmed by Albert Hoffmann et al. in 1959. Hoffmann, A., Heim. R., Brack, A. and Kobel, H., 'Experientia', 1958, 14, 107-9; Hoffmann, A., Heim, R., Brack, A., Kobel, H., Frey, A., Ott, H., Petrzilka, T. and Troxler, F., 'Psilocybin und Psilocin, zwei psychotrope Wirkstoffe aus mexikanischen Rauschpilzen', Helvetica Chimica Acta, 1959, 42, 1557-72



Chemical structures of DMT (A), 5-MeO-DMT (B) and the generic structure of tryptamine derivatives (C). The structural differences between 5-MeO-DMT and the related DMT (internationally controlled substance) is highlighted in red. (C) Represents the generic structure of tryptamine derivatives, showing five of the positions that have been modified so far to produce synthetic tryptamines.

Description

Street names for some tryptamines include *'Foxy-Methoxy'* (5-MeO-DIPT); *'alpha-O'*, *'alpha'* and *'O-DMS'* (5-MeO-AMT); '*5-MEO*' (5-MeO-DMT). Natural tryptamines are commonly available in preparations of dried or brewed mushrooms, while tryptamine derivatives are sold in capsule, tablet, powder or liquid form. Tryptamines are generally swallowed, sniffed, smoked or injected.

Reported adverse effects

Toxicological studies on tryptamines remain limited. Reported adverse effects related to the use of *'foxy methoxy'* include restlessness, agitations, gastrointestinal distress, and muscle tension.[112] Rhabdomyolosis after ingestion of '*Foxy*' has also been described in a case study.[113] Other fatalities associated with the use of '*Foxy*' and other tryptamines have also been described in scientific literature.[114]

[112] Alatrash, G., Majhail, N.S. and Pile, J.C., 'Rhabdomyolysis after ingestion of "Foxy," a hallucinogenic tryptamine derivative', Mayo Clinic Proceedings, 2006, 81 (4), 550-1

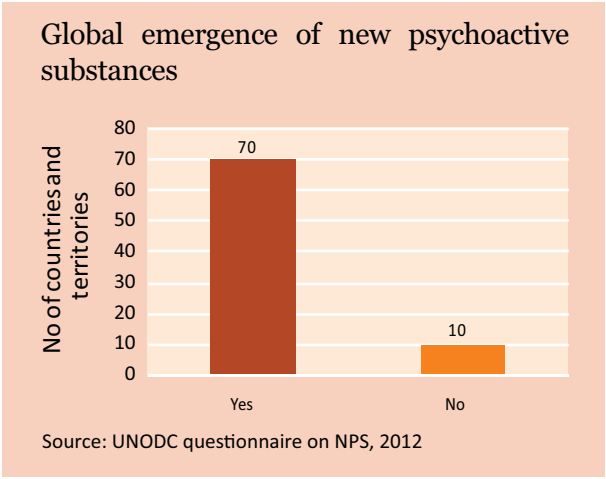
[113] Alatrash, G., Majhail, N.S. and Pile, J.C., 'Rhabdomyolysis after ingestion of "Foxy," a hallucinogenic tryptamine derivative', Mayo Clinic Proceedings, 2006, 81 (4), 550-1

[114] Einosuke, T., Tooru, K., Munehiro, K., Hitoshi, T. and Katsuya, H., 'A fatal poisoning with 5-methoxy-N, N-diisopropyltryptamine, Foxy', Forensic Science International, 2006, 163, 152–4; Sklerov, J., Levine, B., Moore, K.A., King, T. and Fowler, D., 'A fatal intoxication following the ingestion of 5-methoxy-N,N-dimethyltryptamine in an ayahuasca preparation', Journal of Analytical Toxicology, 2005, 29 (8), 838-41

3. THE GLOBAL SPREAD OF NEW PSYCHOACTIVE SUBSTANCES

3.1. Emergence of new psychoactive substances

Prior to the present report, no information was available on the global spread of NPS, due to the absence of a global early warning system which monitors the appearance of new substances. The UNODC questionnaire on NPS, which was used to collect information on this issue, received more than 240 responses from 80 countries and territories, indicating a high level of interest in the subject.[115] Most questionnaires were received from countries in Europe (33), which might be due to the high degree of awareness of the problem in that region, followed by Asia (23 countries and territories), Americas (12 countries), Africa (10 countries) and Oceania (2 countries).



All 80 countries and territories from all regions provided data on the emergence of NPS, with 70 countries and territories[116] (87%) indicating that NPS had appeared on their drugs market, compared to 10 countries[117] (13%) which reported otherwise. Responses indicate a worldwide spread of NPS, with countries and territories reporting their appearance in Europe (31 countries or 94% of respondents), followed by Asia (19 countries and territories or 86% of respondents), the Americas (11 countries or 92% of respondents), Africa (7 countries or 70% of respondents) and Oceania (2 countries or all respondents).

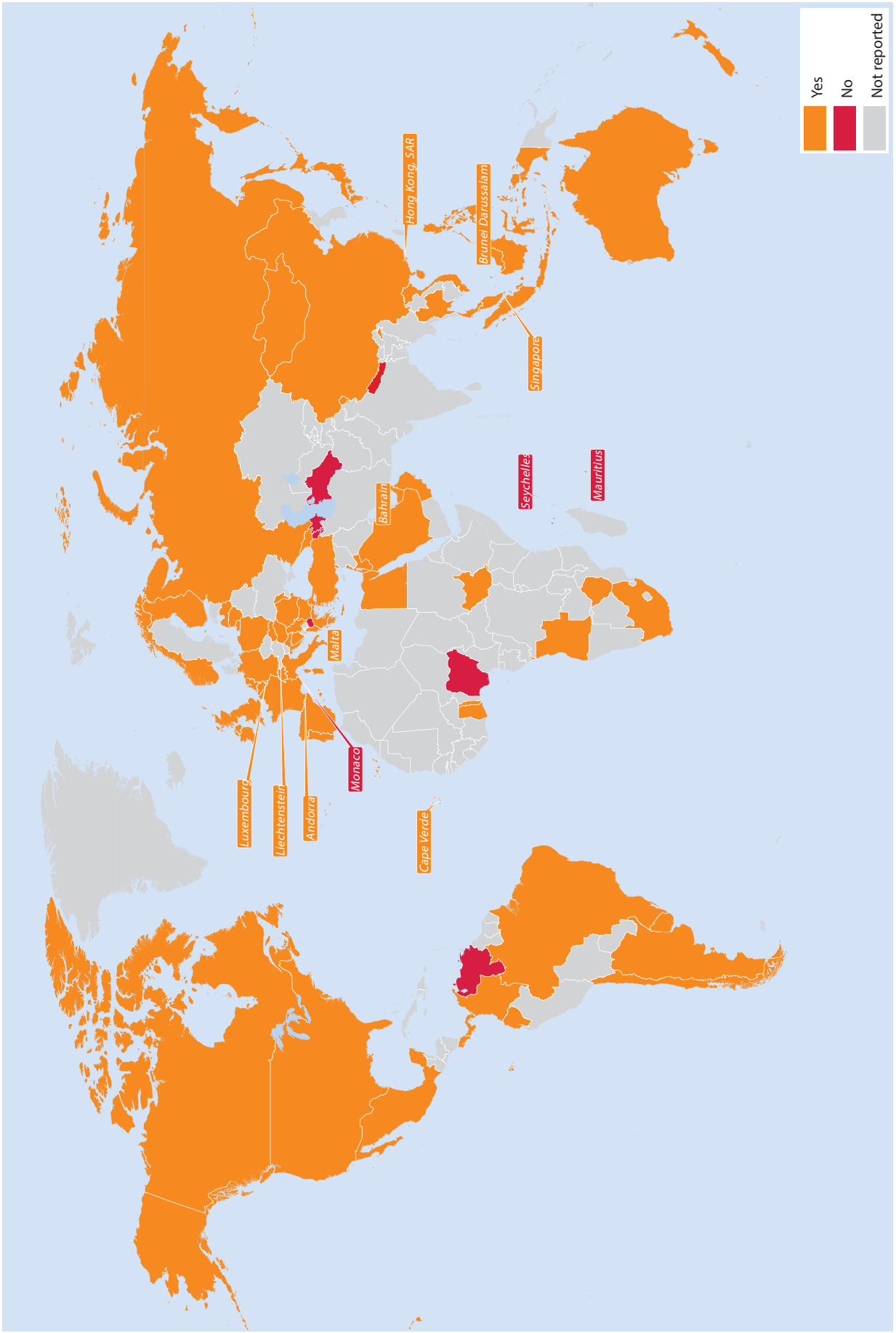
With respect to the global emergence by NPS groups, ketamine as well as plant-based substances were reported by 44 respondents (83%), followed by piperazines with 41 respondents (77%) and synthetic cannabinoids with 40 respondents (75%). The least reported NPS group were phenethylamines, reported by 32 respondents (60%).

[115] Multiple responses were received from some countries, as questionnaires were frequently circulated to various authorities working on this issue. In the analysis of the data, only respondents that provided full identifying information (institutions, country/territory) were considered.

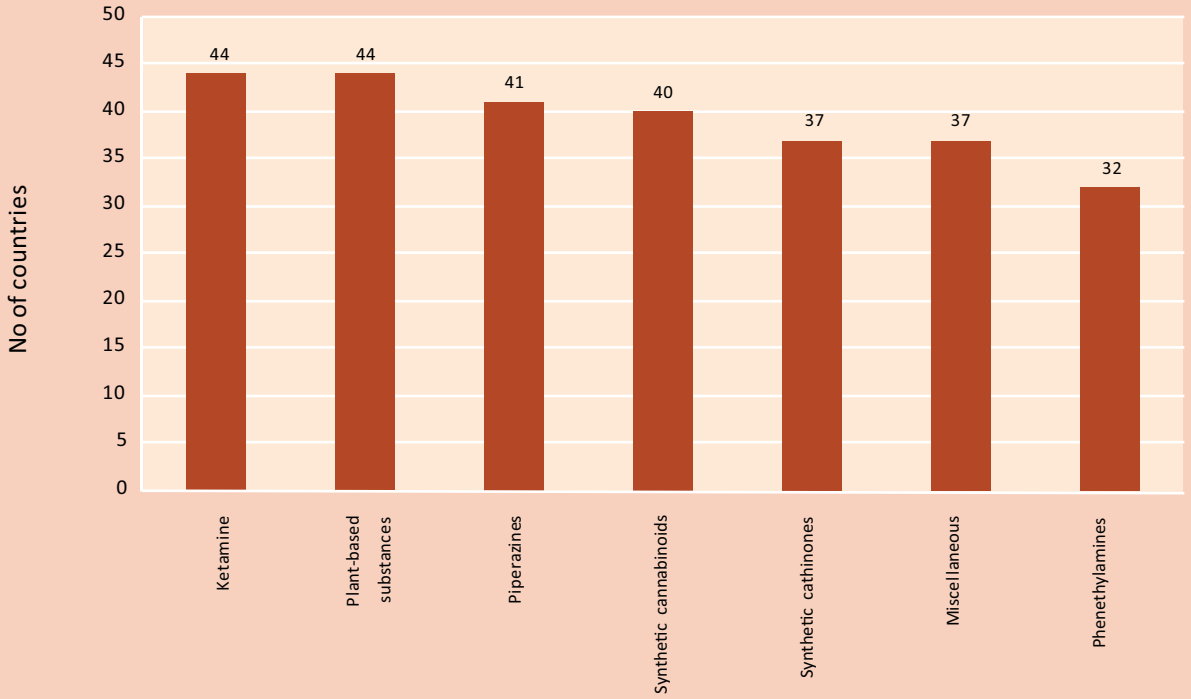
[116] Countries and territories reporting emergence of NPS: Albania, Andorra, Angola, Argentina, Australia, Bahrain, Belgium, Bosnia and Herzegovina, Brazil, Brunei Darussalam, Bulgaria, Canada, Cape Verde, Chile, China, Colombia, Costa Rica, Croatia, Ecuador, Egypt, Finland, France, Georgia, Germany, Ghana, Greece, Hong Kong SAR, Hungary, Indonesia, Ireland, Israel, Italy, Japan, Jordan, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mexico, Republic of Moldova, Mongolia, Netherlands, New Zealand, Norway, Oman, Panama, Philippines, Poland, Portugal, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, South Africa, Spain, Switzerland, Thailand, Togo, Turkey, United Arab Emirates, United Kingdom, United States of America, Uruguay, Viet Nam, Zimbabwe.

[117] Countries, which reported that NPS had not emerged: Armenia, Azerbaijan, the former Yugoslav Republic of Macedonia, Mauritius, Monaco, Nepal, Nigeria, Seychelles, Turkmenistan and Venezuela (Bolivarian Republic of).

Map 1: Global emergence of new psychoactive substances

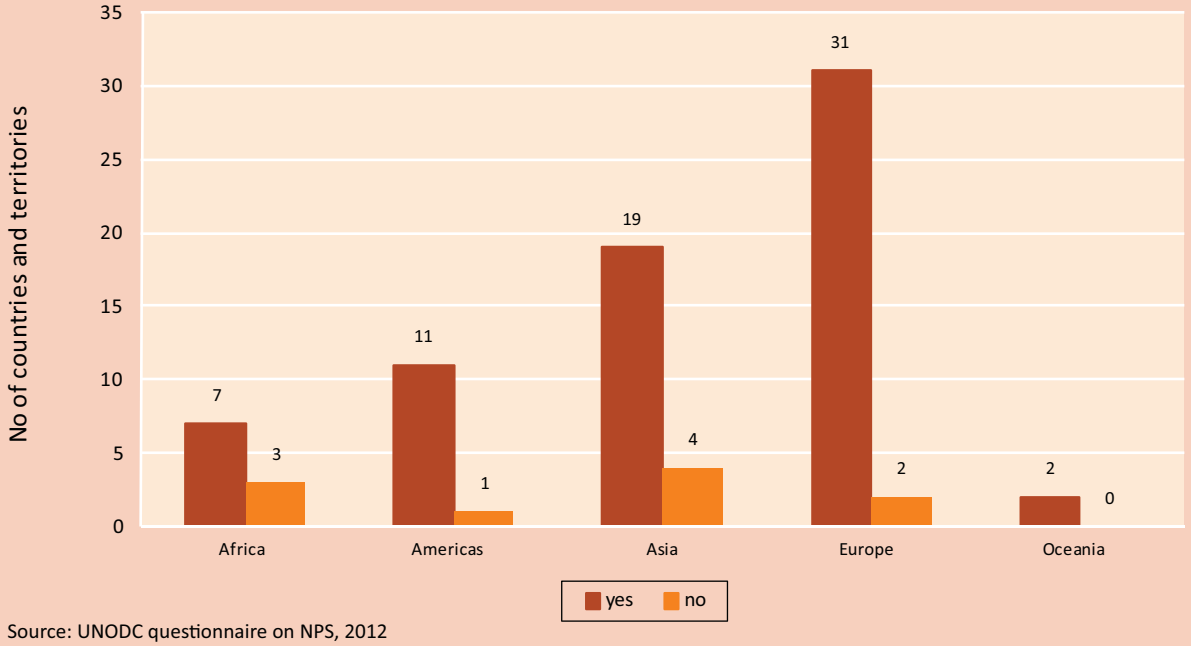


Global emergence by new psychoactive substances group



Source: UNODC questionnaire on NPS, 2012

Regional emergence of new psychoactive substances



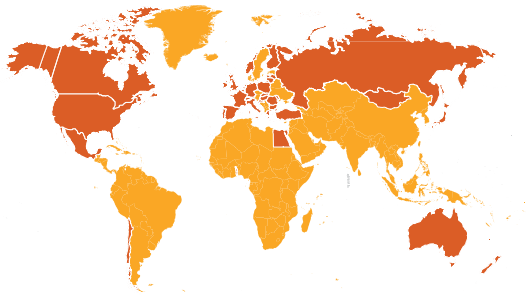
Source: UNODC questionnaire on NPS, 2012

All NPS groups have emerged in all regions, except Africa where, so far, no synthetic cathinones and phenethylamines have been reported.

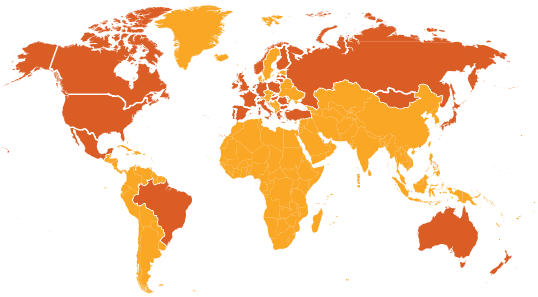
The appearance of the NPS groups over time shows that all groups appeared before 2008, with ketamine being the most widely reported NPS (79%), followed

Map 2: Global emergence of the new psychoactive substances group

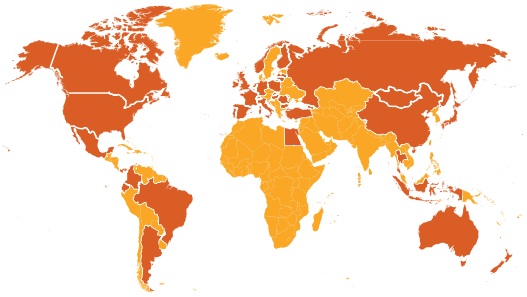
Synthetic cannabinoids



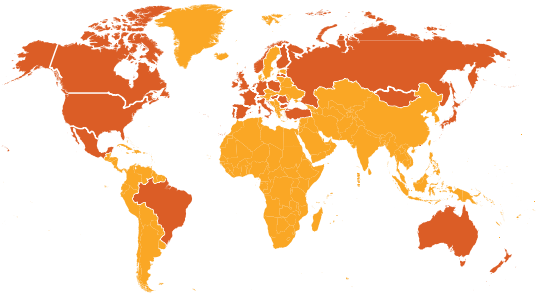
Synthetic cathinones



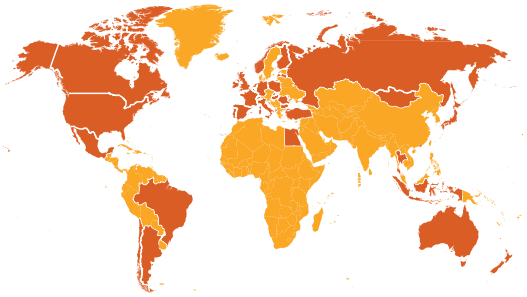
Ketamine



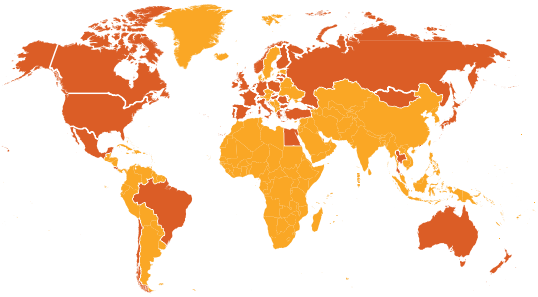
Phenethylamines



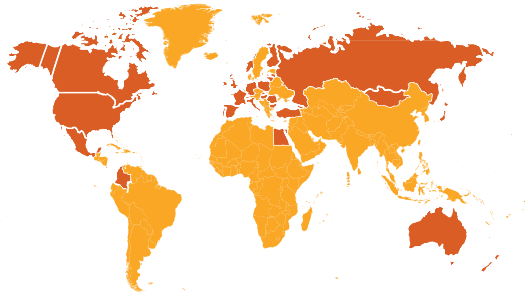
Piperazines



Plant-based substances

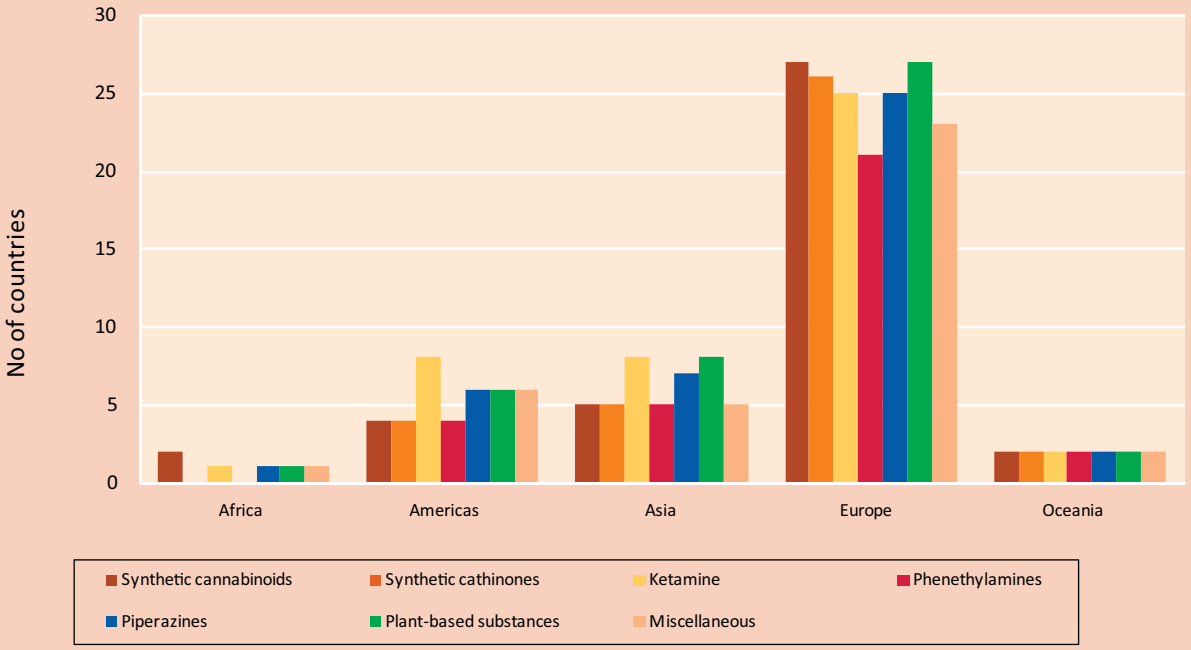


Miscellaneous



Source: UNODC questionnaire on NPS, 2012

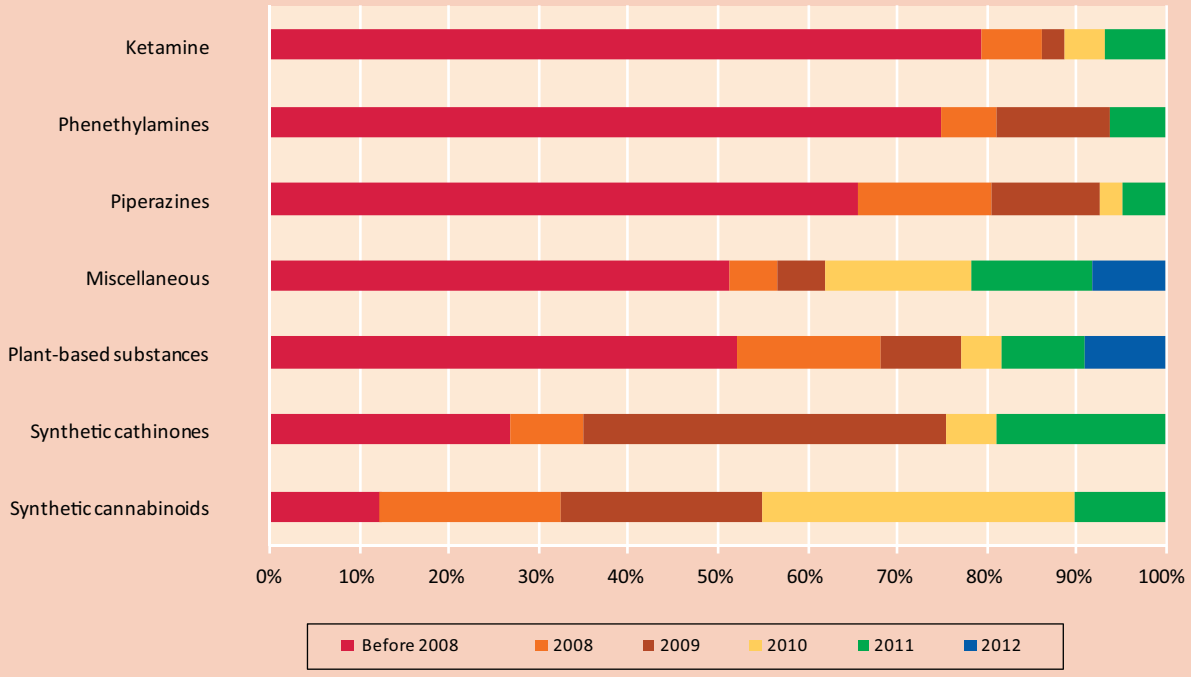
Regional emergence by new psychoactive substances group



Source: UNODC questionnaire on NPS, 2012

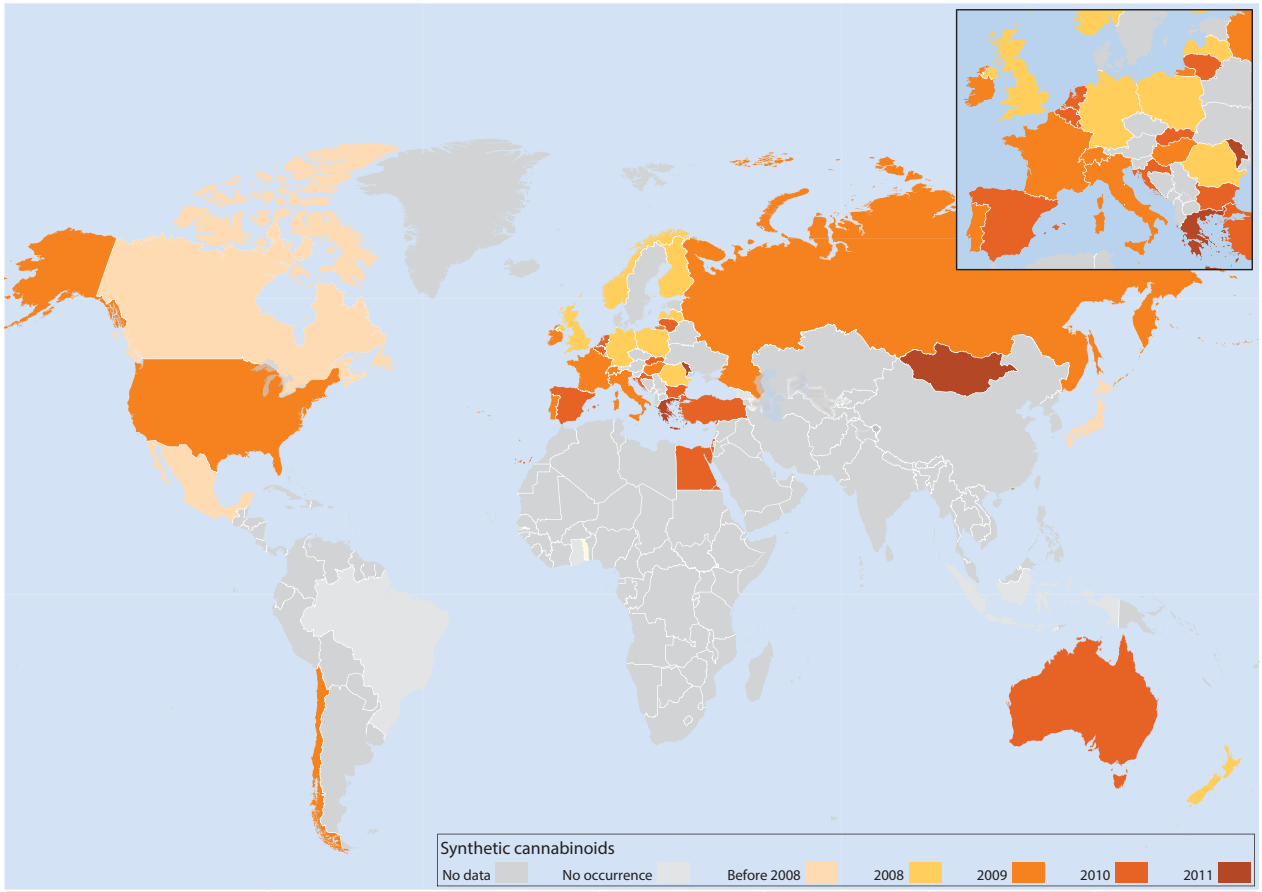
by phenethylamines (75%) and piperazines (66%). Synthetic cathinones made their largest first appearance on the market in 2009. Synthetic cannabinoids, on the other hand, rarely known before 2008, became more widespread until 2010, the year when their appearance was most frequently reported.

Appearance of new psychoactive substances groups up to 2012



Source: UNODC questionnaire on NPS, 2012

Map 3: Emergence of synthetic cannabinoids by region up to 2012



	Before 2008	2008	2009	2010	2011	2012
Africa	1	-	-	1	-	-
Americas	2	-	2	-	-	-
Asia	1	-	-	2	2	-
Europe	1	7	7	10	2	-
Oceania	-	1	-	1	-	-

Source: UNODC questionnaire on NPS, 2012

Synthetic cannabinoids

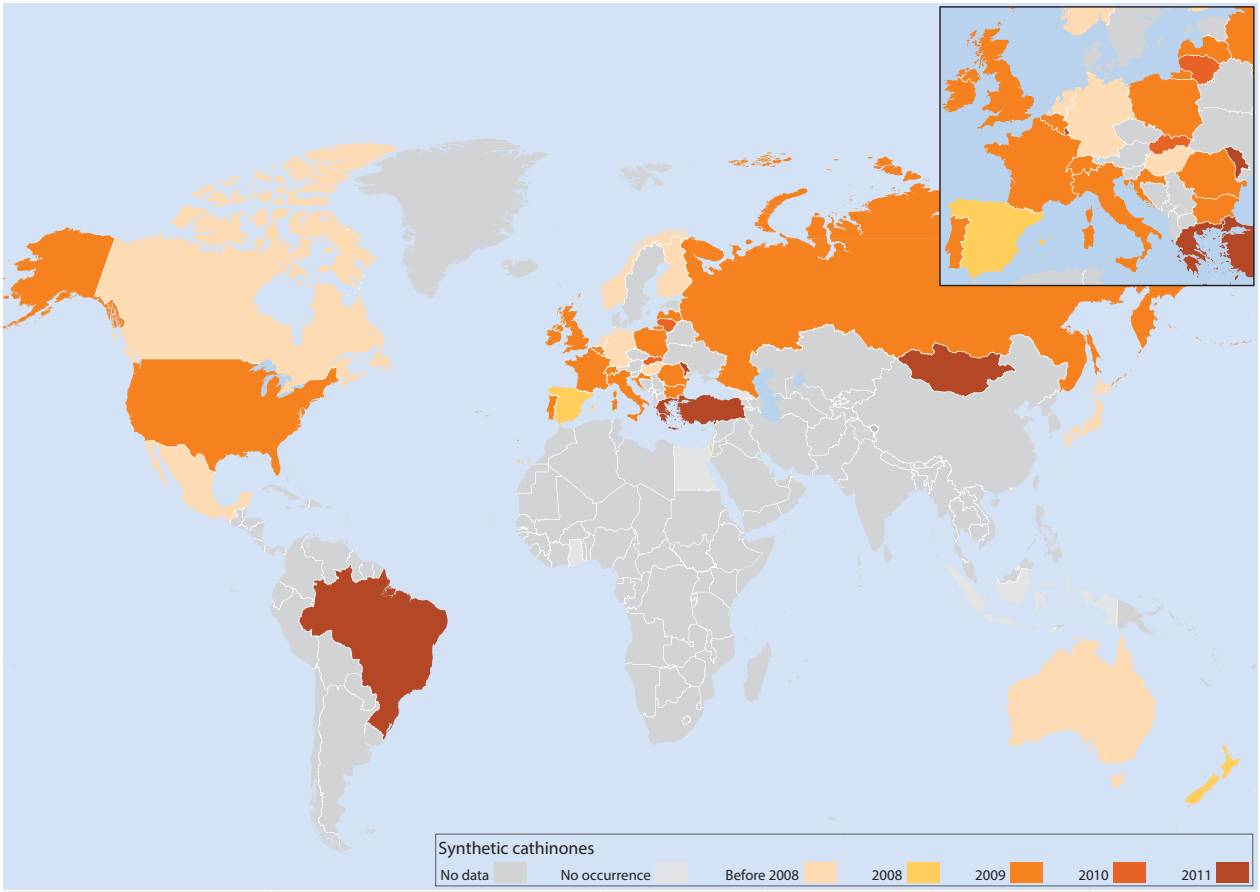
Canada, Japan, Liechtenstein, Mexico and Togo reported that synthetic cannabinoids appeared on their markets before 2008, while New Zealand reported their first appearance in 2008. In Europe, synthetic cannabinoids started to emerge on a larger scale in 2008 and 2009, with seven countries reporting every year first appearances In the Americas, synthetic cannabinoids were reported in 2009 from Chile and the United States. In Europe, the appearance of synthetic cannabinoids reached its peak in 2010 when ten countries reported these substances (Belgium, Bulgaria, Croatia, Lithuania, Luxembourg, Malta, Netherlands, Slovakia, Spain and Turkey). Outside Europe, Australia, Egypt, Israel and *Hong Kong SAR* reported their first emergence in 2010. Greece, Moldova, Mongolia and Singapore reported first appearance of synthetic cannabinoids in 2011.

Synthetic cathinones

Finland, Germany, Hungary, Netherlands and Norway as well as Japan and Hong Kong (China) reported the appearance of synthetic cathinones for the first time before 2008 and Israel for 2009. In comparison to synthetic cannabinoids, synthetic cathinones first appeared in Australia before 2008, and then in 2008 in New Zealand. In Canada and Mexico, synthetic cathinones appeared before 2008, followed by the United States in 2009. The highest number of countries, 14 all from Europe [118], first reported synthetic cathinones in 2009. In 2011, this class of substances was also reported by Brazil, Greece, Luxembourg, Moldova, Mongolia, Singapore and Turkey.

[118] Belgium, Bulgaria, Croatia, France, Ireland, Italy, Latvia, Malta, Poland, Portugal, Romania, Russian Federation, Switzerland and the United Kingdom.

Map 4: Emergence of synthetic cathinones by region up to 2012



	Before 2008	2008	2009	2010	2011	2012
Africa	-	-	-	-	-	-
Americas	2	-	1	-	1	-
Asia	2	1	-	-	2	-
Europe	5	1	14	2	4	-
Oceania	1	1	-	-	-	-

Source: UNODC questionnaire on NPS, 2012

The African countries which responded to the questionnaire did not report the appearance of synthetic cathinones.

Ketamine, phenethylamines and piperazines emerged in all regions before 2008. These substance groups are the most widespread, having appeared in almost all countries and territories which responded to the survey. Only a few respondents reported the appearance of ketamine after 2008, including Slovakia which reported its first appearance in 2009, Bulgaria and New Zealand (2010), and Ecuador and Panama (2011). Phenethylamines first appeared in most countries and regions (except Africa) before 2008. Bulgaria, Ireland, Latvia and Turkey reported their first appearance in 2009, while Mongolia and New Zealand reported first appearance of phenethylamines in 2011. Most regions reported the emergence of piperazines before 2008.

Plant-based substances

Twenty-three countries from all regions reported the emergence of plant-based substances before 2008.[119] In 2008, seven European countries (Belgium, Bulgaria, Latvia, Luxembourg, Poland, Portugal and Slovakia) reported plant-based substances. In Asia, first reports of the appearance of plant-based substances were made by Hong Kong (China) in 2009, Lebanon in 2010 and Mongolia in 2011. In 2012, this NPS group emerged in Bahrain and Liechtenstein as well as in Costa Rica and Chile. In Europe, at least one country reported the first appearance of a plant-based substance every year.

[119] Australia, Brazil, Canada, Croatia, Egypt, Finland, France, Georgia, Germany, Ireland, Italy, Japan, Malta, Mexico, Netherlands, Norway, Romania, Russian Federation, Singapore, Switzerland, Thailand, United Kingdom and the United States.

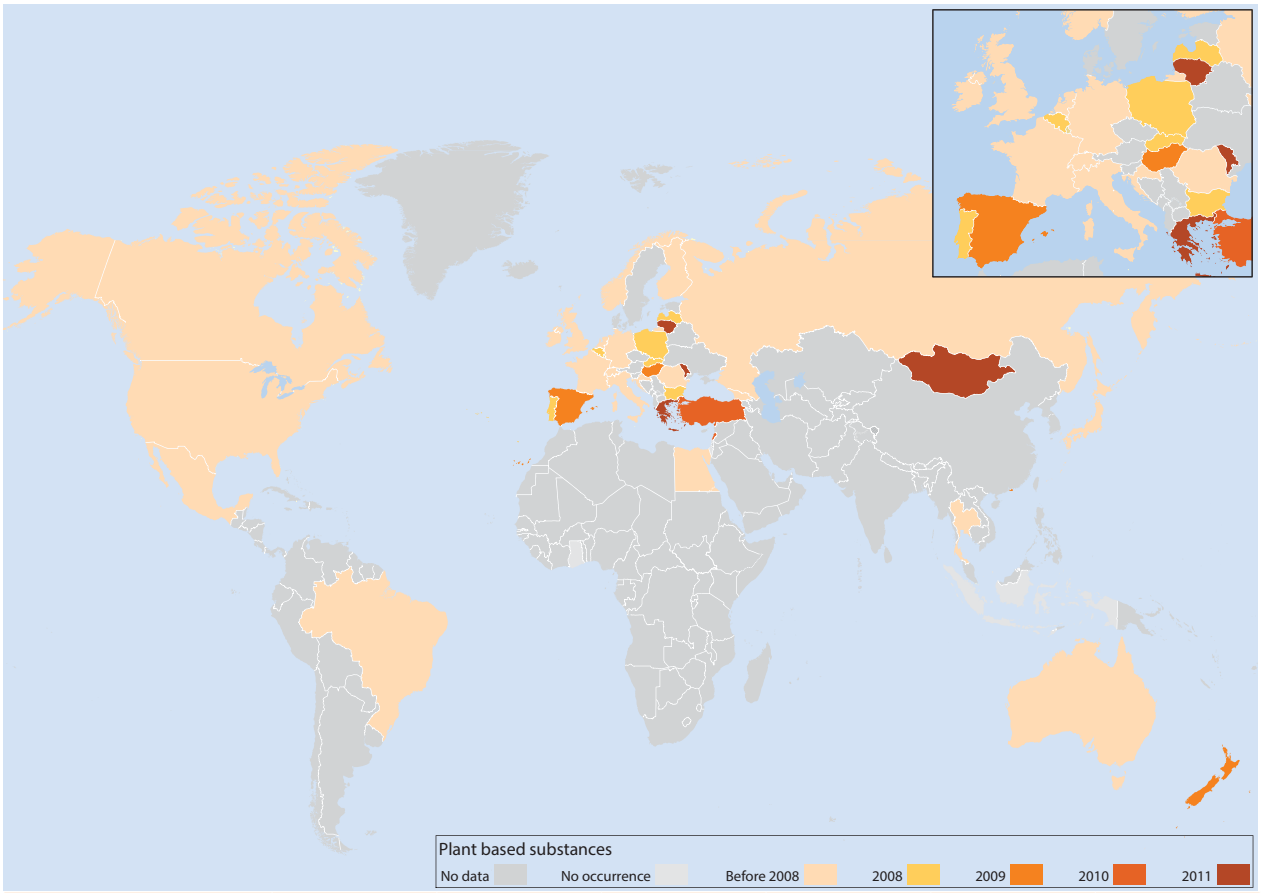
The data confirmed that all NPS groups - synthetic cannabinoids, synthetic cathinones, ketamine, phenethylamines, piperazines, plant-based substances and miscellaneous substances - have emerged globally, except for phenethylamines and synthetic cathinones which were not reported from Africa. However, it should be noted that Africa is the region with the fewest respondents to the questionnaire – responses were received from only 10 countries (Angola, Cape Verde, Egypt, Ghana, Mauritius, Nigeria, Seychelles, South Africa, Togo, Zimbabwe). Less than 20% of African countries and territories submitted UNODC's Annual Reports Questionnaire (ARQ) for 2010.[120]

3.2 Legal situation

3.2.1 The international drug control system

NPS fall outside the global drug control system and are therefore neither included in the schedules of the 1961 Convention nor in those of the 1971 Convention. However, some Governments have adopted national or regional responses to address this issue in a need to meet the increasing concerns on the risks that these substances pose to public health and to address other various aspects of this problem.

Map 5: Emergence of plant-based substances by region up to 2012



	Before 2008	2008	2009	2010	2011	2012
Africa	1	-	-	-	-	-
Americas	4	-	-	-	-	2
Asia	4	-	1	-	1	1
Europe	13	7	2	1	3	1
Oceania	1	-	1	-	-	-

Source: UNODC questionnaire on NPS, 2012

[120] Under the United Nations drug control Conventions, Member States are formally required to provide national drug control related information annually to the Secretary-General of the United Nations. The Commission on Narcotic Drugs, the main drug control policy making body in the United Nations, developed the Annual Reports Questionnaire (ARQ) to collect this information.

As provided for in the 1961 Convention and the 1971 Convention, whenever a Party or the World Health Organization (WHO) has information relating to a substance not yet under international control which in its opinion requires that substance to be added to any of the schedules of the Conventions, "it shall notify the Secretary-General and furnish him with the information in support of that notification", according to article 3(1) of the 1961 Convention and article 2 (1) of the 1971 Convention.[121]

The notification is subsequently transmitted to the Parties, to the Commission on Narcotic Drugs and to the World Health Organization. An assessment of the substance is then carried out by WHO and based on the results of the assessment and the recommendations on control measures, if any, the Commission may decide that the substance shall be added to, transferred from one schedule to another, or removed from any of the schedules of the respective Convention. The decisions of the Commission are subject to review by the Economic and Social Council upon the request of a Party. The Expert Committee on Drug Dependence of WHO has reviewed several NPS, for example BZP or ketamine.

3.2.2. Regional responses: the European Union

So far, the only regional response system to the emergence of NPS is the European Early Warning System (EWS) of the European Union (EU). In 1997, a mechanism for rapid exchange of information on 'new synthetic drugs', the assessment of their risks and the application of existing control measures on psychotropic substances to 'new synthetic drugs' was adopted by the Council of the European Union (Joint Action 97/396/JHA). Building upon this decision, Council Decision 2005/387/JHA was adopted in 2005 which applies to all NPS.

Council Decision 2005/387/JHA[122] provides for an assessment of the risks associated with NPS in order to permit the measures applicable in the EU Member States for control of narcotic and psychotropic substances to be applied also to NPS. According to article 4 (1) (2) of the Council Decision, each EU Member State shall ensure that information on the manufacture of, trafficking in, use of, and of preparations containing NPS is shared through its Europol National Unit and its representative in the Reitox Network.[123] This information is collected by Europol and the EMCDDA and subsequently shared with all EU Member States, the European Commission and the European Agency for the Evaluation of Medicinal Products (EMEA). According to article 5 (1), a 'Joint Report' shall be prepared by Europol and the EMCDDA, if either of them or the Council of the European Union consider that further information on the new psychoactive substance reported is needed.[124] This report is then submitted to the Council of the European Union, the EMEA and the European Commission. If considered necessary by the Council of the European Union, a 'Risk Assessment Report' is prepared by the Scientific Committee of the EMCDDA. This report, as provided for in article 6 (4), shall include a complete assessment of the health and social risks caused by the use of, the manufacture of, and trafficking in the new psychoactive substance, information on any control measure in place in EU Member States and on any assessment of the NPS in the United Nations System, the level of involvement of organized crime, options for control, the possible consequences of control measures, and the chemical precursors used for the manufacture of the substance.

For the purposes of bringing NPS under control, article 8 (1) (2) of the Council Decision 2005/387/JHA states that within six weeks from the date on which the European Commission receive the Risk Assessment Report, it shall present an initiative to the Council of the European Union to place the new psychoactive substance under control. If the European Commission deems it not necessary to present an initiative on submitting the new psychoactive substance to control measures, such an initiative may be presented by one or more EU Member States. It is for the Council of the European Union to decide whether to submit the

121 The wording is identical in both Conventions.

122 Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances. Council of the European Union (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32005D0387:EN:NOT)

123 Reitox is the European information network on drugs and drug addiction created at the same time as the EMCDDA. The abbreviation 'Reitox' stands for the French 'Réseau Européen d´Information sur les Drogues et les Toxicomanies'. European Monitoring Centre on Drugs and Drug Addiction, Reitox Network (http://www.emcdda.europa.eu/about/partners/reitox-network)

124 The report contains preliminary information on the description of the substance, manufacture, risks associated to its use, involvement of organized crime in the manufacture and trafficking, user profile, control status of the substance at the national level in EU Member States and on whether or not the substance is under assessment by the United Nations. Article 5 (2) Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances, Council of the European Union

new psychoactive substance to control measures. If so, article 9 (1) of the Council Decision provides that EU Member States shall endeavour to take as soon as possible, but no later than one year from the date of that decision, the necessary measures, in accordance with their national law, to 'submit' the new psychoactive substance to control measures and criminal penalties as provided under their legislation by virtue of their obligations under the international drug control treaties. As stated in article 9 (3), the obligations set forth in the Council Decision do not preclude the possibility of individual Member States to maintain or introduce any national control measures on NPS. Up to 2012, eleven NPS[125] have been included in the Risk Assessment Reports prepared by EMCDDA in the framework of the Council Decision 2005/387/JHA and the Joint Action 97/396/JHA, 8 of the eleven substances[126] have been subjected to to control measures following a decision of the Council of the European Union. At the time of preparing this report, a new risk assessment on 4-methylamphetamine was being conducted by the EMCDDA.[127]

3.2.3 National responses to new psychoactive substances

Outside Europe, several approaches have been taken to control NPS at the national level. The cases of Japan, New Zealand, the Republic of Korea, and the United States are provided below for illustrative purposes.

In Japan, NPS have been available over the Internet since 2004 and marketed directly in the country around 2009. For the purposes of control, NPS were defined as "new narcotic or psychotropic drugs, in pure form or in preparation, that are not controlled by the 1948 Cannabis Control Law, the 1951 Stimulants Control Law, the 1953 Narcotics and Psychotropics Control Law and the 1964 Opium Law, but which may pose a public health threat". The Tokyo Metropolitan Government responded to this challenge in 2005 by granting the Governor new legislative powers that allow the adoption of ordinances to ban activities related to the supply and production of NPS of concern to the Tokyo Administration. Subsequently, at the national level, the Pharmaceutical Affairs Law was amended in 2007 to allow control over NPS as "designated substances" prohibiting their advertising, sale, supply and production. Penalties for the violation of this law include imprisonment of up to 5 years and/or fines up to 5 million Japanese Yen. The simple possession (for personal use) of a "designated substance" does not constitute an offense. As at November 2012, 90 NPS are controlled under the Pharmaceutical Affairs Law since it came into force in 2007.

In New Zealand, the increasing use of benzylpiperazine (BZP)[128] raised concern among authorities and society about the nature and possible adverse effects associated with this substance, and called for a legislative response. However, BZP was not listed under the Misuse of Drugs Act 1975 since and it had been marketed as a dietary supplement, it was neither subject to a pre-market approval nor to any control on sale or distribution.

According to the Misuse of Drugs Act 1975, it is for the Expert Advisory Committee on Drugs (EACD) to advise the Minister of Health of New Zealand on drug classification of any substance.[129] In 2004, the classification of BZP was considered, but given the scarcity of information on toxicological aspects and on the long-terms effects caused by the substance, the issuance of an advice under the terms set forth in the Act[130] was precluded. The Committee concluded that "there is no current schedule of the Misuse of Drugs Act 1975 under which BZP could reasonably be placed",[131] and recommended that further research be conducted into the potential harms associated with the use of BZP, and to examine options for new categories of classifi-

125 European Monitoring Centre for Drugs and Drug Addiction, 'MBDB, 4-MTA, GHB, ketamine, PMMA, 2C-I, 2C-T-2, 2C-T-7, TMA-2, BZP and mephedrone', May 2012 (http://www.emcdda.europa.eu/html.cfm/index16776EN.html)

126 PMMA, 2C-I, 2C-T-2, 2C-T-7, TMA-2, BZP, mephedrone and 4-MTA.

127 European Monitoring Centre for Drugs and Drug Addiction, '2012 Annual report on the state of the drugs problem in Europe', Lisbon, 2012

128 The New Zealand Ministry of Health estimated that 1.5 to 2 million doses had been sold by one distributor in New Zealand between 2001 and 2003.

129 Section 5AA of the Misuse of Drugs Act 1975

130 According to Section 4B of the Misuse of Drugs Act 1975, the Expert Advisory Committee on Drugs must give advice on: "(a) the likelihood or evidence of drug abuse, including such matters as the prevalence of the drug, levels of consumption, drug seizure trends, and the potential appeal to vulnerable populations; and (b) the specific effects of the drug, including pharmacological, psychoactive, and toxicological effects; and (c) the risks, if any, to public health; and (d) the therapeutic value of the drug, if any; and (e) the potential for use of the drug to cause death; and (f) the ability of the drug to create physical or psychological dependence; and (g) the international classification and experience of the drug in other jurisdictions; and (h) any other matters that the Minister considers relevant.

131 New Zealand, Expert Advisory Committee on Drugs (EACD), 'Advice to the Minister on: Benzylpiperazine (BZP)', 2004 (http://www.ndp.govt.nz/moh.nsf/pagescm/569/$File/eacdbzp.pdf)

cation through which some level of control and regulation could be incorporated, without prohibiting access to these substances completely.[132] Following these recommendations, the Misuse of Drugs Amendment Act, passed in 2005, created a new schedule for 'restricted substances'. The substances listed therein were then subject to control of manufacture and sale but not prohibited. BZP was the first substance initially placed under this schedule, and as such, sale restrictions of BZP to minors were enforced as well as controls on the advertisement and labelling of the product, but the possession of the drug was still legal.

After the initial scheduling of BZP, the publication of further studies on the toxicology of BZP and adverse effects associated with the use of this substance resulted in an interim report presented to the EACD, which in response, and based on the new evidence, issued a follow-up report on BZP in 2006, and advised the Health Minister that this substance posed a 'moderate risk of harm'. BZP was then removed from the 'restricted substances' schedule, and in 2008, it was placed in Schedule 3 (Class C 'Controlled Drugs'),[133] along with other substances that pose a moderate risk of harm, such as cannabis and other piperazines.[134] At the time of writing, NPS legislation is being drafted in New Zealand.

In the Republic of Korea, drugs are controlled under the 'Act on the Control of Narcotics'. In 2000, the three major drug laws to control narcotics, psychotropic substances, opium and cannabis, i.e. the Narcotics Act, the Cannabis Control Act, and the Psychotropic Substances Control Act, were combined into this single Act.

Several NPS, listed as "psychotropic drugs", had been subject to control under the Act on the Control of Narcotics since the mid 2000s.[135] However, the dramatic increase in the volume of newly detected NPS since 2008, prompted an additional Government's response to strength control over the rapid emergence of NPS. In September 2011 a new 'temporary scheduling system', added to the Act on the Control of Narcotics, entered into force. Under the Act, the Korean Food and Drug Administration may temporarily schedule NPS for a year. The synthetic cathinone MDPV (3,4-Methylenedioxypyrovalerone) was the first drug subject to temporary schedule at the end of 2011.

In the United States, the Controlled Substances Act (CSA)[136] contains the federal drug policy under which the manufacture, importation, possession, use and distribution of certain substances is regulated. For purposes of control, the CSA places all substances into one of five schedules, based upon the substance's medicinal value, harmfulness, and potential for abuse or dependence. The initial list contained in the Act has been complemented by legislative amendments,[137] but the Act also provides a mechanism for substances to be controlled, added to a schedule, removed from control, reschedule, or transferred from one schedule to another.[138] Temporary scheduling of new substances to avoid imminent hazard to public safety is also possible under the CSA.[139] In 2011, several synthetic cannabinoids (JWH-018; JWH-073; JWH-200; CP-47,497; CP-47,497 C8 homologue)[140] and some synthetic cathinones (mephedrone; methylone; and (MDPV))[141] were subject to temporary control.

132 New Zealand, Expert Advisory Committee on Drugs (EACD), 'Advice to the Minister on: Benzylpiperazine (BZP)', 2004 (http://www.ndp.govt.nz/moh.nsf/pagescm/569/$File/eacdbzp.pdf)

133 Under the Misuse of Drugs Act 1975, a 'controlled drug' means any substance, preparation, mixture, or article specified or described in Schedule 1, Schedule 2, or Schedule 3; and includes any controlled drug analogue. Controlled drug analogue means any substance, such as the substances specified or described in Part 7 of Schedule 3, that has a structure substantially similar to that of any controlled drug; but does not include—(a) any substance specified or described in Schedule 1 or Schedule 2 or Parts 1 to 6 of Schedule 3; or (b) any pharmacy-only medicine or prescription medicine or restricted medicine within the meaning of the Medicines Act 1981. (Misuse of Drugs Act 1975, Section 2(1)). Schedule 3 Part 1 clause 2 was added on 1 April 2008, by section 4 of the Misuse of Drugs (Classification of BZP) Amendment Act 2008 (2008 No 5)

134 Section 3A (C) of the Misuse of Drugs Act 1975

135 See Article 2(4) (a-b) of the Act on the Control of Narcotics for the definition of psychotropic drugs. NPS regarded as psychotropic drugs and subject to control include, among others, JWH-018 & its analogues, CP-47497 & C6, C8, C9, BZP, 2C-D, 2C-E, MeOPP, HU-210, 4-Acetoxy-DiPT, *m*CPP, TFMPP, Psilocybin, phencyclidine analogues.

136 The CSA was enacted into law as part of the Comprehensive Drug Abuse Prevention and Control Act of 1970

137 For instance, the Drug Prohibition Act of 2000 amended the Controlled Substances Act to direct the emergency scheduling of gamma hydroxybutyric acid

138 Section 811, Controlled Substances Act of 1970

139 Section 811 (h), Controlled Substances Act of 1970. Based on an interim ruling, new substances can be temporarily scheduled up to 12 months (with the possibility of six months extension), after which they can be permanently scheduled, if there is an evaluation and recommendation in favour by the Secretary of Health and Human Services.

140 United States, Drug Enforcement Administration, 'Schedules of controlled substances: temporary placement of five synthetic cannabinoids into Schedule I, Final order', 21 CFR Part 1308 [Docket No. DEA-345F] (http://www.deadiversion.usdoj.gov/fed_regs/rules/2011/fr0301.htm)

141 United States, Drug Enforcement Administration, 'Schedules of controlled substances: temporary placement of three synthetic cathinones into Schedule I', 21 CFR Part 1308 [Docket No. DEA-357] (http://www.deadiversion.usdoj.gov/fed_regs/rules/2011/fr1021_3.htm)

In addition to the CSA, the United States has a Controlled Substances Analogue Enforcement Act, i.e. 'Federal Analogue Act', to control substances not specifically listed in the CSA. The enactment of the Federal Analogue Act in 1986 was a response to the spread of fentanyl derivatives, α-prodine derivatives, phenethylamines related to MDMA, amphetamines and other compounds designed to produce similar effects to the controlled drugs they mimic.[142]

Under section 802 (32)(A) of the CSA, "controlled substance analogue" is defined as a substance (i) whose chemical structure is substantially similar to the structure of a scheduled substance; (ii) whose effects are substantially similar to or greater than the effects of a controlled substance or, (iii) the substance is thought to have such an effect. The use of analogue control operates on a substance by substance basis, and therefore each new substance needs to be assessed individually and a Court should decide whether the substance is or not controlled. Courts in the United States have interpreted the law as meaning that both requirements (similarity in the structure and the effects), must be fulfilled.

The Federal Analogue Act served as a model for other analogue systems adopted during the 1980s (in Canada, New Zealand and parts of Australia), and it has been suggested that it might have been effective in addressing the proliferation of synthetic drugs at that time. While the implementation of the new standards-based model closed some of the loopholes of the CSA, such as the slow and costly process to issue individual prohibitions for each illicit chemical, its implementation has revealed some theoretical and practical problems.[143] For instance, the lack of clarity of the statutory definition of an analogue drug was raised in a Court Case in 1995, but the Court ruled in favour of the Analogue Act, and deemed it not to be constitutionally vague.[144] Moreover, it has been argued that some unique entities, which are unlike any controlled drug (in terms of chemical structure), i.e. plant-based psychoactive substances such as salvia divinorum and kratom (mitragyna speciosa), are beyond the scope of analogue control.[145] For these and other reasons, some analysts have considered the analogue system as an 'imperfect law',[146] and other legislative approaches have been suggested to address the problem of NPS, such as the inclusion of the most problematic groups of NPS in the CSA,[147] or mixing rules and standards in the Federal Analogue Act.[148]

3.2.4 Other regulatory frameworks

The international drug control system laid down in the United Nations drug control Conventions was founded on the basis of concern of public health and social problems resulting from the abuse of certain psychotropic substances and from the addiction to narcotic drugs, and the need to prevent and combat abuse of such substances and the illicit trafficking to which it gives rise. For this purpose, State parties to the Conventions agreed to take the necessary legislative and administrative measures to limit exclusively to medical and scientific purposes the production, manufacture, export, import, distribution of, trade in, use and possession of such drugs, and to treat as a punishable offence, when committed intentionally, any action contrary to a law or regulation adopted in pursuance of its obligations under the Conventions.

Since the adoption of the Conventions, confronted with the challenges posed by NPS and considering that traditional drug control systems require time and basic scientific data on the harms posed by NPS to react, countries have explored different approaches to regulation that give more flexibility to existing drug control systems at the national level or appeal to other regulatory frameworks.

Several countries have amended their legislation to control the manufacture, trafficking, possession, sale

142 King, L.A., Nutt, D., Singleton, N., and Howard, R., 'Analogue controls. An imperfect law', Independent Scientific Committee on Drugs, United Kingdom Drug Policy Commission, 2012

143 Kau, G., 'Flashback to the federal analogue act of 1986: mixing rules and standards in the cauldron', University of Pennsylvania Law Review, 2008, 156, 1078-115

144 United States court of Appeals, United States vs. Allen McKinney, 1995 (http://law.justia.com/cases/federal/appellate-courts/F3/79/105/555999/)

145 King, L.A., Nutt, D., Singleton, N., and Howard, R., 'Analogue controls. An imperfect law', Independent Scientific Committee on Drugs, United Kingdom Drug Policy Commission, 2012

146 Wong, L., Dormont, D. and Matz, H.J., 'United States Controlled Substance Analogue Act: legal and scientific overview of an imperfect law', presented to Advisory Council on Misuse of Drugs, 2010

147 For instance, in 2011 a bill was presented in the United States Congress to include two groups of new psychoactive substances (i.e. cathinone derivatives and cannabinoids antagonists) in Schedule I of the Controlled Substances Act, without relying on the Analogue Act. United States Congress. 'H.R. 1254--112th Congress: Synthetic Drug Control Act of 2011', GovTrack.us (database of federal legislation), 2011, (http://www.govtrack.us/congress/bills/112/hr1254; accessed in: October 2012

148 Kau, G., 'Flashback to the federal analogue act of 1986: mixing rules and standards in the cauldron', University of Pennsylvania Law Review 2008, 156, 1078-115

and use of NPS in the same fashion as with substances controlled under the Conventions, where prohibited substances are listed individually. However, the inclusion of new substances is often a lengthy process that requires in most cases a health risk assessment (based on scientific data and human experience data that in the case of NPS is often scarce), followed by legislative amendments that usually take several months. For these reasons, some countries have adopted a generic or an analogue system to complement and to give more flexibility to the individual listing system, which allows the control of groups of substances or similar substances to those individually listed, without the need to appeal to a legislative reform. For instance, in 2010, the generic system was introduced in the United Kingdom to ban synthetic cathinones, and was introduced in Hungary in 2012 to ban NPS temporarily.[149] In 2009, synthetic cannabinoids were defined as a group of substances controlled in Luxemburg and in 2010, Italy developed a group definition of synthetic cannabinoids and later a group definition of cathinones.[150] Ireland also has a generic system to control NPS. Norway and the United States have an analogue system in place but the definition of 'analogue' differs in the two countries.

Governments have also used 'emergency scheduling' to introduce temporary bans on NPS while the legislative process is being completed and/or a rigorous assessment of the risks is conducted. For instance, in Denmark an Executive Order on Euphoriant Substances can enter into force in two to three days, in Germany the Federal Ministry of Health may publish a regulation in the Federal Law Gazette (with no reference to the Council of Ministers or the Bundesrat) through a process that takes a few weeks, and in Spain, the Minister for Health and Consumer Affairs can prepare an Order that is published in the Spanish Official Journal (with no reference to the Parliament) and the entire process takes between five and 15 days.[151] Australia, China, Croatia, Bahrain, Ghana, Hungary, Ireland, Italy, Netherlands, Russian Federation, Saudi Arabia, United Kingdom and United States reported in the UNODC questionnaire on NPS having used emergency scheduling to temporarily ban NPS.

In addition, alternative, effective and proportionate ways to respond in an equally fast and flexible way to the emergence of NPS has been reflected in the use of other regulatory frameworks. For instance, medicine legislation has been used in at least eight countries, including Finland and the Netherlands.[152] Respondents to the UNODC questionnaire on NPS from Albania, Bahrain, Brunei Darussalam, Bulgaria, and Thailand reported the use of Poison Acts. The use of consumer safety regulations was reported from Bahrain, Bulgaria, Croatia, Hungary, Israel, Italy, Nepal, Poland, Portugal, Romania, Russian Federation, Togo and the United Kingdom. Unlike traditional drug control systems, where the manufacture, trafficking, possession, sale and use of NPS is usually banned and subject to criminal provisions, control measures of NPS under other regulatory frameworks tend to be limited in scope, focusing primarily on the control of the sale of NPS.

The different approaches to regulation are varied among nations, and while some may be considered more advantageous or effective than others, there are no perfect systems. However, monitoring has proved useful in providing timely information to make evidence-based decisions that respond to the rapid changes that encompass the supply and demand of NPS.

149 United Kingdom, Home Office circular 010/2010, 'A change to the Misuse of Drugs Act 1971: Control of mephedrone and other cathinone derivatives', 2010; Hungary adopted the same approach after the Government Decree 66/2012 came into effect on April 2012, whereby a temporary ban on new psychoactive substances was introduced.

150 European Monitoring Centre for Drugs and Drug Addiction, '2012 Annual report on the state of the drugs problem in Europe', Lisbon, 2012

151 Kelleher, C., Christie, R., Lalor, K., Fox, J., Bowden, M. and O'Donnell, C., 'An Overview of New Psychoactive Substances and the Outlets Supplying Them', National Advisory Committee on Drugs, Centre for Social and Educational Research, Dublin Institute of Technology, Dublin, 2011 (http://www.nacd.ie/images/stories/docs/publicationa/head_report2011_overview.pdf)

152 Mephedrone was controlled through medicine legislation in Finland and the Netherlands before it was subject to a risk assessment in the framework of the Council Decision on new psychoactive substances of the European Union; BZP has also been controlled under medicine legislation in Spain. Austria, Germany, Hungary and the United Kingdom, have also used medicine legislation to control synthetic cannabinoids. Winstock, A. and Wilkins, C., '"Legal highs" The challenge of new psychoactive substances', Transnational Institute, Series on Legislative Reform of Drug Policies, 2011, 16, 1-16

4. USE OF NEW PSYCHOACTIVE SUBSTANCES

4.1. Global use estimates

The extent of global use of NPS remains unknown. Thus far, there are no estimates on the prevalence of use of NPS in the general population, but rather limited data collected in few countries, with respect to specific substances and subpopulations.

Concern about the increasing use of NPS and their potential adverse effects has led to a growing need for monitoring these substances and several countries have opted for the inclusion of NPS in national drug surveys. Some limitations of these surveys include the lack of common definitions and of representative samples, the large and increasing number of substances regarded as NPS, and the differences in legislation among countries.

4.2. Regional use estimates

In the framework of the European Union, the attitude of youth towards drugs is regularly examined by the Eurobarometer, which analyses public opinion in Member States of the European Union. Drug use surveys have been conducted among young people in EU Member States in 2002, 2004 and 2008 (Eurobarometer No. 172, 158, and 233). These surveys have studied the attitude of young people toward licit and illicit substances including heroin, cocaine, ecstasy, cannabis, alcohol and tobacco. In 2011, responding to recent developments in the EU drug market, the Eurobarometer "Youth attitudes on Drugs" (No. 330) asked young people for the first time about their experiences and attitudes towards new psychoactive substances or 'legal highs'. For the purposes of the survey, NPS were understood as "a large number of new unregulated compounds that imitate the effects of illicit drugs (so-called new psychoactive substances or 'legal highs')".

The sample size for the 2011 survey included over 12,000 randomly selected young people (aged 15-24) across the 27 EU Member States, who were interviewed by telephone. Youths were asked about their perceptions on the availability of NPS, perceived health risks associated to their use, attitudes towards banning or regulating NPS and about the effectiveness of alternative drug policies.

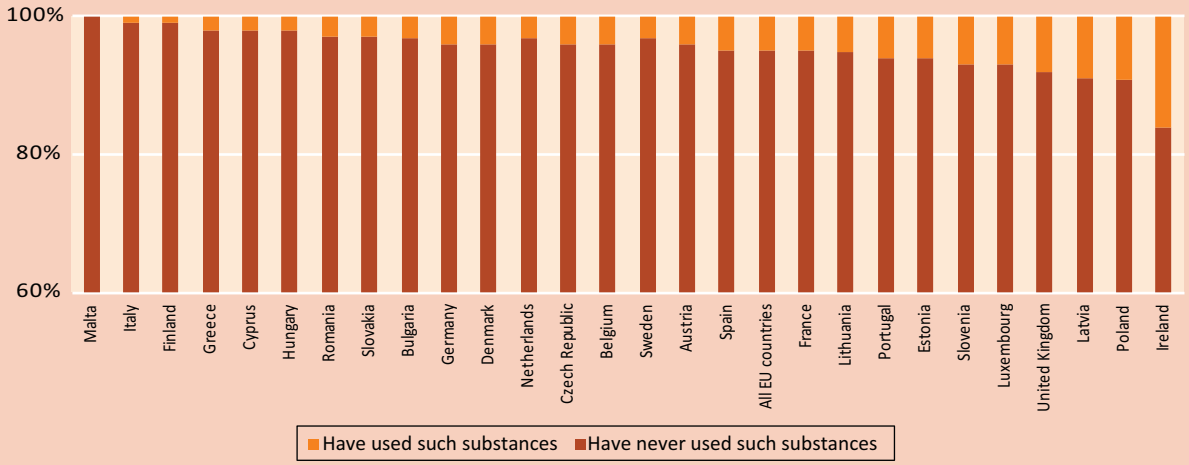
Overall, 5% of the participants reported having used NPS.[153] Ireland (16%), Poland (9%), Latvia (8.8%) and the United Kingdom (8%), were at the higher end of the country ranking, while Italy (0.8%), Finland (1%) and Greece (1.6%) were found at the lower end.[154]

With respect to the supply of NPS, 54% of the respondents who had used NPS reported that they had been offered the substance by friends, 37% had been offered the substances during a party or in a club, 33% had purchased them from a specialized shop, and less than 7% had bought them over the Internet. Older respondents were more likely than their younger counterparts to have been offered such substances at a party or in a club (41% of 22-24 year-olds vs. 32% of 15-18 year-olds), whereas those who had completed their higher education (41% vs. 27% among those who had only completed their primary education at the time of the survey) were more likely to have purchased the substances from a specialized shop.

[153] The wording of the question was as follows: In certain countries some new substances that imitate the effects of illicit drugs are being sold as legal substances in the form of -for example -powders, tablets/pills or herbs. Have you ever used such substances? European Commission, Youth attitudes on drugs, Flash Eurobarometer 330, 2011, 18

[154] European Commission, 'Youth attitudes on drugs', Flash Eurobarometer 330, 2011 (http://ec.europa.eu/public_opinion/flash/fl_330_en.pdf)

European Union: lifetime prevalence of NPS use in EU Member States



Source: Flash Eurobarometer 330. Youth Attitudes on Drugs. Analytical report. May 2011.
Base: all respondents, % by country

Young people who reported having used NPS were also less likely to recognize the seriousness of the risks associated with regular and occasional use of various illicit and licit substances. Sixty percent of those who had never used NPS thought that using ecstasy occasionally posed a high risk to a person's health and 26% saw a medium risk. By comparison, only 40% of those who had used NPS perceived the health risks caused by occasional ecstasy use as high, and 34% as medium. A similar pattern follows the perception of the risks associated to cannabis use.[155]

With respect to responding to NPS, only 1% - 4% of the interviewees considered that no action was needed. However, preferences on whether to ban all NPS, to ban only those that pose serious risks to someone's health or to regulate them, varied across EU Member States.

While there are some limitations of the results, including the small sample size in each State (in most EU countries the target sample size was 500 respondents, but in Estonia, Cyprus, Luxembourg, Malta and Slovenia the sample size was 250 respondents) to assess actual use and the lack of a common understanding on what constitutes a new psychoactive substance, the survey nevertheless provides a glimpse into the use of these substances by young people.

[155] European Commission, 'Youth attitudes on drugs', Flash Eurobarometer 330, 2011 (http://ec.europa.eu/public_opinion/flash/fl_330_en.pdf)

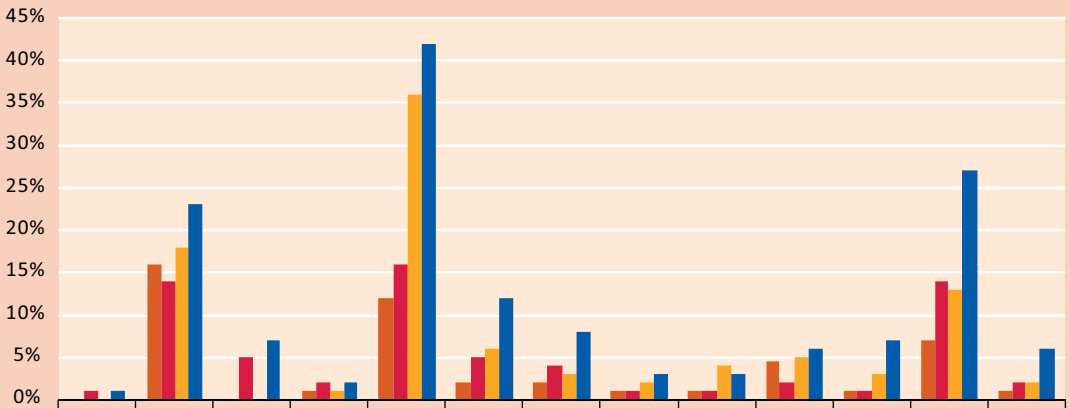
4.3. National use estimates

Apart from the above-mentioned regional estimates, national surveys in a general population and/or subpopulations have also been conducted in few countries to estimate the use of NPS. It should be noted, however, that often only a limited number of NPS (or even just a single one) is included in these estimates.

In Australia, information on the prevalence of use of NPS has been included since 2010 in the Drug Trends in Ecstasy and Related Drug Markets (EDRS) report. The 2011 report presents the most recent findings on the markets for ecstasy and related drugs[156] based on data collected in all states and territories in Australia from surveys with regular ecstasy users, surveys with key experts who have contact with regular ecstasy users and the analysis of existing data sources that contain information on ecstasy and related drugs. Although the results from the regular ecstasy users surveys are

[156] "The term 'ecstasy and related drugs' includes drugs that are routinely used in the context of entertainment venues and other recreational locations including nightclubs, dance parties, pubs and music festivals. ERD include ecstasy (MDMA, 3,4-methylenedioxymethamphetamine), methamphetamine, cocaine, LSD (d-lysergic acid), ketamine, MDA (3,4-methylenedioxyamphetamine) and GHB (gamma-hydroxybutyrate)." Sindicich, N. and Burns L., 'Australian trends in ecstasy and related drug markets 2011, findings from the ecstasy and related drugs reporting system (EDRS)', Australian Drug Trends Series No.82, National Drug and Alcohol Research Centre, University of New South Wales, Sydney 2012 (http://ndarc.med.unsw.edu.au/sites/ndarc.cms.med.unsw.edu.au/files/ndarc/resources/National_EDRS_2011%20final.pdf)

Australia: prevalence of drug and NPS use among regular ecstasy users (REU), 2010 - 2011



	Spice	Mephedrone	Methylone	MDPV	Ketamine	2C-I	2C-E	DOI	PMA	BZP	*Datura*	DMT	5-MeO-DMT
Recent use prevalence 2010	0.0%	16.0%	0.0%	1.0%	12.0%	2.0%	2.0%	1.0%	1.0%	4.5%	1.0%	7.0%	1.0%
Recent use prevalence 2011	1.0%	14.0%	5.0%	2.0%	16.0%	5.0%	4.0%	1.0%	1.0%	2.0%	1.0%	14.0%	2.0%
Lifetime prevalence 2010	0.0%	18.0%	0.0%	1.0%	36.0%	6.0%	3.0%	2.0%	4.0%	5.0%	3.0%	13.0%	2.0%
Lifetime prevalence 2011	1.0%	23.0%	7.0%	2.0%	42.0%	12.0%	8.0%	3.0%	3.0%	6.0%	7.0%	27.0%	6.0%

Source: data from the 2011 EDRS report
Fields displayed as 0.00% indicate that data is not available

not representative of ecstasy users and their other drug use in the general population, the data provided is indicative of patterns of drug use. In the 2011 EDRS survey, 574 regular ecstasy users were interviewed. Participants were recruited primarily through street press adverts and word-of-mouth.

According to the findings for 2011, ketamine use remained limited to Victoria, New South Wales and the Australian Capital Territory, with 16% of the national sample reporting recent use, [157] a significant increase from 2010 (12%). A small proportion of regular ecstasy users reported the use of some NPS, for example, synthetic cannabinoids ('spice'), synthetic cathinones (mephedrone, methylone, MDPV), phenethylamines (2C-I, 2C-E, 2,5-dimethoxy-4-iodoamphetamine (DOI)), piperazines (BZP), tryptamines and plant-based substances (*datura*). While in 2011, lifetime and recent use of 'spice' was low among the sample (1% and <1% respectively), five per cent of the national sample believed that they have used other form of synthetic cannabinoids.[158]

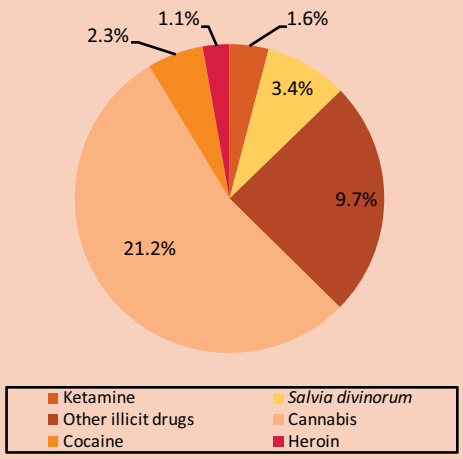
In 2011, ketamine, DMT (an internationally controlled substance) and mephedrone were the substances with the highest rate of lifetime prevalence. From 2010 to 2011, there was a significant decrease in recent use of mephedrone (16% vs. 14%). Regular ecstasy users reported in 2011 lifetime and recent use of methylone at 7% and 5% , while only a small number (2%) reported lifetime and recent use of MDPV in the same year. The use of phenethylamines showed significant increases in 2011, however the number reporting use remained low. Both lifetime (12%) and recent use (5%) of 2C-I (compared to 6% and 2% in 2010) increased as did lifetime (8%) and recent use (4%) of 2C-E (compared to 3% and 2% in 2010). Six per cent of the participants reported having tried a 2C-class drug (apart from those mentioned above) and thirty participants of the entire sample (5%) reported lifetime use of 'other' 2C-class drugs, including 2C-B-Fly, 2C-P, 2C-T-2, 2C-T-7. There was a decline in the number of users that reported recent use of BZP (2% vs. 4.5% in 2010). To a lesser extent, recent use of the plant based substance datura was reported by three of the participants (1%).[159]

[157] Recent use in the EDRS report refers to prevalence of use in the past six months.

[158] Sindicich, N. and Burns L., 'Australian trends in ecstasy and related drug markets 2011, findings from the ecstasy and related drugs reporting system (EDRS)', Australian Drug Trends Series No.82, National Drug and Alcohol Research Centre, University of New South Wales, Sydney 2012 (http://ndarc.med.unsw.edu.au/sites/ndarc.cms.med.unsw.edu.au/files/ndarc/resources/National_EDRS_2011%20final.pdf)

[159] Sindicich, N. and Burns L., 'Australian trends in ecstasy and related drug markets 2011, findings from the ecstasy and related drugs reporting system (EDRS)', Australian Drug Trends Series No.82, National Drug and Alcohol Research Centre, University of New South Wales, Sydney 2012 (http://ndarc.med.unsw.edu.au/sites/ndarc.cms.med.unsw.edu.au/files/ndarc/resources/National_EDRS_2011%20final.pdf)

Canada: last-year prevalence of drug and NPS use among secondary school students – Youth Smoking Survey, 2010 - 11



Source: data from the YSS 2010-11

In Canada, the use of NPS was recently included in the biennial 'Youth Smoking Survey' (YSS) conducted since 2002. The YSS helps schools and government agencies across Canada assess youth substances use and related health behaviours. The 2010-11 school-based survey included a representative sample of 50,949 (representing approximately 3 million youth) secondary school students from all provinces of Canada except New Brunswick.[160] Survey results showed a higher last year prevalence of the use of NPS (*salvia divinorum* (3.4%), ketamine (1.6%), and 'other illicit drugs'[161] (9.7%)) than for other illicit drugs, such as cocaine (2.3%) and heroin (1.1%).[162] Cannabis remained the top illicit drug of choice (21.2%).

Questions on NPS were included for the first time in the Drug Prevalence Survey 2010/11 on drug use in Ireland and Northern Ireland. This survey included a sample of 7,669 people aged 15-64 (5,134 in Ireland and 2,535 in the United Kingdom (Northern Ireland)). In Ireland, NPS included 'herbal smoking mixtures/incense, party pills or herbal highs, bath salts, plant feeders or other powders, kratom (krypton), *salvia divinorum*, magic mint, divine mint or sally D and other NPS mentioned by the respondent', while in Northern Ireland, NPS (called 'legal highs') comprised 'party pills, herbal highs, party powders, kratom and *salvia divinorum*'. Limitations of this survey include the lack of coverage of some groups with high drug use prevalence (e.g. the homeless, those in prison), refusal to participate in the survey or under-reporting of drug use, and, in some cases, the small sample size.

According to the 2010/11 results from the survey, lifetime and last year prevalence of NPS use in Northern Ireland were 2.4% and 1.0%, respectively. Both lifetime and last year use were higher among men (3.0%) than women (1.8%) and significantly higher for young adults (aged 15-34) than for older adults (aged 35-64) (4.8% vs. 0.6%). There was a separate question on the use of mephedrone in Northern Ireland and responses showed similar percentages of use to NPS in both lifetime (2.0% vs. 2.4%) and last year prevalence (1.1% vs. 1.0%). In Ireland, there is no data available on lifetime prevalence of NPS but last year prevalence among adults was 3.5%. Cannabis remains the most commonly used illicit drug in both Northern Ireland and in Ireland. However, in Ireland, after cannabis, NPS and cocaine (including crack) were the most frequently reported substances.[163]

In New Zealand, the most recent national survey data on the use of NPS is available from the New Zealand Drug Use Survey 2007/2008, which measured self-reported alcohol and drug use in the adult population. The survey collected information on 6,784 New Zealanders aged 16–64 years, including 1,825 Maori and 817 Pacific respondents.[164] According to the results of this survey, lifetime and last year use of BZP (reported at 13.5% and at 5.6% respectively) was even higher than the use of amphetamines (7.2% and 2.1% respectively) or cocaine (3.6% and 0.6%). BZP users were significantly more likely to be male, aged between 18-34, and

160 Canada, Health Canada, 'Summary of results of 2010-11 Youth Smoking Survey', Controlled Substances and Tobacco Directorate, Waterloo, May 2012 (http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_survey-sondage_2010-2011/result-eng.php)

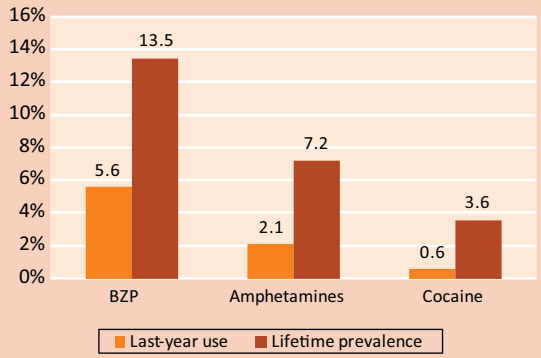
161 Other illicit drugs include, among others, hallucinogens (LSD, PCP, acid, magic mushrooms, mesc); ketamine (special k, kit-kat); GHB (G, liquid X, goop); Salvia (Divine Sage, Magic Mint, Sally D); Jimson weed (locoweed, stinkweed, mad apple). Canada, Health Canada, 'Supplementary tables, Youth Smoking Survey 2010-11', Controlled Substances and Tobacco Directorate (http://www.yss.uwaterloo.ca/results/YSS2010-2011_supplementary_tables_en.pdf)

162 Canada, Health Canada,, 'Supplementary tables, Youth Smoking Survey 2010-11', Controlled Substances and Tobacco Directorate (http://www.yss.uwaterloo.ca/results/YSS2010-2011_supplementary_tables_en.pdf)

163 Ireland and Northern Ireland (United Kingdom), National Advisory Committee on Drugs and Public Health Information and Research Branch, 'Drug use in Ireland and Northern Ireland 2010/11: Drug Prevalence Survey: Regional Drug Task Force (Ireland) and Health and Social Care Trust (Northern Ireland) Results', 2012

164 New Zealand, Ministry of Health, 'Drug use in New Zealand: key results of the 2007/08 New Zealand Alcohol and Drug Use Survey', January 2010 (http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/surveys/current-recent-surveys/alcohol-and-drug-use-survey)

New Zealand: prevalence of drug and NPS use in the adult population of New Zealand, 2007 - 08



Source: data from the New Zealand Drug Use Survey 2007-2008
Base: all respondents %

more likely to be Maori. Moreover, hospital discharge data corresponding to 37 people discharged for cases involving NPS between 2009-2011, showed that users of NPS were reportedly younger compared with people discharged for cannabis use, less likely to be Maori (41% compared to 51% of cannabis users) and less likely to be living in an area of high deprivation (27% compared to 40% for cannabis users).[165] Prevalence of use of NPS approved under the legislation that is being drafted will be monitored through national surveys.

In the United Kingdom, new measures of drug use were added to the 2010/11 British Crime Survey (BCS), with the inclusion of drugs recently classified under the Misuse of Drugs Act.[166] According to the findings from the 2010/11 survey, an estimated 8.8% of adults in England and Wales had used an illicit drug in the last year (almost 2.9 million people). Last year use of mephedrone[167] (1.4 %) for adults aged 16-59, was at a similar level as ecstasy use (1.4%), the third most prevalent drug for this age group. For younger adults (aged 16-24), mephedrone use (4.4%) was at a similar level of use as cocaine (4.4%), the second most used drug in this age group. The use of synthetic cannabinoids, khat and BZP was only of 0.4%, 0.3%, and 0.2% respectively. Adults aged 16-24 showed higher rates of prevalence for both mephedrone (4.4%) and synthetic cannabinoids (0.4%) than adults aged 16-59 (0.6% and 0.1% respectively). Cannabis remained the most commonly used type of illicit drug with 6.8% of adults (aprox. 2.2. million people) having used this drug in the last year, followed by cocaine (2.1%, around 0.7 million adults) and ecstasy (1.4%, 0.5 million adults).[168]

In the United States, the 'Monitoring the Future' survey has been conducted annually since 1975 to generate national data on drug use of American adolescents, college students and adults through the age of 50. In 2011, a question about the use of synthetic cannabinoids ('spice' and K2)[169] was included for the first time in the survey, asking 12th graders about their use in the previous 12 months. The sample size of the 2011 survey encompassed about 46,700 secondary school students in 400 schools nationwide.[170] According to the findings of the survey, synthetic cannabinoids ranked second only to natural cannabis in annual prevalence among 12th graders. Some 11.4% of 12th graders reported having used synthetic cannabinoids in the previous 12 months, while 5.9% of these users reported last year use of *salvia divinorum*. Overall, last-year use of NPS among 12th graders surpassed the use of other illicit drugs such as cocaine (2.9%) and heroin (0.80%) in 2011. Among all young adults aged 19-30, the annual prevalence of synthetic cannabinoids was 6.5%, but there were considerable differences by age. With annual prevalence rates in 2011 between 2% and 5%, *salvia divinorum* seems to be more widespread among 19-24 years olds than among those aged 25 to 30, where annual prevalence was less than 1%.

165 New Zealand, Ministry of Health, 'Regulatory impact statement, new regulatory regime for psychoactive substances', the Treasury, Wellington, July 2012 (http://www.treasury.govt.nz/publications/informationreleases/ris/pdfs/ris-moh-rrps-jul12.pdf)

166 Development of the BCS questionnaire takes place on an annual basis and aims to reflect emerging issues. Questions about the use of ketamine were added to the BCS in 2006/07, questions about synthetic cannabinoids and benzylpiperazine (BZP) were added in October 2009, and questions about the use of mephedrone were added to the 2010/11 BCS questionnaire. Smith, K. and Flatley, J., 'Drug misuse declared: findings from the 2010/11 British Crime Survey England and Wales', Statistical Bulletin, United Kingdom Home Office, 2011

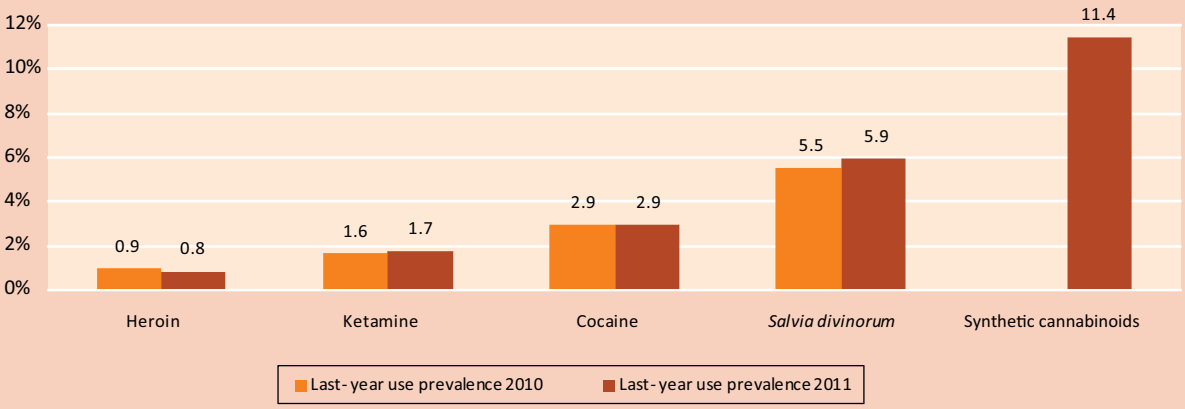
167 In 2010, mephedrone was classified in the United Kingdom as a Class B substance under the Misuse of Drugs Act

168 Smith, K. and Flatley, J., 'Drug misuse declared: findings from the 2010/11 British Crime Survey England and Wales', Statistical Bulletin, United Kingdom Home Office, 2011

169 In the survey, synthetic cannabinoids were understood as a substance that "goes by such names as 'Spice' and K-2, and is an herbal drug mixture that usually contains designer chemicals that fall into the cannabinoid family". Johnston, L. D., O'Malley, P.M., Bachman, J.G. and Schulenberg, J.E., 'Monitoring the Future, national results on adolescent drug use, overview of key findings, 2011', The University of Michigan, sponsored by The National Institute on Drug Abuse, National Institutes of Health, February 2012 (http://monitoringthefuture.org/pubs/monographs/mtf-overview2011.pdf)

170 Johnston, L. D., O'Malley, P.M., Bachman, J.G. and Schulenberg, J.E., 'Monitoring the Future, national results on adolescent drug use, overview of key findings, 2011', The University of Michigan, sponsored by The National Institute on Drug Abuse, National Institutes of Health, February 2012 (http://monitoringthefuture.org/pubs/monographs/mtf-overview2011.pdf)

United States: prevalence of drug and NPS use among 12th graders, 2010 - 2011



Source: data from the MTF Survey 2010-2011
Base: 12th graders %
Question on synthetic cannabinoids was introduced in 2011 for the first time

4.4. National treatment data estimates

Given their relatively recent emergence in the drug markets, treatment data on NPS is almost non-existent but some Governments have started to collect data on the impact of the use of NPS on public health systems.

In the United Kingdom, treatment data on ketamine and mephedrone were included for the first time in the 2012 report of the National Treatment Agency for Substances Misuse (NTA). The report showed that while the number of people entering treatment for ecstasy has halved from 2,138 in 2006-07 to 1,018 in 2011-12, ketamine and mephedrone cases have risen. Ketamine presentations continuously increased between 2005-06 and 2010-11, from 114 to 845, falling back to 751 in 2011-12. In 2012, 900 over-18s started treatment for mephedrone, compared to 839 in the previous year. The high numbers could indicate a potential strain on public health although it is not possible to predict long-term treatment demand on the basis of data for two years. In addition, many persons demanding treatment for NPS were relatively young. In 2011, 56% of all over-18s treated for mephedrone were aged 18-24.[171]

The 2011 annual report of the National Programme on Substance Abuse Deaths (np-SAD) of the United Kingdom revealed an increase in the number and range of NPS identified in post mortem toxicology results and/or as cause of death of cases notified to the Programme. NPS include *para*-methoxyamphetamine (PMA) (an internationally controlled substance), fluoroamphetamine (4-FA), tryptamines (5-MeO-DALT) as well as mephedrone, MDPV and naphyrone. The number of cases where mephedrone and MDPV were mentioned increased significantly in 2010: according to post mortem toxicology results, mephedrone rose to 46 reports (compared to 8 reports in 2009) and MDPV to 9 reports in 2010 (compared to 0 in 2009). Cause of death cases notified to the Programme also registered an increase in 2010 for both mephedrone (29) and MDPV (6) (compared to 5 and 0 cases in 2009, respectively).[172]

In the United States, the first report on synthetic cannabinoids from the Drug Abuse Warning Network revealed that an estimated 11,406 visits of the approximately 2,300,000 emergency department visits that involved drug use in 2010 were specifically linked to synthetic cannabinoids. Three quarters of these emergency department visits involved patients aged 12 to 29 (75 percent or 8,557 visits), of which 78 percent were male, and in the majority (59 percent) of these cases, no other substances were involved. The average patient age for synthetic cannabinoids-related visits was 24 years, while it was 30 years for cannabis. Overall, synthetic cannabinoid-related visits were concentrated in the younger age groups: 75 percent of the visits involved patients aged 12 to 29, with 33 percent of the patients aged 12 to 17. In comparison, 58 percent of cannabis-related visits involved patients aged 12 to 29, with 12 percent in the 12 to 17 age group.[173]

[171] National Treatment Agency for Substances Misuse, "Club drugs: emerging trends and risks", 2012 (http://www.nta.nhs.uk/uploads/clubdrugsreport2012%5B0%5D.pdf ; accessed in: November 2012)

[172] United Kingdom, National Programme on Substance Abuse Deaths (np-SAD), 'Drug-related deaths in the UK. Annual report 2011', 2012

[173] United States, Drug Abuse Warning Network, 'Drug-related Emergency Department visits involving synthetic cannabinoids', 2012

4.5. Internet surveys on the use of new psychoactive substances

Internet surveys have been conducted to assess the use of NPS. It should be noted that all known surveys on NPS have been conducted in Europe and that they are limited by the self-nominating nature of the sample and are therefore unrepresentative of the general population. The use of an online method of data collection implies that those who respond are likely to be more active online and that some populations with higher than average levels of drug use (e.g. the homeless and those in prison) as well as those with no access to the Internet are excluded.

In Germany, an online survey on use experiences and use patterns of various NPS[174] was conducted in 2011. The survey was addressed to those with drug use experience and invitations to participate were extended to them via social networks, internet shops that offer legal highs, online forums on drug-related topics and prevention websites. The survey was completed online by 860 individuals (89% of the respondents were male and the average age was 24.2 years) from all over Germany. Reported lifetime prevalence of illegal drugs among the respondents was at 99%. Synthetic cannabinoids were reportedly the most prevalent new psychoactive substance, with a lifetime prevalence of 86%. Lifetime prevalence of research chemicals[175] was at 39% and at 35% for 'other legal highs'.[176] More than half of the respondents reported having used at least one NPS in the last month. The users of synthetic cannabinoids were reportedly older on average and more frequently living in small towns. Current users of research chemicals were especially likely to be experienced and regular users of various illegal drugs. Overall, the respondents named more than 300 different substances which they had tried at least once. More than three out of five respondents indicated the legal availability of NPS as a major motivation for use.[187]

In the United Kingdom, the British electronic dance and clubbing magazine 'MixMag' has conducted two surveys on NPS, in 2009 and 2011. The survey had been traditionally addressed to young club goers, but over the last few years it has attempted to involve a wider segment of the population. The first survey, carried out in 2009 (results were published in January 2010), collected data of lifetime, last year and last month drug use on 29 substances, including NPS such as synthetic cannabinoids, synthetic cathinones (MDPV, mephedrone, methylone), phenethylamines (2C-I, and 2C-T-7), piperazines (BZP), *salvia divinorum* and 'other new psychoactive substances'. Although 3,500 responses had been received as of February 2010, the analysis here presented is based on a subset of 2,295 UK respondents, the majority of them aged between 18-27.[178]

The 2009 survey shows that lifetime and last-month prevalence of other NPS surpassed the use of illicit drugs such as heroin and methamphetamine. Last year prevalence showed ketamine as the most common new psychoactive substance (51%), followed by synthetic cathinones (mephedrone 37.3%), piperazines (BZP 12.1%), and, to a lesser extent, plant-based substances (*salvia divinorum* 8.9%) and synthetic cannabinoids ('spice' 6.2%).

The second Mixmag survey was carried out in 2010, with results published in March 2011. More than 15,500 people worldwide took part in a similar MixMag/the Guardian Drugs Survey, which makes it "the biggest ever survey of drug use among clubbers", according to the organizers. Three quarters of the respondents were aged between 18-27 and two-thirds were male (69%). Two NPS were added to the 2010

174 New psychoactive substances were broken down in herbal blends; other legal highs/bath salts; etc., and research chemicals. Werse, B. and Morgenstern, C., 'Short report, Online survey on the topic of "legal highs"', Centre for Drug Research, Goethe University, Frankfurt am Main, 2011

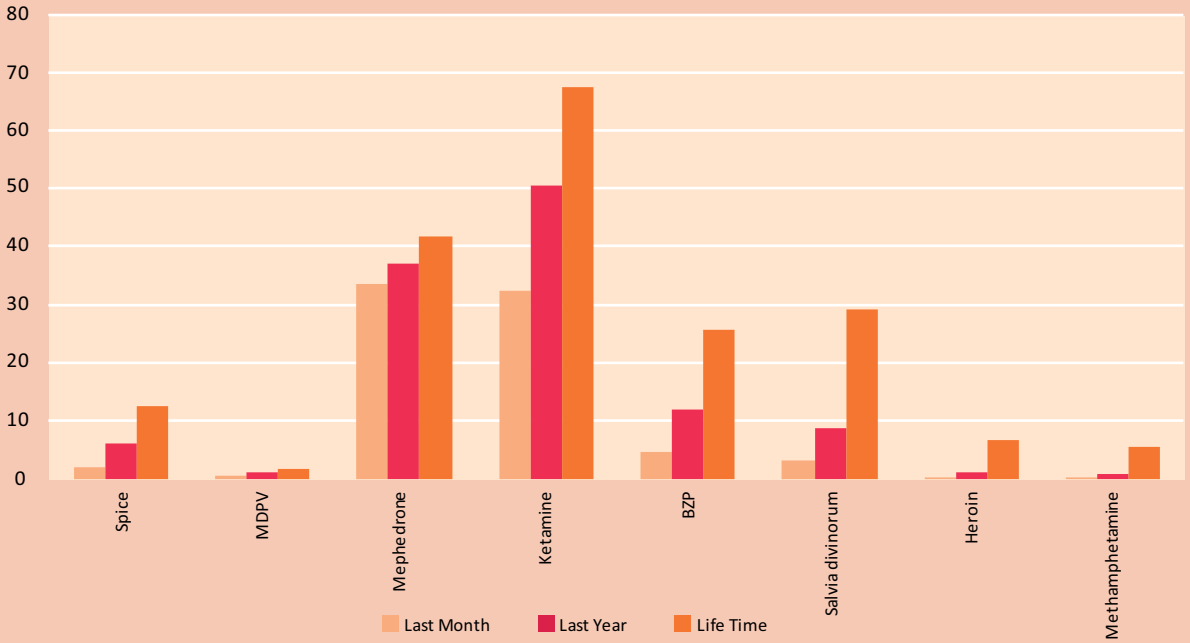
175 Research chemicals refer to "new synthetic drugs that are (at least according to the declaration) sold in pure form under their actual chemical name. The generic term is independent of the activity profile and, in principle, it considers the whole spectrum of all the possible drug effects, even though there are focus areas. Research chemicals are, in some cases, labelled as "only for research purposes". Werse, B. and Morgenstern, C., 'Short report, online survey on the topic of "legal highs"', Centre for Drug Research, Goethe University, Frankfurt am Main, 2011

176 Other legal highs "includes all products except cannabis-like smoking blends, which are (mainly deliberately) wrongly labelled as "bath salts", "air fresheners", "plant food" etc. and contain synthetic psychoactive substances. It mostly includes drugs which have stimulant and entactogenic / empathogenic effects, and are therefore substitutes for popular party drugs' such as amphetamine, ecstasy/ MDMA or cocaine". Werse, B. and Morgenstern, C., 'Short report, online survey on the topic of "legal highs"', Centre for Drug Research, Goethe University, Frankfurt am Main, 2011

177 Legal highs refer to synthetic cannabinoids; other legal highs/bath salts, etc., and research chemicals. Werse, B. and Morgenstern, C., 'Short report, online survey on the topic of "legal highs"', Centre for Drug Research, Goethe University, Frankfurt am Main, 2011

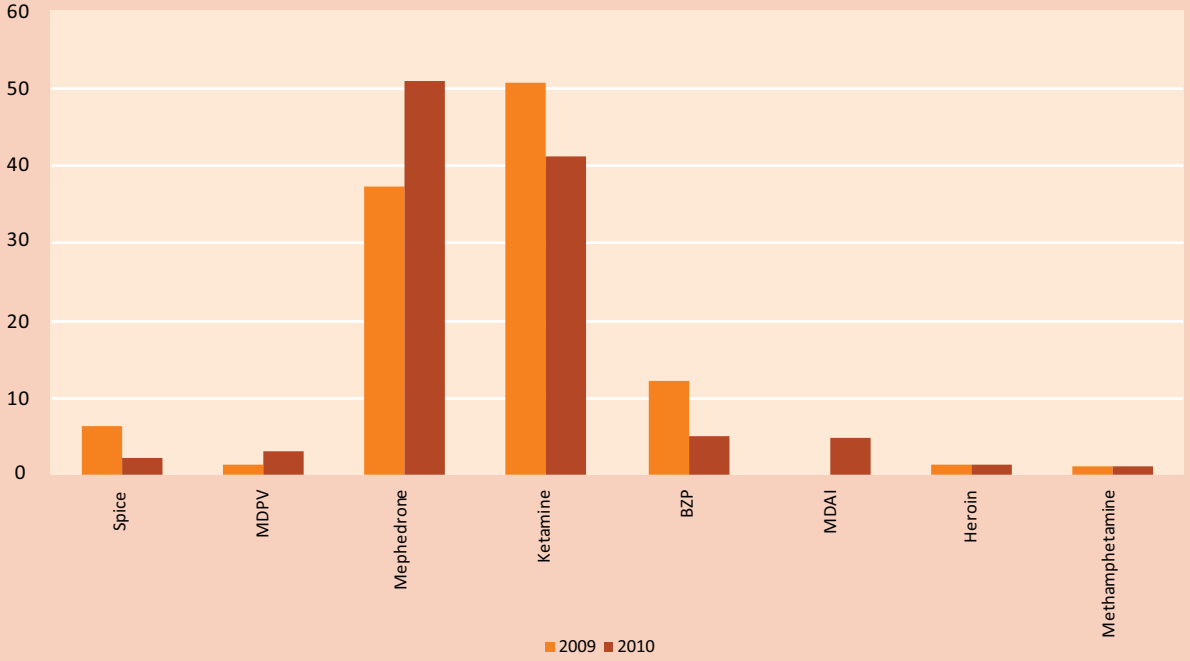
178 Winstock, A., 'Brief summary of the 2009/10 Mixmag's survey (Winstock and Mitcheson) for the EMCCDA Annual report', (http://ewsd.wiv-isp.be/Publications%20on%20new%20psychoactive%20substances/Mephedrone/Brief%20summary%20of%20the%202009-10_mixmag%20survey.pdf)

Internet survey: prevalence of drug and NPS use – Mixmag, 2009



Source: data from the Mixmag Drug Survey, 2009.[179]

Internet survey: last year prevalence of drug and NPS use – Mixmag, 2009 and 2010



Source: data from the Mixmag Drug Survey, 2010.[180]
It should be noted that samples for 2009 and 2010 are slightly different.

[179] Winstock, A., 'Brief summary of the 2009/10 Mixmag's survey (Winstock and Mitcheson) for the EMCCDA Annual report', (http://ewsd.wiv-isp.be/Publications%20on%20new%20psychoactive%20substances/Mephedrone/Brief%20summary%20of%20the%202009-10_mixmag%20survey.pdf)

[180] Winstock, A., 'The 2011 MixMag drugs survey', MixMag, London, 2011 (http://issuu.com/mixmagfashion/docs/drugsurvey)

survey; aminoindane derivative 5,6-methylenedioxy-2-aminoindane (MDAI) and phenethylamine derivative 6-APB (Benzofury). Although the results are not directly comparable from year to year as the composition of the sample is slightly altered, the 2010 survey findings showed a higher last year prevalence of mephedrone (51% in 2010 vs. 37% in 2009),[181] and a fall in last year use of ketamine from 2009 to 2010 (50.7% vs. 41.2%). All in all, in 2010 last year use of several NPS such as synthetic cannabinoids ('spice') (2.2%), MDPV (3%), or BZP (5%) remained higher than last year use of drugs such as heroin (1.2%) and methamphetamine (1.0%).[182]

[181] Winstock, A., 'The 2011 MixMag drugs survey', MixMag, London, 2011 (http://issuu.com/mixmagfashion/docs/drugsurvey)

[182] Winstock, A., 'The 2011 MixMag drugs survey', MixMag, London, 2011 (http://issuu.com/mixmagfashion/docs/drugsurvey)

5. THE SOURCES* OF NEW PSYCHOACTIVE SUBSTANCES

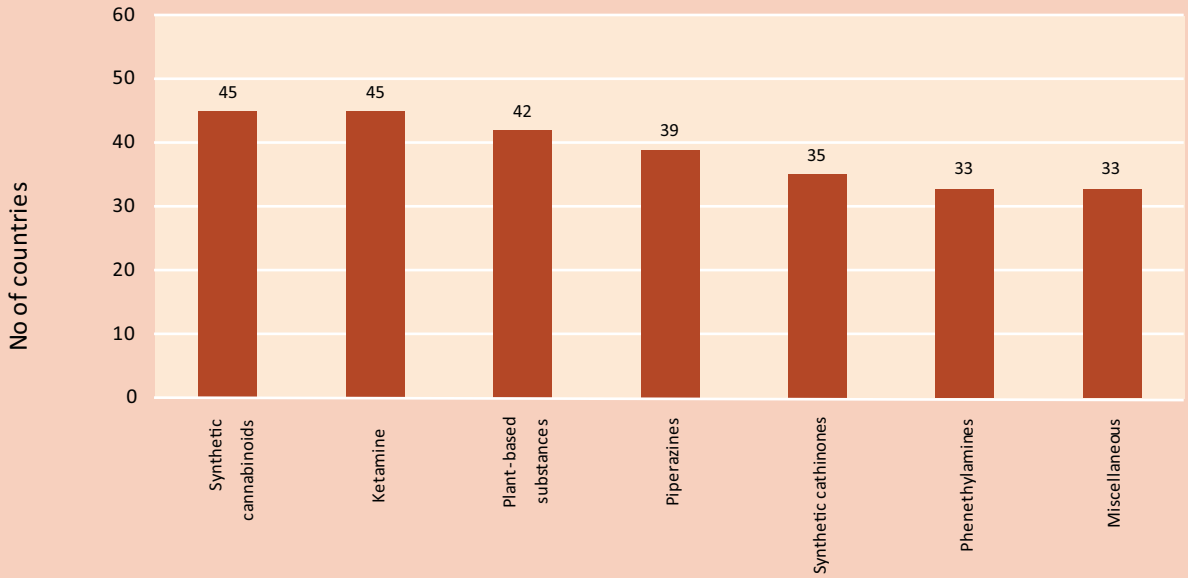
5.1 Countries reporting seizures of new psychoactive substances

From a total of 80 countries and territories reporting, 61 (76%) stated having seized NPS, almost half of those respondents were European countries. Most countries and territories (45) reported having seized synthetic cannabinoids and ketamine (75%), followed by 42 having seized plant-based substances (68%) and 39 having seized piperazines (65%).

Twenty-four countries, 18 from Europe[183], two each from the Americas (Canada and the United States), Asia (Japan and Singapore) and Oceania (Australia and New Zealand) reported having made seizures from each NPS group. In Europe, seizures were made across the region, from Portugal to the Russian Federation and from Norway to Italy.

In Africa and Europe, most NPS seizures concerned synthetic cannabinoids. Ketamine is the most widely seized NPS in the Americas and Asia. With regard to Oceania, all NPS groups of substances have been seized in Australia and New Zealand. Africa is the only region in the world which did not report the emergence or seizures of synthetic cathinones and phenethylamines.

Number of countries reporting NPS seizures

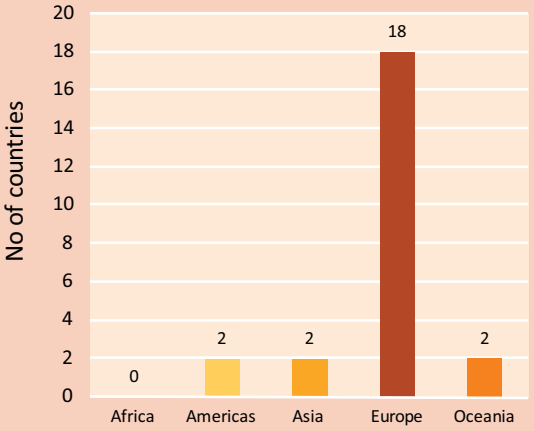


Source: UNODC questionnaire on NPS, 2012

[183] Belgium, Bulgaria, Croatia, Finland, France, Germany, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Romania, the Russian Federation, Spain, Switzerland, Turkey and the United Kingdom

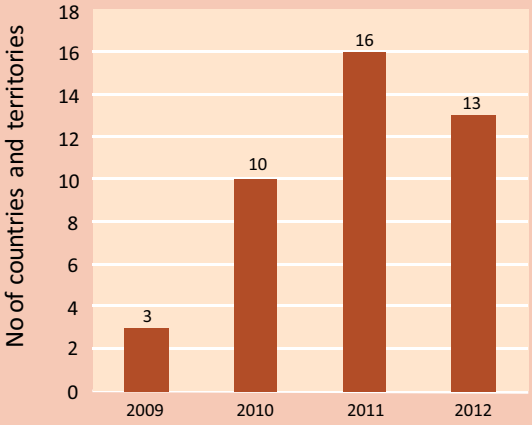
* Sources are reported by respondents and have not been validated scientifically as manufacturing/production sites.

Countries with seizures of all NPS groups, up to 2012



Source: UNODC questionnaire on NPS, 2012

Seizures of more than 1 kg of for synthetic cannabinoids, 2009-2012



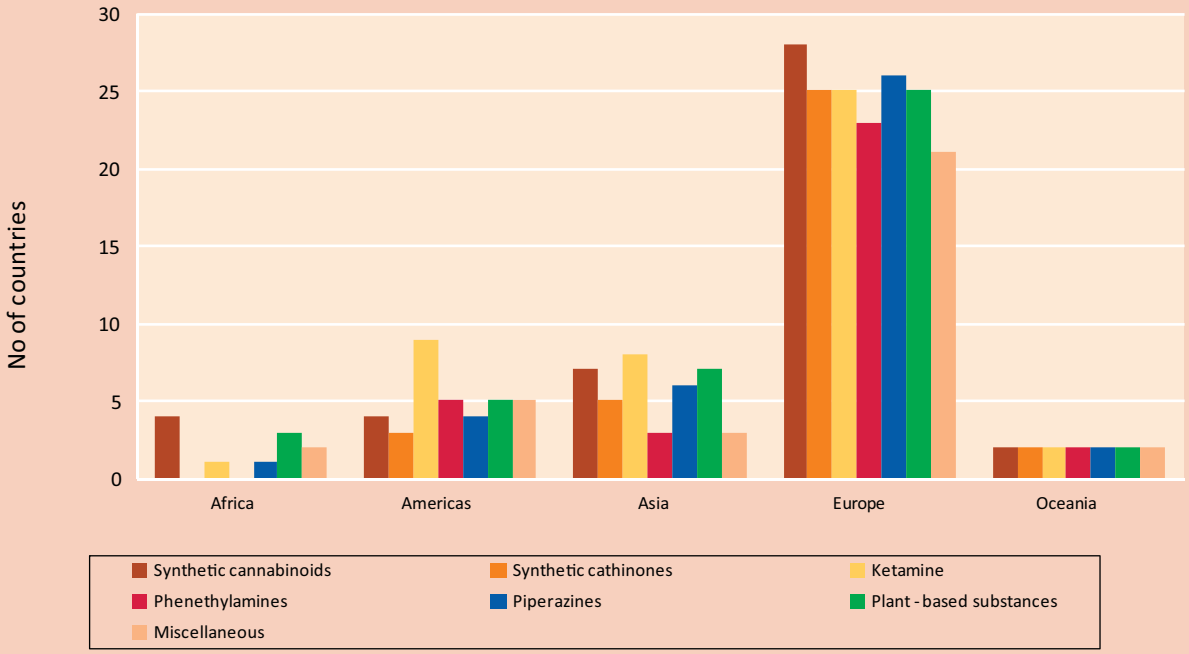
Source: UNODC questionnaire on NPS, 2012

Synthetic cannabinoids

Synthetic cannabinoids are the most frequently seized NPS, with seizures reported from all regions. Over the last four years, seizures of synthetic cannabinoids have spread geographically. Whereas for 2009, only three countries (Finland, France and Germany) reported seizures of more than 1 kg of synthetic cannabinoids, that number had increased to 10 in 2010, 9 from Europe as well as the United States. In 2011, 16 countries reported seizures of synthetic cannabinoids, indicating a further spread to new regions, namely Oceania (New Zealand) and Asia (Saudi Arabia). Some countries reported particularly high increases, in the United States, for example, only 23 seizure cases were reported in 2009, rising to 22,000 cases in 2011.

Several European countries reported significant seizures of synthetic cannabinoids. In Germany, 261 kg

NPS seizures by region, 2009 - 2012



Source: UNODC questionnaire on NPS, 2012
Note: Seizures were reported from: Africa (6 countries reporting), the Americas (10 countries reporting), Asia (14 countries and territories reporting), Europe (29 countries reporting) and Oceania (2 countries reporting)

Seizures of more than 1 kg of synthetic cannabinoids by country, 2009 - 2012

	2009	2010	2011	2012
Belgium				●
Bulgaria		●		●
Croatia			●	
Cyprus		●		
Finland	●	●	●	●
France	●			
Germany	●	●	●	
Hungary		●	●	
Ireland			●	●
Italy		●	●	
Latvia		●	●	●
Netherlands			●	●
New Zealand			●	●
Norway			●	●
Poland			●	
Romania		●	●	
Russian Federation		●	●	●
Saudi Arabia			●	
Slovakia				●
Spain			●	●
Turkey				●
United States		●	●	●

Source: UNODC questionnaire on NPS, 2012

of synthetic cannabinoids were seized in 2009. Cyprus, Hungary, Italy and Romania also reported seizures of more than 10 kg. In 2011, the EMCDDA reported that 20,000 packages containing several synthetic cannabinoids were seized at one facility in the Netherlands. [184]

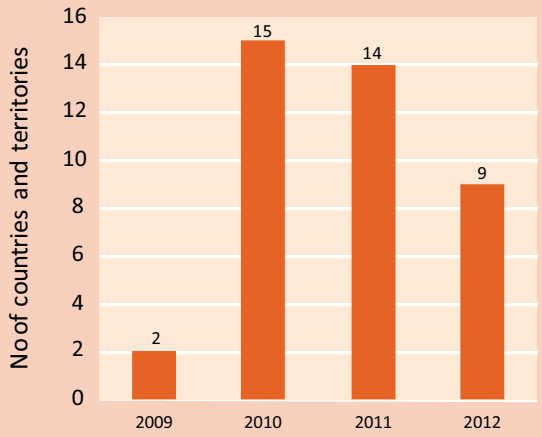
Various countries initiated special operations targeting NPS. The Drug Enforcement Administration of the United States, for example, conducted a nationwide operation in July 2012 which resulted in the seizures of 4.8 million packages of synthetic cannabinoids as well as large quantities of synthetic cathinones.

Synthetic cathinones

Seizure data of synthetic cathinones indicate the emergence on a larger scale in 2010 and 2011. Whereas only Finland and the Netherlands, reported seizures of more

[184] European Monitoring Centre for Drugs and Drug Addiction, '2012 Annual report on the state of the drugs problem in Europe', Lisbon, 2012

Seizures of more than 1 kg of synthetic cathinones, 2009- 2012



Source: UNODC questionnaire on NPS, 2012

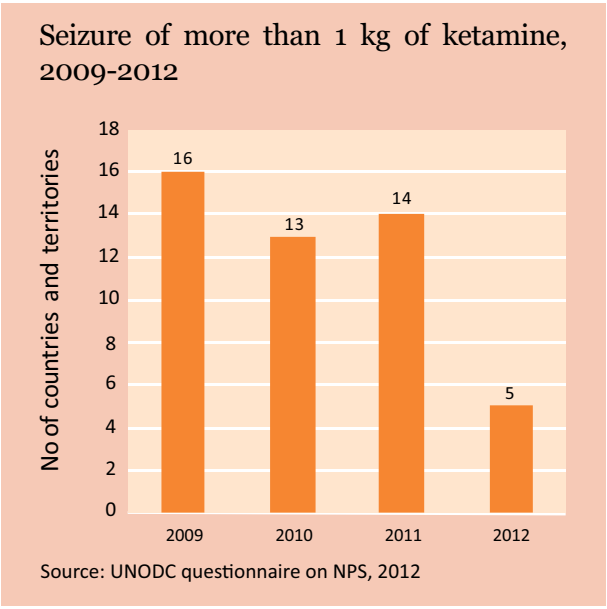
than 1 kg of synthetic cathinones in 2009, 15 countries reported seizures in 2010 and 14 in 2011. In 2012, 9 countries reported, however, as the questionnaire was circulated in July, data for that year is not complete.

Mephedrone appears to be the most widely seized synthetic cathinone. Hungary reported mephedrone to be the most frequently seized synthetic substance in 2010 (ARQ data). In the Netherlands, in October 2009, more than 130 kg of mephedrone were seized from a pill-pressing site and four related storage loca-

Seizures of more than 1 kg of synthetic cathinones by country, 2009 - 2012

	2009	2010	2011	2012
Bulgaria		●	●	●
Croatia		●		
Finland	●	●	●	●
France		●		
Germany		●	●	
Hungary			●	
Ireland		●	●	●
Italy		●		
Latvia		●	●	●
Malta		●	●	
Netherlands	●	●	●	●
New Zealand		●	●	
Norway		●	●	
Poland		●	●	●
Romania		●	●	●
Russian Federation		●	●	●
Spain			●	●

Source: UNODC questionnaire on NPS, 2012



tions.[185] Germany and the United Kingdom have also reported multi-kilo seizures of mephedrone.[186] Seizures of MDPV and 4-methylethcathinone (4-MEC) were also reported from European countries. Canada and the United States reported numerous seizure cases of synthetic cathinones.

Ketamine

Seizures of ketamine were stable, which might result from the fact that ketamine is a fairly established substance in ATS markets around the world. Sixteen countries reported more than 1 kg ketamine seizures in 2009, ten Asian countries and territories (Cambodia, China, India, Indonesia, Malaysia, Myanmar, Philippines, Singapore, Thailand and *Hong Kong SAR*), five European countries (France, Hungary, Italy, Netherlands and Spain) as well as Canada. In 2012, the year for which only partial data is available as the questionnaire was circulated in July, France, Malaysia, Singapore, Spain and *Hong Kong SAR* reported ketamine seizures.

The most significant seizures of ketamine have been made in Asia, with multi-ton seizures made in China

Seizures of more than 1 kg of ketamine by country, 2009 - 2012

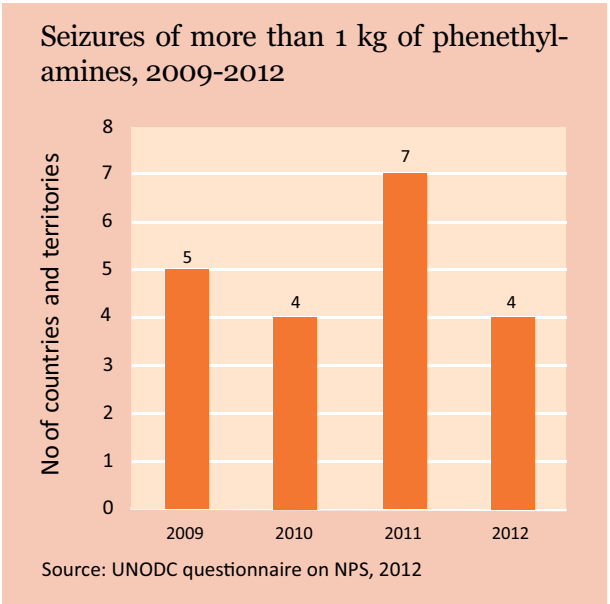
	2009	2010	2011	2012
Canada	●	●	●	
Cambodia	●			
China	●	●	●	
France	●		●	●
Hong Kong SAR	●	●	●	●
Hungary	●	●	●	
India	●	●	●	
Indonesia		●	●	
Italy	●	●	●	
Malaysia	●	●	●	●
Myanmar	●		●	
Netherlands	●	●	●	
Philippines	●			
Singapore	●	●	●	●
Spain	●	●	●	●
Thailand	●	●	●	
United States		●		

Source: UNODC questionnaire on NPS, 2012, ARQ and DAINAP

(5.3 mt), India (1 mt) and Malaysia (1.1 mt) in 2009. Outside Asia, significant ketamine seizures are reported by Canada, where 2.3 mt were seized in 2010. France, Hungary, Netherlands and the United States also reported seizures.

Phenethylamines

Most countries reporting more than 1 kg seizures of phenethylamines are from Europe. From 2009 to 2012, phenethylamines were seized in nine different



[185] European Monitoring Centre for Drugs and Drug Addiction, 'Report on the risk assessment of mephedrone in the framework of the Council Decision on new psychoactive substances', Risk Assessments Issue 9, Lisbon, 2011 (http://www.emcdda.europa.eu/attachements.cfm/att_116646_EN_ TDAK11001ENC_WEB-OPTIMISED%20FILE.pdf)

[186] European Monitoring Centre for Drugs and Drug Addiction, 'Report on the risk assessment of mephedrone in the framework of the Council Decision on new psychoactive substances', Risk Assessments Issue 9, Lisbon, 2011 (http://www.emcdda.europa.eu/attachements.cfm/att_116646_EN_ TDAK11001ENC_WEB-OPTIMISED%20FILE.pdf)

Seizures of more than 1 kg of phenethylamines by country, 2009 - 2012

	2009	2010	2011	2012
Belgium			●	●
Bulgaria			●	●
Finland	●		●	
Ireland			●	
Netherlands	●	●	●	
New Zealand	●			
Norway		●	●	●
Romania		●		
Russian Federation	●	●	●	●
Spain	●			

Source: UNODC questionnaire on NPS, 2012

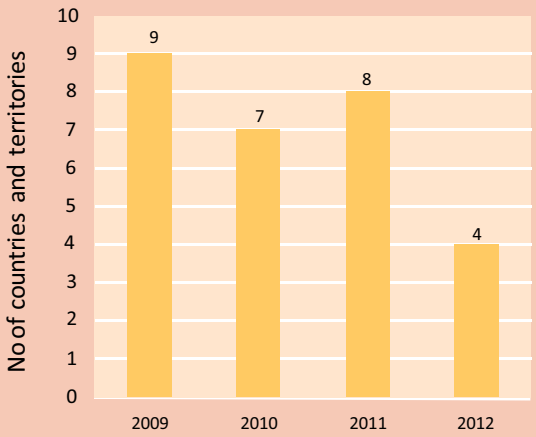
European countries as well as New Zealand. Whereas countries from the Americas and Asia reported smaller quantities, Romania reported the seizure of 77 kg of phenethylamines in 2010 and New Zealand reported having seized almost 6 kg in 2009.

Piperazines

Given that piperazines have emerged in almost all regions (Africa being the notable exception) before 2008, seizures during the last four years have been relatively constant, with a slightly decreasing trend in 2012.

Almost all countries reporting seizures are in Europe. In 2010, ARQ data from Finland shows seizures of 56 kg of *m*CPP pills. Romania also reported seizures of 7 kg of unspecified "piperazines".

Seizures of more than 1 kg of piperazines, 2009-2012



Source: UNODC questionnaire on NPS, 2012

Seizures of more than 1 kg of piperazines by country, 2009 - 2012

	2009	2010	2011	2012
Bulgaria	●		●	
Finland		●	●	
Germany	●			
Hungary	●			
Ireland			●	●
Latvia			●	
Netherlands	●	●	●	●
New Zealand	●	●	●	●
Norway	●	●		
Romania		●		
Russian Federation	●		●	●
Spain	●	●	●	
Turkey	●	●		

Source: UNODC questionnaire on NPS, 2012

In Ireland, BZP was often seized in combination with TFMPP.[187] Norway has reported seizures of BZP in powder, capsules or pill form.[188]

Plant-based substances

Seizures of plant based-substances have been reported from all regions and by most countries. Thirty-seven countries reported seizing more than 1 kg of a plant-based substance over the past four years. The most significant general seizures of plant-based substances were reported by Italy for all four years with 386 kg in 2009, 663 kg in 2010, 867 kg in 2011 and 161 kg in 2012 (until 26th July). New Zealand seized 137 kg in 2009 (65 seizure cases), 75 kg (40 cases) in 2011 and 39 kg (21 cases) in 2012.

Khat was the most frequently reported plant-based substance by by respondents to the questionnaire. The highest seizures in 2010 were made in Saudi Arabia with 374 mt, followed by the United States with 90 mt and Germany with 30.4 mt. ARQ data indicates further that multi-ton khat seizures were reported by

187 Kelleher, C., Christie, R., Lalor, K., Fox, J., Bowden, M. and O'Donnell, C., 'An overview of new psychoactive substances and the outlets supplying them', National Advisory Committee on Drugs, Centre for Social and Educational Research, Dublin Institute of Technology, Dublin, 2011 (http://www.nacd.ie/images/stories/docs/publicationa/head_report2011_overview.pdf)

188 European Monitoring Centre for Drugs and Drug Addiction and European Police Office, 'EMCDDA–Europol 2011 Annual report on the implementation of Council Decision 2005/387/JHA', Lisbon, 2012, 18 (http://www.emcdda.europa.eu/attachements.cfm/att_70975_EN_EMCDDA _risk_assessment_8.pdf)

Seizures of more than 1 kg of plant-based substances by country, 2009 - 2012

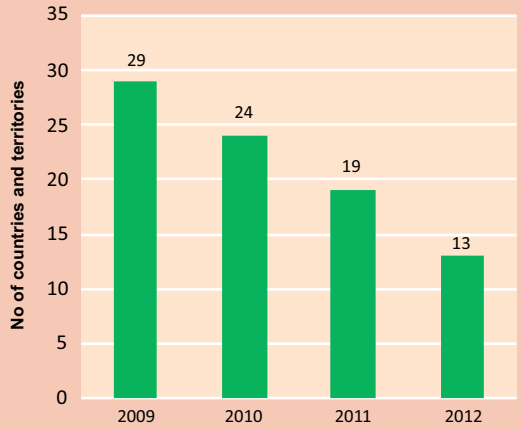
	2009	2010	2011	2012
Australia	●			
Bahrain				●
Belgium	●	●		
Bulgaria			●	
Canada	●	●	●	
Denmark	●	●		
Egypt	●	●	●	●
Estonia	●			
Finland	●	●	●	●
France	●	●	●	●
Germany	●	●		
Greece	●			
Hong Kong SAR	●	●		●
Hungary			●	
Ireland	●	●	●	●
Italy	●	●	●	●
Latvia			●	
Lebanon		●	●	
Malaysia	●	●	●	●
Malta	●	●	●	●
New Zealand	●		●	●
Norway	●	●	●	●
Qatar	●			
Panama	●	●	●	●
Romania		●		
Saudi Arabia	●	●	●	
Spain			●	●
Sweeden	●	●		
Switzerland	●	●	●	
Syrian Arab Republic	●			
Tanzania (United Republic of)	●	●		
Thailand	●	●		
Turkey		●	●	
UAE	●			
United States	●	●		
Yemen	●			
Zambia	●	●		

Source: UNODC questionnaire on NPS, 2012 and ARQ

Denmark (2010: 5 mt), Sweden (2010: 14 mt) and United Republic of Tanzania (2010: 10 mt). Several countries experienced significant increases in seizures of khat between 2009 and 2010 such as Saudi Arabia (182 kg to 374 mt), Ireland (50 kg to 218 kg) and Norway (3 mt to 7 mt).

Significant seizures of kratom, a plant indigenous to South-East Asia, were also reported, mostly from that region. The largest kratom seizures were reported by Thailand with 29.9 mt in 2009, 44.2 mt in 2010 and 32.9 mt in 2011.[189] Malaysia seized 2.2 mt in 2010 (ARQ data) and Myanmar seized almost 600 kg in 2009, 375 kg in 2010 and 970 kg in 2011.[190]

Seizures of more than 1 kg of plant-based substances, 2009-2012



Source: UNODC questionnaire on NPS, 2012

The third most widespread plant-based substance is *salvia divinorum*, a plant common to southern Mexico and Central and South America. Although *salvia* has been reported from every region, seizures remain relatively low, with only Germany indicating to have seized 1.3 kg in 2009.

Seizure trends for new psychoactive substances

Trends for the seven NPS groups fluctuate. While seizures of ketamine, phenethylamines and piperazines seem to be more or less stable over the past four years, expert perceptions indicate rising trends for synthetic cannabinoids, synthetic cathinones and plant-based substances.

Trend of NPS seizures, 2009 - 2012

NPS group	2009	2010	2011	2012
Synthetic cannabinoids	↑	↑	↑	↑
Synthetic cathinones	↑	↑	↑	↔
Ketamine	↔	↔	↔	↔
Phenethylamines	↔	↑	↔	↔
Piperazines	↑	↔	↔	↓
Plant-based substances	↑	↑	↑	↔
Miscellaneous	-	↑	↑	↑

↑= Increasing, ↓= Decreasing, ↔ =Stable, - unknown
Source: UNODC questionnaire on NPS, 2012 and ARQ

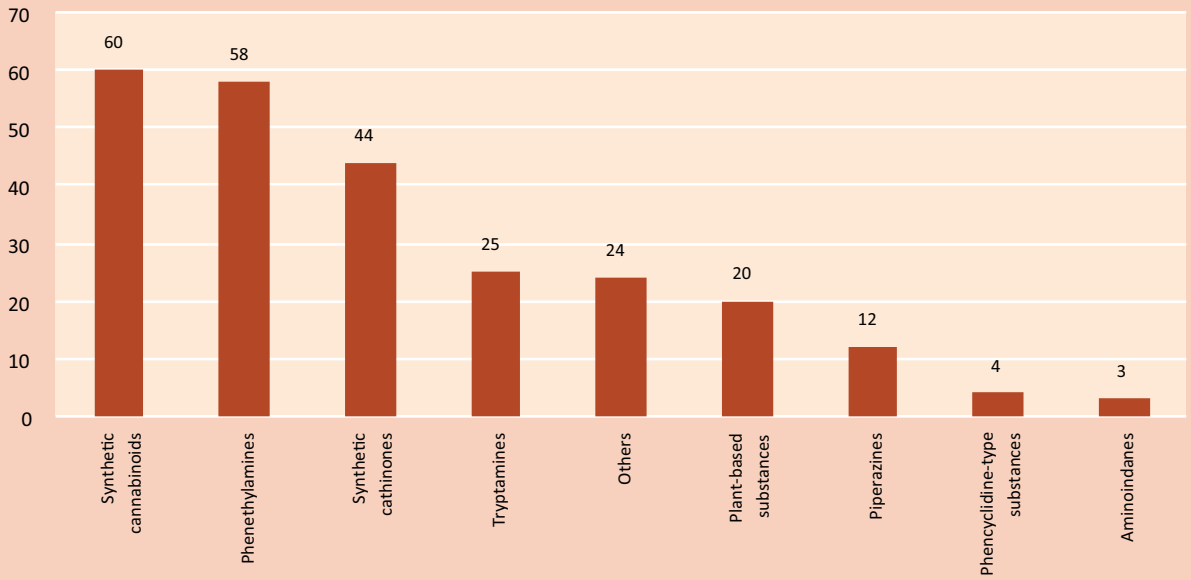
[189] Source(s): DAINAP; ONCB 2012
[190] Source(s): DAINAP; CCDAC 2012

5.2 Number of new psychoactive substances in global markets

A total of 251 NPS (including ketamine) were reported to UNODC by 40 countries and territories up to 2012. Most of the substances reported globally between 2009 and 2012 are synthetic cannabinoids (60 substances), followed by phenethylamines (58 substances) and synthetic cathinones (44 substances).

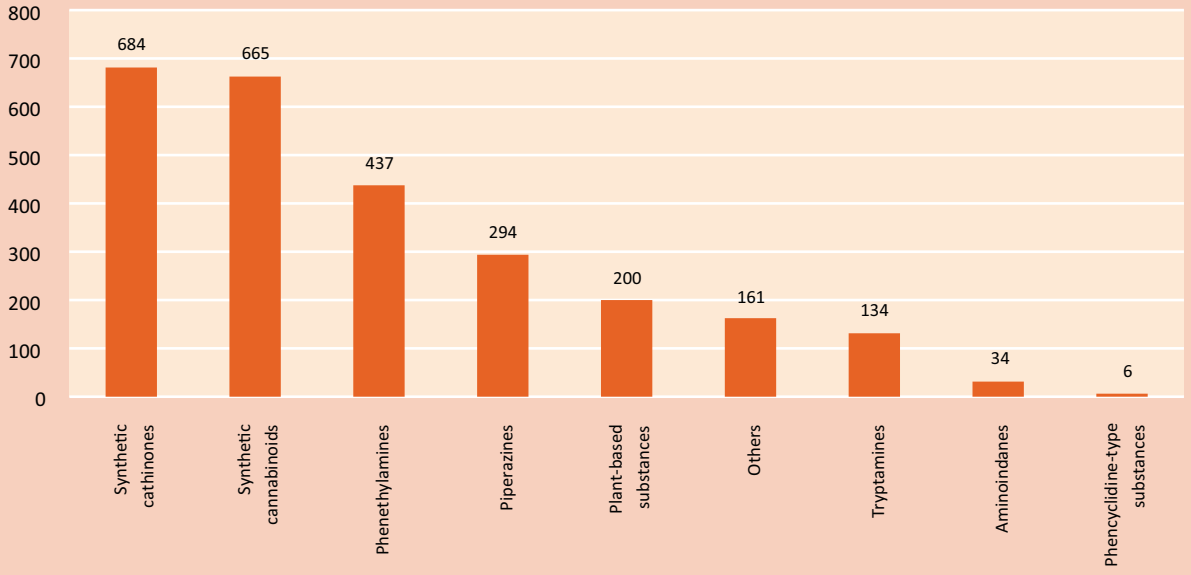
At the global level, most reports pertaining to NPS concern synthetic cathinones, with 684 reports, followed by synthetic cannabinoids with 665 reports. The highest number of reports in each NPS group were received in 2011. In terms of number of substances reported, 2012 ranks second, but it has to be taken into account that 2012 data is limited to the first 7 months or so, as the questionnaire was circulated in the month of July.

Number of NPS reported up to 2012

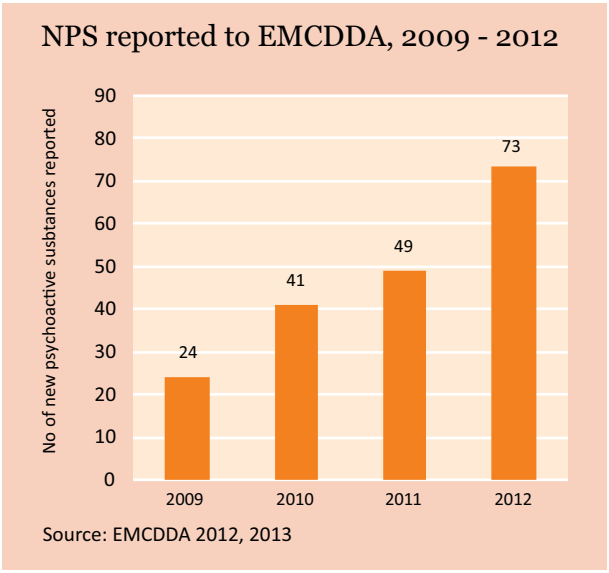


Source: UNODC questionnaire on NPS, 2012

Number of reports on NPS, up to 2012



Source: UNODC questionnaire on NPS, 2012

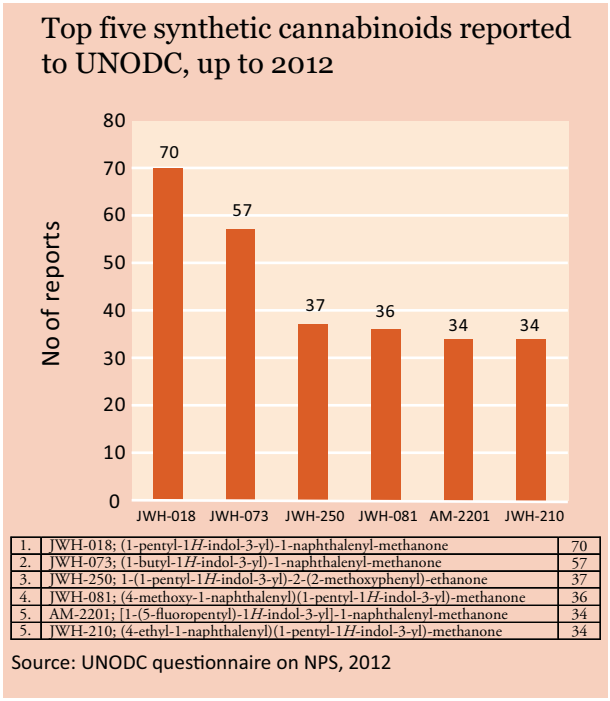


In countries of the European Union, the emergence of NPS is monitored by the EMCDDA which review new substances reported by Member States of the European Union. The number of substances has continuously increased over the years, whereas in 2009 only 24 substances were reported, 41 were formally notified in 2010, 49 in 2011 and 73 NPS reported in 2012.[191,192] In 2010 and 2011, about two thirds of the newly notified substances reported were synthetic cannabinoids or synthetic cathinones.

Synthetic cannabinoids

Respondents to the UNODC questionnaire on NPS reported 60 different synthetic cannabinoids, the most frequently reported substance being JWH-018.

The Republic of Korea reports that 74 per cent of all synthetic cannabinoids analysed by the Customs Laboratory between January 2009 to August 2012 belonged to the JWH class.[193] Similarly, data on synthetic cannabinoids submitted through the National Forensic Laboratory Information System (NFLIS)[194] of the United States, found that most belonged to the JHW class; in 2010, 63 per cent of them were identified as JWH-018, followed by JWH-250 (14%) and JWH-073 (9%).[195]



1.	JWH-018; (1-pentyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	70
2.	JWH-073; (1-butyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	57
3.	JWH-250; 1-(1-pentyl-1*H*-indol-3-yl)-2-(2-methoxyphenyl)-ethanone	37
4.	JWH-081; (4-methoxy-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	36
5.	AM-2201; [1-(5-fluoropentyl)-1*H*-indol-3-yl]-1-naphthalenyl-methanone	34
5.	JWH-210; (4-ethyl-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	34

Source: UNODC questionnaire on NPS, 2012

Synthetic cathinones

Respondents to the UNODC questionnaire on NPS reported 44 different synthetic cathinones. The most frequently reported substance is mephedrone.

Mephedrone and MDPV are the most widespread synthetic cathinones. Analysis from NFLIS in the United States show the upsurge of these substances within a very short time. Whereas in 2009, only 34 reports of synthetic cathinones were received, this number increased to 628 reports of synthetic cathinones in 2010. Most were mephedrone (48%), followed by MDPV (40%).[196] At 29 per cent, MDPV is the most frequently detected synthetic cathinone analysed by the Customs Laboratory of the Republic of Korea.[197]

191 European Monitoring Centre for Drugs and Drug Addiction, '2012 Annual report on the state of the drugs problem in Europe', Lisbon, 2012

192 European Monitoring Centre for Drugs and Drug Addiction and European Police Office, 'EU drug markets report: A strategic analysis', The Hague, 2013

193 Yuk, S., 'Designer drug situation and activities of customs laboratories in Korea', Korea Customs Service, presented at the Group of European Customs Laboratories workshop on designer drugs, Berlin, 27 – 28 September 2012

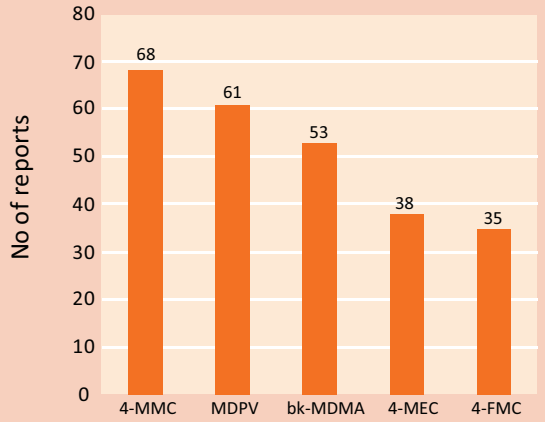
194 The National Forensic Laboratory Information System (NFLIS) is a programme of the Office of Diversion Control of the Drug Enforcement Administration that systematically collects drug identification results from drug cases conducted by state and local forensic laboratories across the U.S.

195 United States, Drug Enforcement Administration, 'Special report: synthetic cannabinoids and synthetic cathinones reported in NFLIS (National Forensic Laboratory Information System), 2009-2010', Department of Justice, Springfield, 2011 (http://www.deadiversion.usdoj.gov/nflis/2010rx_synth.pdf)

196 United States, Drug Enforcement Administration, 'Special report: synthetic cannabinoids and synthetic cathinones reported in NFLIS (National Forensic Laboratory Information System), 2009-2010', Department of Justice, Springfield, 2011 (http://www.deadiversion.usdoj.gov/nflis/2010rx_synth.pdf)

197 Yuk, S., 'Designer drug situation and activities of customs laboratories in Korea', Korea Customs Service, presented at the Group of European Customs Laboratories workshop on designer drugs, Berlin, 27 – 28 September 2012

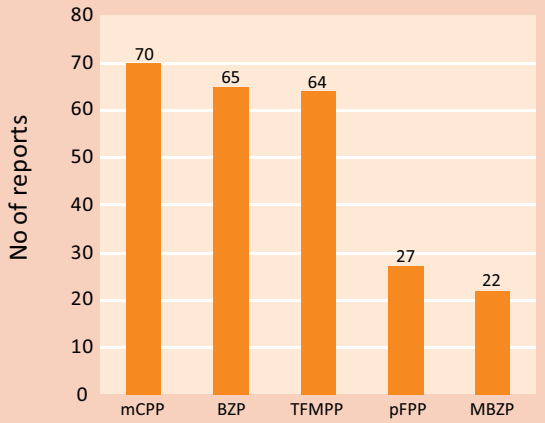
Top five synthetic cathinones reported to UNODC, up to 2012



1.	4-MMC; Mephedrone (4-methylmethcathinone)	68
2.	MDPV; 3,4-Methylenedioxypyrovalerone	61
3.	bk-MDMA; Methylone	53
4.	4-MEC; 4-Methylethcathinone	38
5.	4-FMC; 4-Fluoromethcathinone (flephedrone)	35

Source: UNODC questionnaire on NPS, 2012

Top five piperazines reported to UNODC, up to 2012



1.	*m*CPP; 1-(3-Chlorophenyl)piperazine	70
2.	BZP; 1-Benzylpiperazine	65
3.	TFMPP; 1-(3-Trifluoromethylphenyl)piperazine	64
4.	*p*FPP; 1-(4-Fluorophenyl)piperazine	27
5.	MBZP; 1-Benzyl-4-methylpiperazine	22

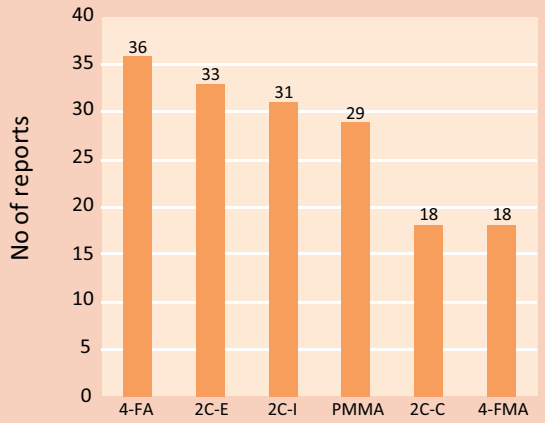
Source: UNODC questionnaire on NPS, 2012

Phenethylamines

Respondents to the UNODC questionnaire on NPS reported 58 different phenethylamines. The most frequently reported substance is 4-Fluoroamphetamine.

The 2C-phenethylamines are also widely reported from the United States. An estimated 580 reports of 2C-phenethylamines were submitted to State and local forensic laboratories in the United States from January 2006 through December 2010. In 2010, 2C-phenethylamines were identified in 32 States; 33% as 2C-E and 23% as 2C-I.[198]

Top five phenethylamines reported to UNODC, up to 2012



1.	4-FA; 4-Fluoroamphetamine	36
2.	2C-E; 4-ethyl-2,5-dimethoxyphenethylamine	33
3.	2C-I; 4-iodo-2,5-dimethoxyphenethylamine	31
4.	PMMA; *p*-Methoxymethamphetamine	29
5.	2C-C; 4-Chloro-2,5-dimethoxyphenethylamine	18
5.	4-FMA; 4-Fluoromethamphetamine	18

Source: UNODC questionnaire on NPS, 2012

Piperazines

Respondents to the UNODC questionnaire on NPS reported 12 different piperazines. The most frequently reported substance is *m*CPP.

The EMCDDA estimates that by 2006 almost 10% of illicit pills sold in the European Union, as part of the illicit ecstasy market contained *m*CPP. At the end of 2008 and beginning of 2009, this percentage seems to have increased up to 50% in some Member States of the European Union. Apart from *m*CPP, the next most commonly-found piperazine was 1-(3-trifluoromethyl-phenyl)piperazine (TFMPP), although it was nearly always seen in combination with BZP.[199] Between 2006 to 2010, about 38,230 reports of piperazines were submitted to the United States National Forensic Laboratory Information System, reaching its peak in 2009 with 17,580 reports. In 2010, pip-

[198] United States, Drug Enforcement Administration, 'Special report: emerging 2C-phenethylamines, piperazines, and tryptamines in NFLIS (National Forensic Laboratory Information System), 2006-2011', Department of Justice, Springfield, 2012 (https://www.nflis.deadiversion.usdoj.gov /DesktopModules/ReportDownloads/Reports/NFLIS_SR_Emerging_II.pdf)

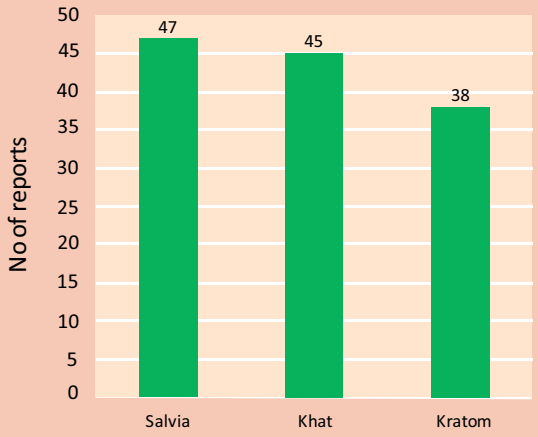
[199] European Monitoring Centre for Drugs and Drug Addiction, "BZP and other piperazines', drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles/bzp)

erazines had been reported from 44 States, with BZP (80%) and TFMPP (18%) being the most common.[200]

Plant-based substances

Respondents to the UNODC reported 20 different substances of plant-based substances. The most frequently reported substance is *salvia divinorum*. The multitude of other plant-based substances, that were reported by the respondents were country-specific, with only up to four countries reporting them.

Top three plant-based substances reported to UNODC, up to 2012



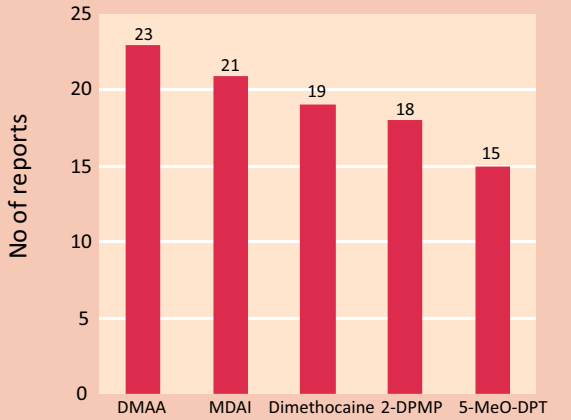
1.	Salvia - *salvia divinorum* - active ingredient: salvinorin A	47
2.	Khat - *catha edulis* - active ingredient: cathinones and cathine	45
3.	Kratom - *mitragyna speciosa* Korth - active ingredient : mitragynine	38

Source: UNODC questionnaire on NPS, 2012

Miscellaneous substances

Respondents to the UNODC questionnaire on NPS reported 56 different substances of miscellaneous substances, mostly tryptamines (27). The most frequently reported substance is DMAA (1,3-dimethylamylamine).

Top five miscellaneous substance reported to UNODC, up to 2012



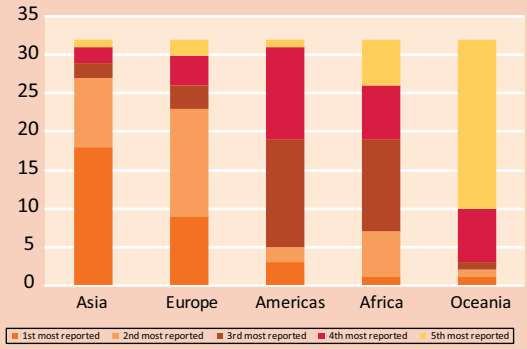
1.	DMAA; 1,3-Dimethylamylamine (Others)	23
2.	MDAI; 5,6-Methylenedioxy-2-aminoindane (Aminoindane)	21
3.	Dimethocaine; 3-(Diethylamino)2,2-dimethylpropyl4-aminobenzoate (Others)	19
4.	2-DPMP; 2-(Diphenylmethyl)piperidine (Others)	18
5.	5-MeO-DPT; 5-Methoxy-N,N-dipropyltryptamine (Tryptamine)	15

Source: UNODC questionnaire on NPS, 2012

5.3 Perceived sources* of new psychoactive substances and the role of the Internet

The primary region from where NPS originate was identified to be Asia, followed by Europe, the Americas, Africa and Oceania. In Asia, China and India are frequently named as sources of NPS whereas in Europe, various countries were named (Czech Republic, Hungary, Netherlands, Portugal, Spain, Ukraine and United Kingdom). Domestic manufacture was reported by several countries from the Americas, Asia and Europe.

Regions cited as primary sources of NPS



Source: UNODC questionnaire on NPS, 2012

[200] United States, Drug Enforcement Administration, 'Special report: emerging 2C-phenethylamines, piperazines, and tryptamines in NFLIS (National Forensic Laboratory Information System), 2006-2011', Department of Justice, Springfield, 2012 (https://www.nflis.deadiversion.usdoj.gov/DesktopModules /ReportDownloads/Reports/NFLIS_SR_Emerging_II.pdf)

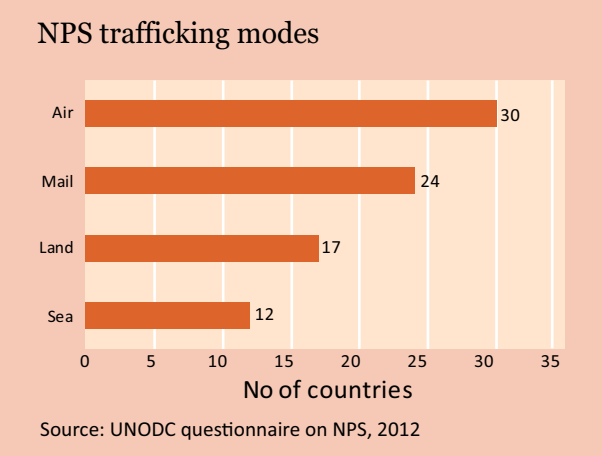
* Sources are reported by the respondents and have not been validated scientifically as manufacturing/production sites.

Sources are reported by the respondents and have not been validated scientifically as manufacturing/production sites.

The mode of trafficking named by most respondents was trafficking by air (30 countries) followed by trafficking by mail (24 countries), without any regional variations.

The Internet was named as a source of NPS from all regions. The significant informational, promotional and distributional capacity of the Internet plays an important role in the NPS market and global web-based marketing and distribution distinct from illegal street markets has developed in past years.[201]

The Internet offers many advantages to NPS suppliers as it provides access to a vast number of potential users, suppliers do not need large up-front investments and can retain some level of anonymity. In addition, suppliers may be able to bypass the laws of different countries, thus making enforcement or legal action in response to their activities very difficult. Products sold on the Internet may also stay under the radar for some time as illustrated in the case of 'spice', a product containing synthetic cannabinoids. Initially sold largely over the Internet and specialized shops, its distribution took place in a 'grey zone' where the potentially responsible institutions (public health authorities, consumer protection agencies or the competent authorities for medicinal products) did not assume direct responsibility.[202]



[201] Winstock, A. and Wilkins, C., "'Legal highs" The challenge of new psychoactive substances', Transnational Institute, Series on Legislative Reform of Drug Policies, 2011, 16, 1-16 (http://www.tni.org/sites/www.tni.org/files/download/dlr16.pdf)

[202] European Monitoring Centre for Drugs and Drug Addiction, 'Understanding the 'Spice' phenomenon', EMCDDA Thematic Paper, Lisbon, 2009

The significant distributional capacity of the Internet is evidenced in studies which have estimated online NPS availability. Internet snapshots produced by EMCDDA have shown an increase in the online availability of NPS over the years, with the number of online shops increasing from 170 in January 2010, to 314 shops in January 2011 and 690 online shops in January 2012. Little information is provided to users on the type of substance that is being bought. A 2011 review of UK-based websites selling NPS showed that, in many cases, sellers fail to list ingredients, side effects or drug interactions of the advertised product.[203]

The Internet serves as a repository of information for several groups of people. Drug users can obtain information through online forums, chat rooms and blogs and find out about new products. They can also communicate with other users on their experiences, the effects of the substances as well as the recommended sources and avenues of delivery. [204] On the other hand, the Internet is also used frequently by health and law enforcement authorities to expand their knowledge on the subject. Respondents from 62 countries and territories (out of 71) to the UNODC questionnaire on NPS indicated, for example, that their level of knowledge on the manufacturing process for NPS is low and that the Internet is frequently used to learn about synthesis routes and other fact pertaining to NPS.

5.4 Identification of new psychoactive substances

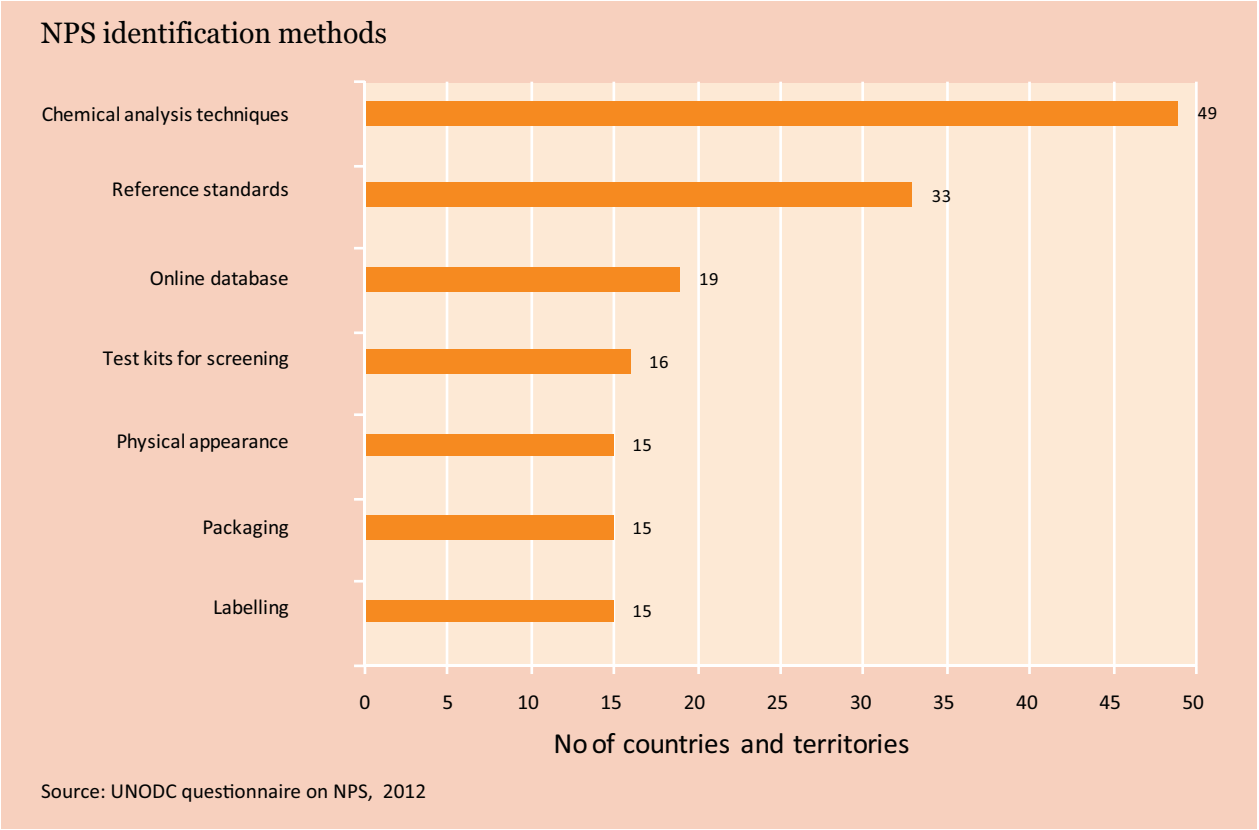
Respondents from 60 countries and territories provided information on the methods used in the identification of NPS. Most respondents indicated using chemical analysis techniques (49), followed by reference standards (33) and online databases (19).

Chemical analysis techniques

A variety of chemical analysis techniques can be used to identify NPS and most respondents to the UNODC questionnaire on NPS reported using gas chro-

[203] Schmidt, M.M., Sharma, A., Schifano, F. and Feinmann, C., "'Legal highs" on the net-Evaluation of UK-based websites, products and product information', Forensic Science International, 2011, 206, 1, 92–7

[204] Kelleher, C., Christie, R., Lalor, K., Fox, J., Bowden, M. and O'Donnell, C., 'An overview of new psychoactive substances and the outlets supplying them', National Advisory Committee on Drugs, Centre for Social and Educational Research, Dublin Institute of Technology, Dublin, 2011 (http://www.nacd.ie/images/stories/docs/publicationa/head_report2011_overview.pdf)



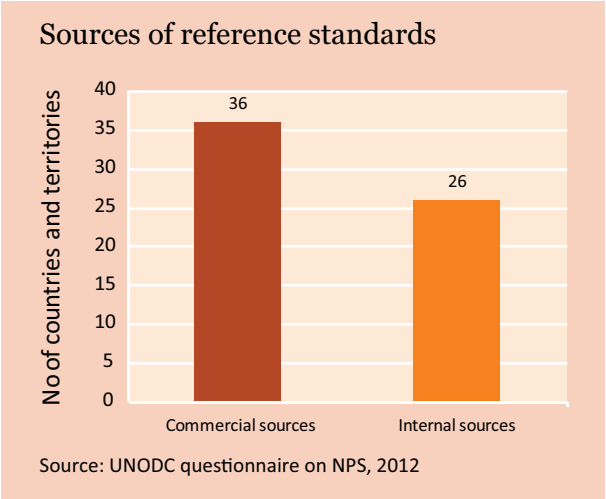
matography - mass spectrometry (GC-MS), which enables the separation of mixtures of molecules into individual components, followed by identification and quantification individually. The data collected from electron ionization mass spectrometry is checked against fragmentation libraries. Liquid chromatography–mass spectrometry (LC–MS) also has been used to analyse NPS. Other analytical techniques reported by laboratories are high performance liquid chromatography (HPLC) and fourier transform infrared spectroscopy (FTIR). Nuclear magnetic resonance (NMR) spectrometry has been employed by the laboratories for identification as well as elucidation of the chemical structure of substances. All of these methods have their limitations, with GC-MS, for example, it is not always possible to distinguish between different synthetic cannabinoids from the JWH class. Various difficulties are encountered in identifying the active ingredients of NPS due to the presence of isomers and possible similarities between certain compounds of the same class.

Reference standards

Reference standards are a useful tool in the identification of drugs and NPS. These standards are certified samples of NPS with the highest quality and purity which serve as a measurement base for similar substances. The results of NPS identification are based on matches achieved through mass spectra libraries and mass spectra sourced from other agencies.[205] Reference standards can be obtained from commercial sources. It may also be possible to make reference materials from internal sources, e.g. from seized materials. Most respondents indicated that their main source of reference standards were commercial sources.

However, even the availability of commercial reference standards is limited. In addition, with the high number of NPS circulating in the market, a large stock is required to keep up to date with the latest emergent substances. The cost is high, to stock up on the top 10 substances costs several thousand dollars which may be beyond the financial resources available to many drug analysis laboratories in developed and developing countries alike. Obtaining reference standards from internal sources such as seizures, on the other hand, may present further challenges, as

[205] Kelleher, C., Christie, R., Lalor, K., Fox, J., Bowden, M. and O'Donnell, C., 'An overview of new psychoactive substances and the outlets supplying them', National Advisory Committee on Drugs, Centre for Social and Educational Research, Dublin Institute of Technology, Dublin, 2011, 52 (http://www.nacd.ie/images/stories/docs/publicationa/head_report2011_overview.pdf)



they have to be validated. In some countries, the use of seized materials may be impeded by legal issues. Many respondents to the UNODC questionnaire on NPS addressed the issue of the lack of availability and difficulty of obtaining reference standards for NPS.

Online database

Various online databases offer mass spectral libraries for NPS to assist laboratories in their drug identification work and to offer a platform for the exchange of information within the forensic science community. However, in the case of mass spectral libraries, various different formats (NIST, Agilent) are used and these may or may not be searchable. The fact that the mass spectra are not validated represents another challenge.

Physical appearance

Physical appearance also plays an important role in the NPS identification process. Information gained from the physical examination of goods, including their labelling, packaging and presumptive testing results, all contribute to the judgment of authorities with regards to a substance being a NPS. However, in many cases the only way to identify the active ingredient of a suspected NPS is to refer the substance for full forensic analysis.

Annexes

Annex 1. New psychoactive substances reported to UNODC in 2012
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ABBREVIATIONS

The following abbreviations have been used in the list:

ALB	Albania
AUS	Australia
BGR	Bulgaria
BHR	Bahrain
BRA	Brazil
CAN	Canada
CHE	Switzerland
CHL	Chile
CRI	Costa Rica
EGY	Egypt
ESP	Spain
FIN	Finland
GBR	United Kingdom of Great Britain and Northern Ireland
HKG	China, Hong Kong Special Administrative Region
HRV	Croatia
HUN	Hungary
IDN	Indonesia
IRL	Ireland
ISR	Israel
ITA	Italy
LVT	Latvia
MDA	Republic of Moldova
MYS	Malaysia
NLD	Netherlands
NOR	Norway
NZL	New Zealand
OMN	Oman
POL	Poland
PRT	Portugal
ROU	Romania
RUS	Russian Federation
SGP	Singapore
SVK	Slovakia
FYROM	The former Yugoslav Republic of Macedonia
TGO	Togo
TUR	Turkey
USA	United States of America

Annex 1. New psychoactive substances reported to UNODC in 2012

a) Synthetic cannabinoids

Common name	Reporting countries	Total
HU-210	ISR	1
CP-47,497	HRV; USA	2
CP-47, 497-C8	CAN; LVT; USA	3
AM-1220	CAN; ESP; TUR; USA	4
AM-1220 azepane isomer	AUS; ISR; USA	3
AM-2201	BGR; CAN; FIN; GBR; HRV; IRL; ISR; LVT; NLD; NOR; NZL; PRT; SGP; SVK; TUR; USA	16
AM-2232	ROU	1
JWH-015	NLD; NZL	2
JWH-018	BGR; BRA; CAN; ESP; GBR; HRV; IRL; ISR; LVT; NLD; NOR; NZL; OMN; PRT; SGP; SVK; TUR; USA	18
JWH-018 *N*-(5-chloropentyl)	ESP	1
JWH-019	ESP; ISR; NZL; USA	4
JWH-022	CAN; ESP; HRV; ISR; NZL; PRT; ROU; TUR; USA	9
JWH-073	CAN; ESP; HRV; IRL; ISR; LVT; NLD; NOR; NZL; PRT; SGP; TUR; USA	13
JWH-073 (4-methylnaphthyl)	IRL; TUR	2
JWH-081	BGR; CAN; ESP; HKG; HRV; IRL; ISR; LVT; PRT; TUR; USA	11
JWH-122	CAN; HRV; ISR; ITA; LVT; NOR; NZL; PRT; TUR; USA	10
JWH-122 (5-fluoropentyl)	CAN; HUN; ISR; TUR	4
JWH-200	NLD; NZL; USA	3
JWH-210	BGR; CAN; HRV; ISR; LVT; NLD; NOR; NZL; PRT; TUR; USA	11
JWH-387	ROU	1
JWH-398	HRV	1
AM-694	BGR; GBR; HUN; IRL; ISR; NOR; TUR; USA	8
AM-694 (chloro)	IRL	1
AM-2233	CAN; HUN; ISR; LVT; NOR; USA	6
RCS-4	BGR; CAN; IRL; ISR; LVT; NOR; TUR; USA	8
RCS-4 ortho isomer	HRV; ROU; SVK	3
JWH-203	LVT; NLD; PRT; TUR; USA	5
JWH-250	BGR; CAN; ESP; GBR; HRV; ISR; NLD; NOR; PRT; TUR; USA	11
JWH-251	CAN; NLD; USA	3

Common name	Reporting countries	Total
AB-001	CAN; CHE; IRL; ISR; NZL; OMN; ROU	7
CRA-13	AUS; ROU; RUS	3
JWH-175	CAN	1
JWH-307	ITA; TUR	2
STS 135	RUS	1
UR-144	AUS; PRT	2
XLR11	NOR; PRT	2

b) Synthetic cathinones

Common name	Reporting countries	Total
N-Allylmethylone	CAN	1
BMDP	CAN; GBR; LVT; TUR	4
Brephedrone	AUS; FIN; NOR	3
Buphedrone	ESP; FIN; HRV; NOR; USA	5
Butylone	AUS; BGR; CAN; ESP; FIN; GBR; HKG; HRV; NOR; NZL; PRT; SVK; TUR; USA	14
Dibutylone	NOR; USA	2
Dimethoxymethcathinone	AUS	1
Dimethylcathinone	CAN; FIN; GBR	3
3,4-Dimethylmethcathinone	AUS; CAN; FIN; GBR; HRV; NZL; USA	7
Dimethylone	FIN; USA	2
Ethcathinone	AUS; FIN; GBR; LVT; USA	5
N-Ethylbuphedrone	NOR; USA	2
4-Ethylmethcathinone	BGR; CAN; USA	3
Ethylone	AUS; GBR	2
2-Fluoromethcathinone	ESP; USA	2
3-Fluoromethcathinone	FIN; GBR; SGP; USA	4
4-Fluoromethcathinone (flephedrone)	BGR; CAN; ESP; FIN; GBR; NOR; TUR; USA	8
Mephedrone	AUS; BRA; CAN; ESP; FIN; GBR; IRL; LVT; NLD; NOR; PRT; SGP; SVK; TUR; USA	15
Methedrone	ESP; GBR; IRL; LVT; TUR; USA	6
4-Methoxy-α-pyrrolidinopropiophenone	USA	1
4-Methylbuphedrone	CAN; FIN	2

Common name	Reporting countries	Total
3,4-Methylenedioxypyrovalerone	AUS; BGR; CAN; ESP; FIN; GBR; HRV; IRL; ISR; LVT; NLD; NOR; PRT; SGP; SVK; TUR; USA	17
3,4-Methylenedioxy-α-pyrrolidinobutyro-phenone	AUS; BGR; CAN; FIN; IRL; USA	6
3,4-Methylenedioxy-α-pyrrolidinopropio-phenone	BGR; ESP; FIN; ISR; USA	5
3-Methylethcathinone	BGR; CAN; ESP; USA	4
4-Methylethcathinone	AUS; BGR; CAN; ESP; FIN; GBR; HKG; LVT; NLD; NOR; PRT; SGP; USA	13
Methylone	AUS; BGR; CAN; ESP; GBR; HRV; IRL; NLD; NOR; PRT; SGP; USA	12
4-Methyl-α-pyrrolidinohexiophenone	BGR	1
4-Methyl-α-pyrrolidinopropiophenone	AUS; BGR; CAN; ESP; FIN	5
1-napthalen-1-yl-2pyrrolidin-1-yl pentan-1-one	GBR	1
Naphyrone	ESP; GBR; IRL; LVT; NLD; USA	6
Pentedrone	BGR; CAN; FIN; LVT; NLD; POL; PRT; USA	8
Pentylone	AUS; FIN; GBR; ROU; USA	5
α-Pyrrolidinobutiophenone	CAN; HUN; ISR; USA	4
α-Pyrrolidinopentiophenone	CAN; ESP; FIN; GBR; ISR; ITA; MDA; NZL; USA	9
α-Pyrrolidinopropiophenone	FIN; ISR; NLD; POL	4

c) Phenethylamines

Common name	Reporting countries	Total
4-(2-Aminopropyl)benzofuran	FIN	1
5-(2-Aminopropyl)benzofuran	BGR; ESP; FIN; GBR; ITA; NLD	6
6-(2-Aminopropyl)benzofuran	AUS; CAN; ESP; FIN; NLD; NOR	6
3,4-Dimethoxymethamphetamine	BRA; CAN; ISR; NLD; ROU	5
N,*N*-dimethylamphetamine	AUS; ESP; HKG; USA	4
N,*N*-dimethylphenethylamine	ESP	1
2-Fluoroamphetamine	CAN; FIN; USA	3
3-Fluoroamphetamine	CAN; FIN; NLD; ROU; USA	5
4-Fluoroamphetamine	AUS; CAN; ESP; FIN; GBR; ITA; NLD; NOR; USA	9
3-Fluoromethamphetamine	FIN	1
4-Fluoromethamphetamine	CAN; ESP; FIN; IRL; USA	5
Methoxyphenamine	CAN	1
p-Methoxymethamphetamine	AUS; BGR; ESP; FIN; GBR; HKG; IRL; NLD; NOR	9
4-Methylamphetamine	ESP; GBR; HRV; NLD; TGO	5

Common name	Reporting countries	Total
N-methyl-5-APB	NLD	1
4-methylmethamphetamine	ROU	1
Methylthienylpropamine	AUS; CAN; FIN; GBR; NOR	5
Phenethylamine	BGR; CAN; NLD	3
2-Phenylpropanamine	NLD	1
2C-C	FIN; NLD; NOR; USA	4
2C-C-NBOMe	AUS; CAN; FIN; NLD; NOR; NZL	6
2C-D	FIN	1
2C-D-NBOMe	NOR	1
2C-E	AUS; CAN; ESP; FIN; NLD; NOR; USA	7
2C-I	AUS; CAN; ESP; FIN; GBR; NLD; USA	7
2C-P	FIN; NOR	2
2C-T-4	FIN; NOR	2
2C-T-7	NOR	1
25I - NBOMe	FIN	1
2,5-dimethoxy-4-chloroamphetamine	FIN	1
2,5-dimethoxy-4-iodoamphetamine	AUS; NLD	2
N-Benzyl-1-phenethylamine	ESP	1
Bromo-Dragonfly	FIN	1
Camfetamine	FIN; ISR	2

d) Piperazines

Common name	Reporting countries	Total
1-Benzylpiperazine	AUS; CAN; CRI; EGY; ESP; GBR; IDN; IRL; NOR; SGP; TUR; USA	12
1-Benzyl-4-methylpiperazine	ESP; GBR; IRL; ITA; NLD	5
1,4-Dibenzylpiperazine	CAN; ESP; GBR; USA	4
1-(3-Chlorophenyl)piperazine	ALB; CAN; ESP; FIN; FYROM, GBR; IRL; LVT; MDA; NLD; NOR; RUS; SVK; TUR; USA	15
1-(4-Fluorophenyl)piperazine	ESP; GBR; NLD; NOR; USA	5
MeOPP	GBR	1
1-(3-Trifluoromethylphenyl)piperazine	AUS; CAN; CRI; ESP; GBR; HKG; IRL; ISR; NLD; NOR; SGP; USA	12

e) Plant-based substances

Common and binomial name	Reporting countries	Total
Akuamma seed (*Picralima nitida)*	FIN	1
Ayahuasca (*Banisteriopsis caapi)*	ESP	1
Blue Egyptian water lily (*Nymphea caerulea)*	FIN	1
Calea zacatechichi (*Calea ternifolia* Kunth*)*	FIN	1
Chacruna (*Psychiotria viridis)*	FIN	1
Damiana (*Turnera aphrodisiaca/diffusa*)	FIN	1
Hawaiian Baby Woodrose (*Argyreia nervosa*)	FIN; NOR	2
Kanna (*Sceletium tortuosum*)	FIN	1
Kava (*Piper methysticum)*	FIN	1
Khat (*Catha edulis*)	AUS; BHR; CAN; FIN; HKG; IRL; ISR; NOR; TUR; USA	10
Kratom (*Mitragyna speciosa* Korth)	CAN; ESP; FIN; HRV; IRL; ISR; MYS; NLD; NOR; USA	10
Lion's Tail (or Wild Dagga) (*Leonotis leonurus*)	FIN	1
Mimosa hostilis (*Mimosa tenuiflora*)	NOR	1
Salvia (*Salvia divinorum)*	BGR; CAN; CHL; EGY; FIN; IRL; NOR; USA	8
Syrian rue (*Peganum harmala*)	FIN; NOR	2
Wild lettuce (*Lactuca virosa*)	FIN	1

f) Miscellaneous

i) Aminoindanes

Common name	Reporting countries	Total
5,6-Methylenedioxy-2-aminoindane	AUS; BGR; FIN; GBR	4
5-Iodo-2-aminoindane	FIN; LVT	2

ii) Phencyclidine-type substances

No phencyclidine-type substances were reported.

iii) Tryptamines

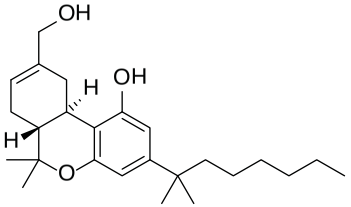
Common name	Reporting countries	Total
4-AcO-DALT	FIN	1
4-AcO-DET	FIN; NLD	2
4-AcO-DiPT	FIN; NOR	2
4-AcO-DMT	FIN	1
4-AcO-DPT	FIN	1
4-AcO-MiPT	FIN; NOR	2
4-AcO-MET	CAN; FIN	2
5-HO-DMT (Bufotenine)	GBR; NOR	2
4-HO-MiPT	FIN	1
4-HO-MET	NOR	1
5-HTP	FIN; NLD	2
5-MeO-DALT	AUS; GBR; NLD; PRT	4
5-MeO-DPT	BGR; FIN; ISR; NLD; USA	5
5-MeO-MiPT	AUS; NOR	2
5-MeO-AMT	ESP	1
DiPT	FIN	1
αMT	FIN; NLD; NOR; RUS	4

iv) Others

Common name	Reporting countries	Total
1,4-Butanediol	NOR	1
2-(Diphenylmethyl)piperidine	EGY; ESP; FIN; SGP	4
3-Amino-1-phenylbutane	NLD; NOR	2
4-Benzylpiperidine	CAN; EGY; ESP	3
1,3-Dimethylamylamine	AUS; BGR; ESP; FIN; HRV; NLD	6
5-(2-Aminopropyl)indole	FIN; NLD	2
Arecoline	CAN; FIN	2
O-Desmethyltramadol	FIN; NOR	2
Dimethocaine	FIN; IRL; NLD	3
2-(Diphenylmethyl)pyrrolidine	BGR; CAN; PRT	3
Etaqualone	USA	1
Ethylphenidate	AUS; CAN; FIN; NLD; POL; ROU	6
Etizolam	NOR	1
Flourotropacocaine	CAN; IRL	2
Methoxetamine	ESP; GBR; NOR	3
Tropacocaine	FIN; NLD	2

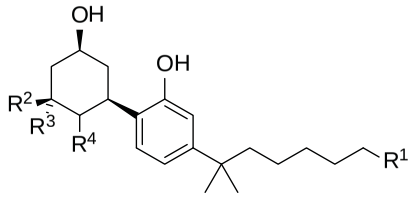
Annex 2. Synthetic cannabinoids (60 substances)

a) Classical cannabinoid



Common name	Chemical name	CAS number	Molecular Formula
HU-210 *Synonym:* 11-Hydroxy-Δ-8-THC-DMH	3-(1,1'-dimethylheptyl)-6*aR*,7,10,10*aR*-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-9-methanol	112830-95-2	$C_{25}H_{38}O_3$

b) Nonclassical cannabinoids

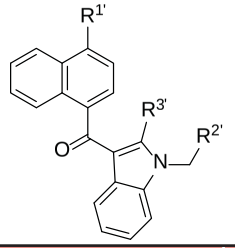


Common name	Chemical name	CAS number	Molecular Formula	R¹	R²	R³	R⁴
CP-47,497	*rel*-2[(1*S*,3*R*)-3-hydroxycyclohexyl]-5-(2-methyloctan-2-yl) phenol	70434-82-1	$C_{21}H_{34}O_2$	CH_3	H	H	H
CP-47,497-C6	*rel*-2[(1*S*,3*R*)-3-hydroxycyclohexyl]-5-(2-methylheptan-2-yl) phenol	-	$C_{20}H_{32}O_2$	H	H	H	H
CP-47,497-C8 *Synonym:* Cannabicyclohexanol	*rel*-2-[(1*S*,3*R*)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl) phenol	70434-92-3	$C_{22}H_{36}O_2$	C_2H_5	H	H	H

Common name	Chemical name	CAS number	Molecular Formula	R^1	R^2	R^3	R^4
CP-47,497-C9	*rel*-2[(1*S*,3*R*)-3-hydroxycyclohexyl]-5-(2-methyldecan-2-yl) phenol	-	$C_{23}H_{38}O_2$	C_3H_7	H	H	H
CP-55,940	*rel*-2-((1*R*,2*R*,5*R*)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl)-5-(2-methyloctan-2-yl)phenol	83003-12-7	$C_{24}H_{40}O_3$	CH_3	H	H	3-hydroxy propyl
Dimethyl CP-47,497-C8	*rel*-2-[(1*S*,3*R*)-3-hydroxy-5,5-dimethylcyclohexyl]-5-(2-methylnonan-2-yl)phenol	-	$C_{24}H_{40}O_2$	C_2H_5	CH_3	CH_3	H

c) Aminoalkylindoles

i) Naphthoylindoles

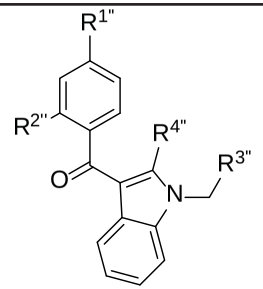


Common name	Chemical name	CAS number	Molecular Formula	$R^{1'}$	$R^{2'}$	$R^{3'}$
AM-1220	[1-[(1-methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl]-1-naphthalenyl-methanone	137642-54-7	$C_{26}H_{26}N_2O$	H	1-methyl-2-piperidinyl	H
AM-1220 azepane isomer	[1-[(1-methylazepan-3-yl)methyl]-1*H*-indol-3-yl]-1-naphthalenyl-methanone	-	$C_{26}H_{26}N_2O$	H	1-methylazepan-3-yl	H
AM-2201	[1-(5-fluoropentyl)-1*H*-indol-3-yl]-1-naphthalenyl-methanone	335161-24-5	$C_{24}H_{22}FNO$	H	4-fluorobutyl	H
AM-2232	3-(1-naphthalenylcarbonyl)-1*H*-Indole-1-pentanenitrile	335161-19-8	$C_{24}H_{20}N_2O$	H	butanenitrile	H
JWH-007	(2-methyl-1-pentyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	155471-10-6	$C_{25}H_{25}NO$	H	C_4H_9	CH_3
JWH-015	(2-methyl-1-propyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	155471-08-2	$C_{23}H_{21}NO$	H	C_2H_5	CH_3
JWH-018 *Synonym:* AM678	(1-pentyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	209414-07-3	$C_{24}H_{23}NO$	H	C_4H_9	H

Common name	Chemical name	CAS number	Molecular Formula	R1'	R2'	R3'
JWH 018 *N*-(5-chloropentyl)	(1-(5-chloropentyl)-1*H*-indol-3-yl)(naphthalen-1-yl) methanone	-	$C_{24}H_{22}ClNO$	H	4-chlorobutyl	H
JWH 018 *N*-(5-hydroxypentyl)	(1-(5-hydroxypentyl)-1*H*-indol-3-yl)(naphthalen-1-yl)-methanone	-	$C_{24}H2_3NO_2$	H	4-hydroxybutyl	H
JWH-019	(1-hexyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	209414-08-4	$C_{25}H_{25}NO$	H	C_5H_{11}	H
JWH-022	[1-(4-penten-1-yl)-1*H*-indol-3-yl]-1-naphthalenyl-methanone	209414-16-4	$C_{24}H_{21}NO$	H	3-buten-1-yl	H
JWH-073	(1-butyl-1*H*-indol-3-yl)-1-naphthalenyl-methanone	208987-48-8	$C_{23}H_{21}NO$	H	C_3H_7	H
JWH-073 (4-methylnaphthyl) *Synonym:* JWH 122 *N*-butyl analog	(1-butyl-1*H*-indol-3-yl)(4-methylnaphthalen-1-yl)-methanone	-	$C_{24}H_{23}NO$	CH_3	C_3H_7	H
JWH-081	(4-methoxy-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	210179-46-7	$C_{25}H_{25}NO_2$	CH_3O	C_4H_9	H
JWH-122	(4-methyl-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	619294-47-2	$C_{25}H_{25}NO$	CH_3	C_4H_9	H
JWH-122 (5-fluoropentyl) *Synonyms:* MAM2201; AM2201 4-methylnaphthyl analog	[1-(5-fluoropentyl)-1*H*-indol-3-yl](4-methyl-1-naphthalenyl)-methanone	1354631-24-5	$C_{25}H_{24}FNO$	CH_3	4-fluorobutyl	H
JWH 122 N-(5-hydroxypentyl)	(1-(5-hydroxypentyl)-1*H*-indol-3-yl)(4-methylnaphthalen-1-yl)-methanone	-	$C_{25}H_{25}NO_2$	CH_3	4-hydroxybutyl	H
JWH-200 *Synonym:* WIN 55,225	[1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]-1-naphthalenyl-methanone	103610-04-4	$C_{25}H_{24}N_2O_2$	H	4-morpholinyl methyl	H
JWH-210	(4-ethyl-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	824959-81-1	$C_{26}H_{27}NO$	C_2H_5	C_4H_9	H
JWH-387	(4-bromonaphthalen-1-yl)(1-pentyl-1*H*-indole-3-yl)-methanone	207227-49-4	$C_{24}H_{22}BrNO$	Br	C_4H_9	H
JWH-398	(4-chloronaphthalen-1-yl)(1-pentyl-1*H*-indole-3-yl)-methanone	1292765-18-4	$C_{24}H_{22}ClNO$	Cl	C_4H_9	H
JWH-412	(4-fluoronaphthalen-1-yl)(1-pentyl-1*H*-indole-3-yl)-methanone	-	$C_{24}H_{22}FNO$	F	C_4H_9	H

c) Aminoalkylindoles

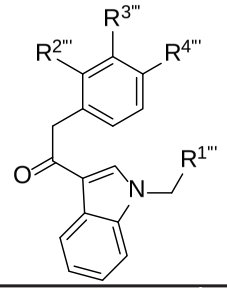
ii) Benzoylindoles



Common name	Chemical name	CAS number	Molecular Formula	R1"	R2"	R3"	R4"
AM-694	[1-(5-fluoropentyl)-1*H*-indol-3-yl](2-iodophenyl)-methanone	335161-03-0	$C_{20}H_{19}FINO$	H	I	4-fluorobutyl	H
AM-694 (chloro)	[1-(5-chloropentyl)-1*H*-indol-3-yl](2-iodophenyl)-methanone	-	$C_{20}H_{19}ClINO$	H	I	4-chlorobutyl	H
AM-2233	(2-iodophenyl)[1-[(1-methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl]-methanone	444912-75-8	$C_{22}H_{23}IN_2O$	H	I	1-methyl-2-piperidinyl	H
RCS-4 *Synonyms:* SR-19; OBT-199; BTM-4; E-4	(4-methoxyphenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	1345966-78-0	$C_{21}H_{23}NO_2$	CH_3O	H	C_4H_9	H
RCS-4 ortho isomer *Synonym:* RCS-4 2-methoxy isomer	(2-methoxyphenyl)(1-pentyl-1*H*-indol-3-yl)-methanone	-	$C_{21}H_{23}NO_2$	H	CH_3O	C_4H_9	H
RCS-4 butyl homologue	(4-methoxyphenyl)(1-butyl-1*H*-indol-3-yl)-methanone	-	$C_{20}H_{21}NO_2$	CH_3O	H	C_3H_7	H
WIN 48,098 *Synonym:* Pravadoline	(4-methoxyphenyl)[(2-methyl)-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]-methanone	92623-83-1	$C_{23}H_{26}N_2O_3$	CH_3O	H	4-morpholinyl methyl	CH_3

c) Aminoalkylindoles

iii) Phenylacetylindoles

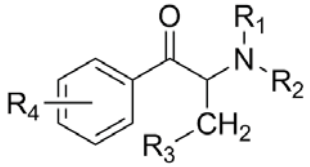


Common name	Chemical name	CAS number	Molecular Formula	R1'''	R2'''	R3'''	R4'''
JWH-201	2-(4-methoxyphenyl)-1-(1-pentyl-1*H*-indol-3-yl)-ethanone	864445-47-6	$C_{22}H_{25}NO_2$	C_4H_9	H	H	CH_3O
JWH-203	2-(2-chlorophenyl)-1-(1-pentyl-1*H*-indol-3-yl)-ethanone	864445-54-5	$C_{21}H_{22}ClNO$	C_4H_9	Cl	H	H
JWH-250	1-(1-pentyl-1*H*-indol-3-yl)-2-(2-methoxyphenyl)-ethanone	864445-43-2	$C_{22}H_{25}NO_2$	C_4H_9	CH_3O	H	H
JWH-250 derivative *Synonym:* Cannabipiperidiethanone	2-(2-methoxyphenyl)-1-[1-[(1-methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl]-ethanone	1345970-43-5	$C_{24}H_{28}N_2O_2$	1-methyl-2-piperindinyl	CH_3O	H	H
JWH-251	2-(2-methylphenyl)-1-(1-pentyl-1*H*-indol-3-yl)-ethanone	864445-39-6	$C_{22}H_{25}NO$	C_4H_9	CH_3	H	H
JWH-302	2-(3-methoxyphenyl)-1-(1-pentyl-1*H*-indol-3-yl)-ethanone	864445-45-4	$C_{22}H_{25}NO_2$	C_4H_9	H	CH_3O	H
RCS-8 *Synonyms:* SR-18; BTM-8	1-(1-(2-cyclohexylethyl)-1*H*-indol-3-yl)-2-(2-methoxyphenyl)-ethanone	1345970-42-4	$C_{25}H_{29}NO_2$	cyclohexyl methyl	CH_3O	H	H

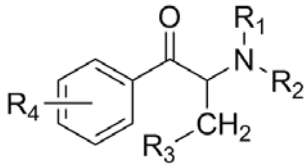
d) Others

Common name	Chemical name	CAS number	Molecular Formula
AB-001 *Synonym:* JWH-018 (adamantyl)	1-adamantyl (1-pentyl-1*H*-indol-3-yl)methanone	-	$C_{23}H_{31}NO$
AKB48 *Synonym:* APINACA	1-pentyl-*N*-tricyclo[3.3.1.13,7]dec-1-yl-1*H*-indazole-3-carboxamide	1345973-53-6	$C_{23}H_{31}N_3O$
AM-356 *Synonym:* R-1 Methanandamide; (*R*)-(+)-Arachidonyl-1'-Hydroxy-2'-Propylamide	*N*-(2-hydroxy-1*R*-methylethyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide	157182-49-5	$C_{23}H_{39N}O_2$
AM-1248	[1-[(1-methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl]tricyclo[3.3.1.13,7]dec-1-yl-methanone	335160-66-2	$C_{26}H_{34}N_2O$
CRA-13 *Synonyms:* CB-13; SAB-378	1-naphthalenyl[4-(pentylox)-1-naphthalenyl]-methanone	432047-72-8	$C_{26}H_{24}O_2$
HU-308	4-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methanol	256934-39-1	$C_{27}H_{42}O_3$
JWH-175	3-(1-naphthalenylmethyl)-1-pentyl-1*H*-indole	619294-35-8	$C_{24}H_{25}N$
JWH-307	(5-(2-fluorophenyl)-1-pentylpyrrol-3-yl)-naphthalen-1-yl-methanone	914458-26-7	$C_{26}H_{24}FNO$
JWH-370	[5-(2-methylphenyl)-1-pentyl-1*H*-pyrrol-3-yl]-1-naphthalenyl-methanone	914458-22-3	$C_{27}H_{27}NO$
Org 27569	5-chloro-3-ethyl-1*H*-indole-2-carboxylic acid [2-(4-piperidin-1-yl-phenyl)-ethyl]-amide	-	$C_{24}H_{28}ClN_3O$
Org 27759	5-fluoro-3-ethyl-1*H*-indole-2-carboxylic acid [2-(4-dimethylamino-phenyl)-ethyl]-amide	-	$C_{21}H_{24}FN_3O$
Org 29647	5-chloro-3-ethyl-1*H*-indole-2-carboxylic acid (1-benzyl-pyrrolidin-3-yl)-amide	-	$C_{22}H_{24}ClN_3O$
STS-135 *Synonym: N*-adamantyl-1-fluoropentylindole-3-Carboxamide	1-(5-fluoropentyl)-*N*-tricyclo[3.3.1.13,7]dec-1-yl-1*H*-indole-3-carboxamide	1354631-26-7	$C_{24}H_{31}FN_2O$
UR-144 *Synonym:* KM-X1	(1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone	1199943-44-6	$C_{21}H_{29}NO$
UR-144 *N*-(5-chloropentyl)	(1-(5-chloropentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone	-	$C_{21}H_{28}ClNO$
URB597	(3'-(aminocarbonyl)[1,1'-biphenyl]-3-yl)-cyclohexylcarbamate	546141-08-6	$C_{20}H_{22}N_2O_3$
XLR11 *Synonym:* 5-fluoro UR-144	(1-(5-fluoropentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone	1364933-54-9	$C_{21}H_{28}FNO$

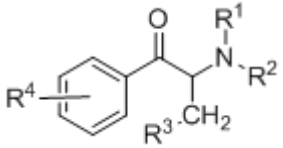
Annex 3. Synthetic cathinones (44 substances)



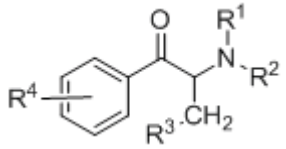
Common name	Abbreviation	Chemical name	CAS number	R_1	R_2	R_3	R_4
N-Allylmethylone	-	2-(allylmethylamino)-1-(3,4-methylenedioxyphenyl)propan-1-one	-	allyl	CH_3	H	3,4-methylene dioxy
Benzedrone (4-methyl-*N*-benzylcathinone)	4-MBC	1-(4-methylphenyl)-2-benzylaminopropan-1-one	17762-90-2	H	benzyl	H	4-CH_3
BMDB (*N*-benzy-1-(3,4-methylenedioxyphenyl)-2-butanamine)	BMDB	1-(3,4-methylenedioxyphenyl)-2-benzylamino butan-1-one	-	H	benzyl	CH_3	3,4-methyl enedioxy
BMDP 3,4-Methylenedioxy-*N*-benzylcathinone	BMDP	1-(3,4-methylenedioxyphenyl)-2-benzylamino propan-1-one	-	H	benzyl	H	3,4-methylene dioxy
Brephedrone (4-bromomethcathinone)	4-BMC	1-(4-bromophenyl)-2-methylaminopropan-1-one	486459-03-4	H	CH_3	H	4-Br
Buphedrone (*α*-methylaminobutyrophenone)	MABP	2-(methylamino)-1-phenylbutan-1-one	408332-79-6	H	CH_3	CH_3	H
Butylone (*β*-keto-*N*-methylbenzodioxolyl-butanamine)	bk-MBDB	1-(3,4-methylenedioxyphenyl)-2-methylamino butan-1-one	17762-90-2	H	CH_3	CH_3	3,4-methylene dioxy
Dibutylone (*β*-keto-*N,N*-dimethylbenzodioxo lylbutanamine)	bk-DMBDB	1-(3,4-methylenedioxyphenyl)-2-dimethylaminobutan-1-one	-	CH_3	CH_3	CH_3	3,4-methylene dioxy
Dimethoxymethcathinone	2,5-DMOMC	1-(2,5-dimethoxyphenyl)-2-methylaminopropan-1-one	-	H	CH_3	H	2,5-dimethoxy
Dimethylcathinone (metamfepramone)	-	1-phenyl-2-dimethylaminopropan-1-one	15351-09-4	CH_3	CH_3	H	H
3,4-Dimethylmethcathinone	3,4-DMMC	1-(3,4-dimethylphenyl)-2-methylaminopropan-1-one	-	H	CH_3	H	3,4-dimethyl



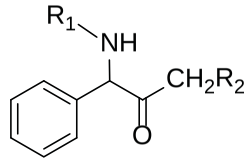
Common name	Abbreviation	Chemical name	CAS number	R_1	R_2	R_3	R_4
Dimethylone (3,4-methylenedioxy-*N*,*N*-dimethcathinone)	bk-MDDMA bk-DMBDP	1-(3,4-methylenedioxyphenyl)-2-dimethylaminopropan-1-one	-	CH_3	CH_3	H	3,4-methylene-dioxy
Ethcathinone (ethylpropion)	EC	2-ethylamino-1-phenylpropan-1-one	51553-17-4	H	C_2H_5	H	H
N-Ethylbuphedrone	NEB	2-ethylamino-1-phenylbutan-1-one	-	H	C_2H_5	CH_3	H
4-Ethylmethcathinone	4-EMC	2-methylamino-1-(4-ethylphenyl)propan-1-one	1225622-14-9	H	CH_3	H	4-C2H5
Ethylone (3,4-methylenedioxy-*N*-ethylcathinone)	bk-MDEA MDEC	1-(3,4-methylenedioxyphenyl)-2-ethylamino propan-1-one	1112937-64-0	H	C_2H_5	H	3,4-methylene-dioxy
2-Fluoromethcathinone	2-FMC	1-(2-fluorophenyl)-2-methylaminopropan-1-one	-	H	CH_3	H	2-F
3-Fluoromethcathinone	3-FMC	1-(3-fluorophenyl)-2-methylaminopropan-1-one	1049677-77-1	H	CH_3	H	3-F
4-Fluoromethcathinone (flephedrone)	4-FMC	1-(4-fluorophenyl)-2-methylaminopropan-1-one	7589-35-7	H	CH_3	H	4-F
HMMC (4-hydroxy-3-methoxymethcathinone)	HMMC	1-(4-hydroxy-3-methoxyphenyl)-2-methylaminopropan-1-one	916177-15-6	H	CH_3	H	3-OCH_3 4-OH
Mephedrone (4-methylmethcathinone)	4-MMC	1-(4-methylphenyl)-2-methylaminopropan-1-one	1189805-46-6	H	CH_3	H	4-CH_3
Methedrone (4-methoxy-*N*-methcathinone, *p*-methoxymethcathinone)	bk-PMMA PMMC	1-(4-methoxyphenyl)-2-methylaminopropan-1-one	530-54-1	H	CH_3	H	4-OCH_3
4-Methoxy-*N*-ethylcathinone (ethedrone)	bk-PMEA	1-(4-methoxyphenyl)-2-ethylaminopropan-1-one	-	H	C_2H_5	H	4-OCH_3



Common name	Abbreviation	Chemical name	CAS number	R_1	R_2	R_3	R_4
4-Methoxy-α-pyrrolidinopropiophenone	MOPPP	1-(4-methoxyphenyl)-2-(1-pyrrolidinyl)propan-1-one	-	NR_1R_2 = 		H	4-OCH_3
4-Methylbuphedrone	-	1-(4-methylphenyl)-2-methylaminobutan-1-one	-	H	CH_3	CH_3	4-CH_3
3,4-Methylenedioxypyrovalerone	MDPV	1-(3,4-methylenedioxyphenyl)-2-(1-pyrrolidinyl) pentan-1-one	687603-66-3	NR_1R_2 = 		C_2H_5	3,4-methylene-dioxy
3,4-Methylenedioxy-α-pyrrolidinobutyro-phenone	MDPBP	1-(3,4-methylenedioxyphenyl)-2-(1-pyrrolidinyl) butan-1-one	24622-60-4	NR_1R_2 = 		CH_3	3,4-methylene-dioxy
3,4-Methylenedioxy-α-pyrrolidinopropio-phenone	MDPPP	1-(3,4-methylenedioxyphenyl)-2-(1-pyrrolidinyl) propan-1-one	24698-57-5	NR_1R_2 = 		H	3,4-methylene-dioxy
3-Methylethcathinone	3-MEC	2-ethylamino-1-(3-methylphenyl)propan-1-one	-	H	C_2H_5	H	3-CH_3
4-Methylethcathinone	4-MEC	2-ethylamino-1-(4-methylphenyl)propan-1-one	1225617-18-4	H	C_2H_5	H	4-CH_3
Methylone (3,4-methylenedioxy-*N*-methcathinone)	bk-MDMA MDMC	2-methylamino-1-(3,4-methylenedioxyphenyl)-propan-1-one	196028-79-5	H	CH_3	H	3,4-methylene-dioxy
4-Methyl-α-pyrrolidinobutiophenone	MPBP	1-(4-methylphenyl)-2-(1-pyrrolidinyl)butan-1-one	-	NR_1R_2 = 		CH_3	4-CH_3
4-Methyl-α-pyrrolidinohexiophenone	MPHP	1-(4-methylphenyl)-2-(1-pyrrolidinyl)hexan-1-one	-	NR_1R_2 = 		C_3H_7	4-CH_3

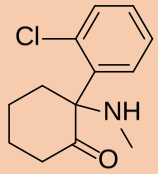


Common name	Abbreviation	Chemical name	CAS number	R_1	R_2	R_3
4-Methyl-α-pyrrolidinopropiophenone	MPPP	1-(4-methylphenyl)-2-(1-pyrrolidinyl)propan-1-one	1313393-58-6	NR_1R_2 = 	H	4-CH_3
1-Naphthalen-1-yl-2-pyrrolidin-1-ylpentan-1-one	-	1-naphthalen-1-yl-2-pyrrolidin-1-ylpentan-1-one	-	NR_1R_2 = 	C_2H_5	2,3-phenyl
Naphyrone (naphthylpyrovalerone)	O-2482	1-naphthalen-2-yl-2-pyrrolidin-1-ylpentan-1-one	850352-53-3	NR_1R_2 = 	C_2H_5	3,4-phenyl
Pentedrone (α-methylaminovalerophenone)	-	1-phenyl-2-methylaminopentan-1-one	879669-95-1	H / CH_3	C_2H_5	H
Pentylone (β-keto-*N*-ethylbenzodioxolylpentanamine)	bk-MBDP bk-Methyl-K	1-(3,4-methylenedioxyphenyl)-2-methylamino pentan-1-one	698963-77-8	H / CH_3	C_2H_5	3,4-methylene-dioxy
α-Phthalimidopropiophenone	PAPP	2-(1-oxo-1-phenylpropan-2-yl)isoindole-1,3-dione	19437-20-8	NR_1R_2 =  phthalimidoyl	H	H
α-Pyrrolidinobutiophenone	α-PBP	1-phenyl-2-(1-pyrrolidinyl)butan-1-one	-	NR_1R_2 = 	CH_3	H
α-Pyrrolidinopentiophenone (α-Pyrrolidinovalerophenone)	α-PVP O-2387	1-phenyl-2-(1-pyrrolidinyl)pentan-1-one	14530-33-7	NR_1R_2 = 	C_2H_5	H
α-Pyrrolidinopropiophenone	α-PPP	1-phenyl-2-(1-pyrrolidinyl)propan-1-one	19134-50-0	NR_1R_2 = 	H	H

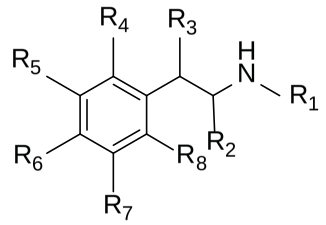


Common name	Abbreviation	Chemical name	CAS number	R_1	R_2
Iso-ethcathinone	-	1-ethylamino-1-phenyl-propan-2-one	-	C_2H_5	H
Iso-pentedrone	-	1-methylamino-1-phenyl-pentan-2-one	-	CH_3	C_2H_5

Annex 4. Ketamine

Common name	Abbreviation	Chemical name	CAS number	Structure
Ketamine	-	2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one	6740-88-1 (free base) 1867-66-9 (hydrochloride salt)	

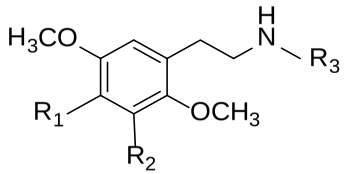
Annex 5. Phenethylamines (58 substances)



Common name	Abbreviation	Chemical name	CAS number	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
4-(2-Aminopropyl)benzofuran	4-APB	1-benzofuran-4-ylpropan-2-amine	-	H	CH_3	H	H	H	H	–O–CH=CH–	
5-(2-Aminopropyl)benzofuran	5-APB	1-benzofuran-5-ylpropan-2-amine	-	H	CH_3	H	H	–CH=CH–O–		H	H
6-(2-Aminopropyl)benzofuran	6-APB	1-benzofuran-6-ylpropan-2-amine	-	H	CH_3	H	H	–O–CH=CH–		H	H
6-(2-Aminopropyl)-2,3-dihydrobenzofuran	6-APDB	1-(2,3-dihydro-1-benzofuran-6-yl)propan-2-amine	152623-93-3	H	CH_3	H	H	–O–CH_2–CH_2–		H	H
Bromo-STP	-	2-(3-bromo-2,5-dimethoxy-4-methylphenyl)ethanamine	-	H	H	H	OCH_3	Br	CH_3	OCH_3	H
3,4-Dimethoxyamphetamine	-	2-(3,4-dimethoxyphenyl)propan-2-amine	120-26-3	H	CH_3	H	H	OCH_3	OCH_3	H	H
3,4-Dimethoxymethamphetamine	DMMA	2-(3,4-dimethoxyphenyl)-N-methylpropan-2-amine	-	CH_3	CH_3	H	H	OCH_3	OCH_3	H	H
N,*N*-Dimethylamphetamine,	DMA	*N*,*N*-dimethyl-1-phenylpropan-2-amine	4075-96-1	NHR_1= dimethyl	CH_3	H	H	H	H	H	H
N,*N*-Dimethylphenethylamine	-	*N*,*N*-dimethyl-1-phenylethan-2-amine	1126-71-2	NHR_1= dimethyl	H	H	H	H	H	H	H
2-Fluoroamphetamine	2-FA	1-(2-fluorophenyl)propan-2-amine	1716-60-5	H	CH_3	H	F	H	H	H	H
3-Fluoroamphetamine	3-FA	1-(3-fluorophenyl)propan-2-amine	1626-71-7	H	CH_3	H	H	F	H	H	H
4-Fluoroamphetamine	4-FA, PFA	1-(4-fluorophenyl)propan-2-amine	459-02-9	H	CH_3	H	H	H	F	H	H

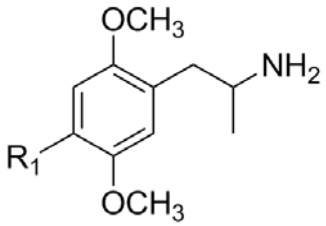
Common name	Abbreviation	Chemical name	CAS number	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
3-Fluoromethamphetamine	3-FMA	*N*-methyl-1-(3-fluorophenyl) propan-2-amine	1049677-77-1	CH_3	CH_3	H	H	F	H	H	H
4-Fluoromethamphetamine	4-FMA	*N*-methyl-1-(4-fluorophenyl) propan-2-amine	351-03-1	CH_3	CH_3	H	H	H	F	H	H
p-Methoxyethylamphetamine	PMEA	*N*-ethyl-1-(4-methoxyphenyl) propan-2-amine	14367-46-5	C_2H_5	CH_3	H	H	H	OCH_3	H	H
Methoxyphenamine, 2-Methoxymethamphetamine	OMMA	*N*-methyl-1-(2-methoxyphenyl) propan-2-amine	93-30-1	CH_3	CH_3	H	OCH_3	H	H	H	H
p-Methoxymethamphetamine, 4-Methoxymethamphetamine	PMMA	*N*-methyl-1-(4-methoxyphenyl) propan-2-amine	3398-68-3	CH_3	CH_3	H	H	H	OCH_3	H	H
4-Methylamphetamine	4-MA	1-(4-methylphenyl)propan-2-amine	22683-78-9	H	CH_3	H	H	H	CH_3	H	H
N-Methyl-5-APB	-	*N*-methyl-5-(2-aminopropyl) benzofuran	-	CH_3	CH_3	H	H	–CH=CH–O–		H	H
4-Methylmethamphetamine	4-MMA	*N*-methyl-1-(4-methylphenyl) propan-2-amine	-	CH_3	CH_3	H	H	H	CH_3	H	H
Methylthienylpropamine *Synonyms*: Methiopropamine, Methedrene, Syndrax	MPA	*N*-methyl-1-(thiophen-2-yl) propan-2-amine	7464-94-0	CH_3	CH_3	H	Phenyl → thiophenyl[1]				
Phenethylamine	PEA	1-phenylethan-2-amine	64-04-0	H	H	H	H	H	H	H	H
Phenpromethamine	-	*N*-methyl-2-phenylpropan-1-amine	93-88-9	CH_3	H	CH_3	H	H	H	H	H
2-Phenylpropanamine, (*β*-methylphenethylamine)	*β*-Me-PEA	2-phenylpropan-1-amine	582-22-9	H	H	CH_3	H				
2-Thiophen-2-yl-ethylamine	-	2-(thiophen-2-yl)ethan-2-amine	-	H	H	H	Phenyl → thiophenyl[1]				
2,4,5-Trimethoxyamphetamine	TMA-2	1-(2,4,5-tirmethoxyphenyl)-propan-2-amine	1083-09-6	H	CH_3	H	OCH_3	H	OCH_3	OCH_3	H
2,4,6-Trimethoxyamphetamine	TMA-6	1-(2,4,6-trimethoxyphenyl) propan-2-amine	15402-79-6	H	CH_3	H	OCH_3	H	OCH_3	H	OCH_3

[1] For the purposes of this report, the substance has been placed in the phenethylamine category to illustrate the slight modification to the parent phenethylamine group.

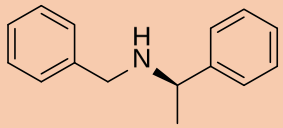
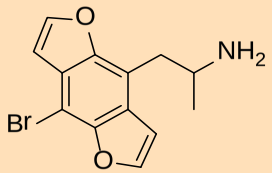
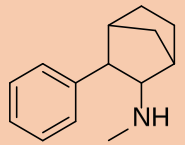
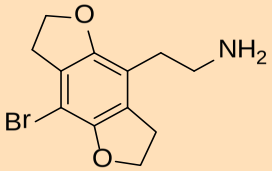
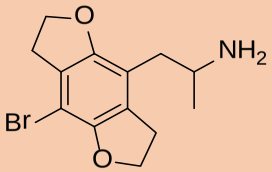
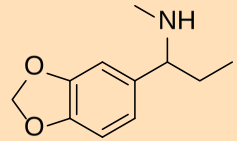


Common name	Chemical name	CAS number	R_1	R_2	R_3
2C-C	4-chloro-2,5-dimethoxyphenethylamine	88441-14-9	Cl	H	H
2C-C-NBOMe	1-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]-2-ethanamine	-	Cl	H	$CH_2C_6H_5OCH_3$
2C-D	4-methyl-2,5-dimethoxyphenethylamine	24333-19-5	CH_3	H	H
2C-D-NBOMe	1-(4-methyl-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]-2-ethanamine	-	CH_3	H	$CH_2C_6H_5OCH_3$
2C-E	4-ethyl-2,5-dimethoxyphenethylamine	71539-34-9	C_2H_5	H	H
2C-F	4-fluoro-2,5-dimethoxyphenethylamine	207740-15-6	F	H	H
2C-G	3,4-dimethyl-2,5-dimethoxyphenethylamine	207740-18-9	CH_3	CH_3	H
2C-H	2,5-dimethoxyphenethylamine	3600-86-0	H	H	H
2C-I	4-iodo-2,5-dimethoxyphenethylamine	69587-11-7	I	H	H
2C-IP	4-isopropyl-2,5-dimethoxyphenethylamine	-	i-Pr (isopropyl)	H	H
2C-N	4-nitro-2,5-dimethoxyphenethylamine	261789-00-8	NO2	H	H
2C-O-4	4-isopropoxy-2,5-dimethoxyphenethylamine	-	isopropoxy	H	H
2C-P	4-propyl-2,5-dimethoxyphenethylamine	207740-22-5	C3H7	H	H
2C-SE	4- methylseleneo-2,5-dimethoxyphenethylamine	-	SeCH3	H	H
2C-T	4-methylthio-2,5-dimethoxyphenethylamine	61638-09-3	SCH_3	H	H

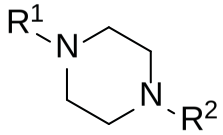
Common name	Chemical name	CAS number	R_1	R_2	R_3
2C-T-2	4-ethylthio-2,5-dimethoxyphenethylamine	207740-24-7	SC_2H_5	H	H
2C-T-4	4-isopropylthio-2,5-dimethoxyphenethylamine	207740-25-8	*i*-PrS (isopropylthio)	H	H
2C-T-7	4-propylthio-2,5-dimethoxyphenethylamine	207740-26-9	SC_3H_7	H	H
2C-TFM	4-trifluoromethyl-2,5-dimethoxyphenethylamine	159277-08-4	CF_3	H	H
2C-V	4-ethenyl-2,5-dimethoxyphenethylamine	-	$CH{=}CH_2$	H	H
2C-YN	4-ethynyl-2,5-dimethoxyphenylethylamine	752982-24-4	C≡CH	H	H
25H-NBOMe	1-(2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl) methyl] ethanamine	-	H	H	$CH_2C_6H_5OCH_3$
25I- NBOMe, 2C-I-NBOMe	1-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl) methyl]ethanamine	919797-19-6	I	H	$CH_2C_6H_5OCH_3$



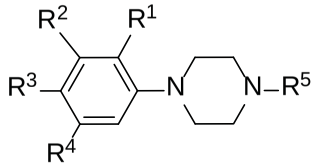
Common name	Abbreviation	Chemical name	CAS number	R_1
2,5-dimethoxy-4-chloroamphetamine	DOC	1-(4-chloro-2,5-dimethoxyphenyl)-propan-2-amine	123431-31-2	Cl
2,5-dimethoxy-4-iodoamphetamine	DOI	1-(4-iodo-2,5-dimethoxyphenyl)-propan-2-amine	82864-02-6	I

Common name	Chemical name	CAS number	Structure
N-Benzyl-1-phenethylamine	*N*-Benzyl-1-phenethylamine	38235-77-7	
Bromo-Dragonfly	1-(4-Bromofuro[2,3-*f*][1]benzofuran-8-yl)propan-2-amine	502759-67-3	
Camfetamine	*N*-methyl-3-phenyl-norbornan-2-amine	92499-19-9	
2C-B-fly	2-(8-bromo-2,3,6,7-tetrahydrofuro [2,3-f][1] benzofuran-4-yl)ethanamine	178557-21-6	
3C-B-fly	1-(8-bromo-2,3,6,7-tetrahydrobenzo[2,3-f][1] benzofuran-4-yl)-propan-2-amine	-	
M-ALPHA, 1-Methylamino-1-(3,4-methylenedioxyphenyl)propane	1-Methylamino-1-(3,4-methylenedioxyphenyl) propane	-	

Annex 6. Piperazines (12 substances)



Common name	Abbreviation	CAS number	R_1	R_2
1-Benzylpiperazine	BZP	2759-28-6	Ph-CH_2	H
1-Benzyl-4-methylpiperazine	MBZP	374898-00-7	Ph-CH_2	CH_3
1,4-Dibenzylpiperazine	DBZP	1034-11-3	Ph-CH_2	C_7H_7
1-Phenylpiperazine	N/A	92-54-6	Ph	H



Common name	Abbreviation	CAS number	R_1	R_2	R_3	R_4	R_5
1-(4-Bromo-2,5-dimethoxybenzyl)piperazine	2C-B BZP	1094424-37-9	OCH_3	H	Br	OCH_3	H
1-(3-Chlorophenyl)piperazine	*m*CPP	6640-24-0	H	Cl	H	H	H
1-(4-Chlorophenyl)piperazine	4-CPP / *p*CPP	38212-33-8	H	H	Cl	H	H
1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine	*m*CPCPP	39577-43-0	H	Cl	H	H	C_3H_6Cl
1-(4-Fluorophenyl)piperazine	4-FPP / *p*FPP	2252-63-3	H	H	F	H	H
1-(2-Methoxyphenyl)piperazine[2]	2-MeOPP / *o*MeOPP	35386-24-4	OCH_3	H	H	H	H
1-(3-Methoxyphenyl)piperazine	3-MeOPP / *m*MeOPP	16015-71-7	H	OCH_3	H	H	H
1-(4-Methoxyphenyl)piperazine	4-MeOPP / *p*MeOPP	38212-30-5	H	H	OCH_3	H	H
2-Methylphenylpiperazine[3]	2-MePP / *o*MePP	39512-51-1	CH_3	H	H	H	H
3-Methylphenylpiperazine	3-MePP / *m*MePP	41186-03-2	H	CH_3	H	H	H
4-Methylphenylpiperazine	4-MePP / *p*MePP	39593-08-3	H	H	CH_3	H	H
1-(3-Trifluoromethylphenyl)piperazine	TFMPP / *m*TFMPP	15532-75-9	H	CF_3	H	H	H

[2] MeOPP was only reported as a generic compound in which the specific isomer was not indicated, and as such counted as one substance. For illustrative purposes, the several position isomers have been here included.
[3] MePP was only reported as a generic compound in which the specific isomer was not indicated, and as such counted as one substance. For illustrative purposes, the several position isomers have been here included.

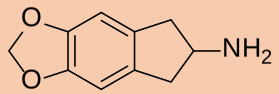
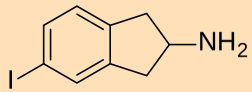
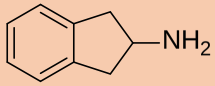
Annex 7. Plant-based substances (20 substances)

Common name	Binomial name	Active ingredient/s
Akuamma seed	*Picralima nitida*	akuammine
Ayahuasca	*Banisteriopsis caapi*	dimethyltryptamine (DMT)
Blue Egyptian water lily	*Nymphea caerulea*	nuciferine, aporphine
Calea zacatechichi	*Calea ternifolia* Kunth	sesquiterpene lactones
Chacruna	*Psychiotria viridis*	dimethyltryptamine (DMT)
Datura	*Datura stramonium*	hyoscyamine (atropine), scopolamine
Damiana	*Turnera diffusa*	not known
Hawaiian Baby Woodrose	*Argyreia nervosa*	ergine (d-lysergic acid amide (LSA))
Kanna	*Sceletium tortuosum*	mesembrine
Kava	*Piper methysticum*	kavalactones[4]
Khat	*Catha edulis*	cathinones, cathine
Kratom	*Mitragyna speciosa* Korth	mitragynine[5]

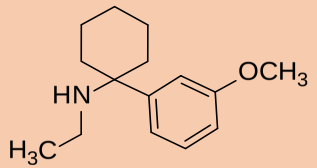
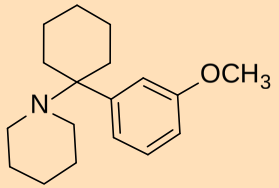
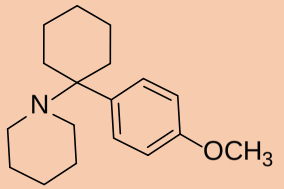
[4] Of the 18 isolated and identified kavalactones, yangonin, methysticin, dihydromethysticin, dihydrokawain, kawain, and desmethoxyyangoin are the six major ones.
[5] Over 25 alkaloids have been isolated from kratom; mitragynine is the primary active alkaloid in the plant.

Common name	Binomial name	Active ingredient/s
Lion's Tail (or Wild Dagga)	*Leonotis leonurus*	leonurine
Mimosa hostilis	*Mimosa tenuiflora*	dimethyltryptamine (DMT)
Morning Glory	*Ipomoea*	ergine (d-lysergic acid amide (LSA))
Peyote cactus	*Lophophora Williamsii*	mescaline
Salvia	*Salvia divinorum*	salvinorinA
Syrian rue	*Peganum harmala*	harmaline, harmine
-	*Voacanga africana*	iboga alkaloids (voacangine, voacamine)
Wild lettuce	*Lactuca virosa*	lactucin

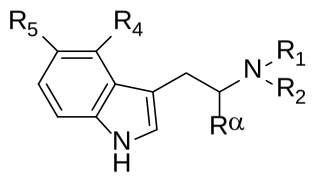
Annex 8. Aminoindanes (3 substances)

Common name	Abbreviation	Chemical name	CAS number	Structure
5,6-Methylenedioxy-2-aminoindane	MDAI	6,7-Dihydro-5*H*-cyclopenta[*f*][1,3]benzodioxol-6-amine	132741-81-2	
5-Iodo-2-aminoindane	5-IAI	5-iodo-2,3-dihydro-1*H*-inden-2-amine	132367-76-1	
2-Aminoindane	2-AI	2,3-dihydro-1*H*-inden-2-amine	2975-41-9	

Annex 9. Phencyclidine-type substances (4 substances)

Common name	Abbreviation	Chemical name	CAS number	Structure
3-Methoxyeticyclidine	3-MeO-PCE	2-(3-methoxyphenyl)-2-(ethylamino)cyclohexane	-	
3-Methoxyphencyclidine	3-MeO-PCP	1-[1-(3-methoxyphenyl)cyclohexyl]piperidine	72242-03-6	
4-Methoxyphencyclidine	4-MeO-PCP	1-[1-(4-methoxyphenyl)cyclohexyl]piperidine	2201-35-6	
5-Methoxyphencyclidine	5-MeO-PCP	1-[1-(5-methoxyphenyl)cyclohexyl]piperidine	-	

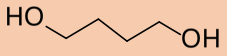
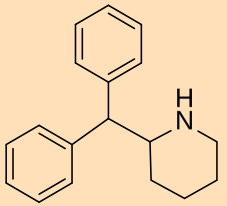
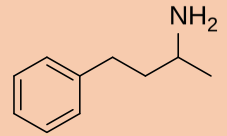
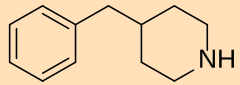
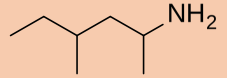
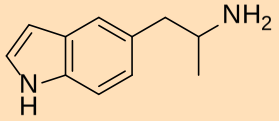
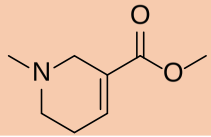
Annex 10. Tryptamines (25 substances)

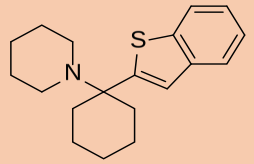
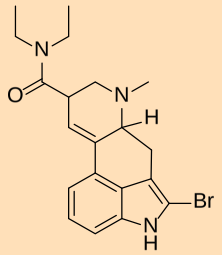
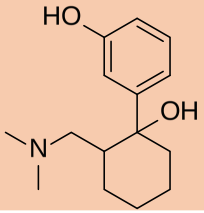
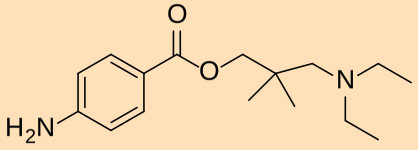
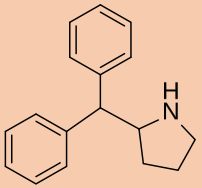


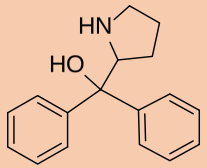
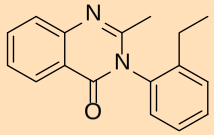
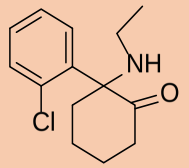
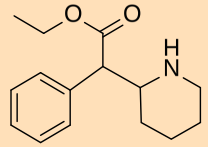
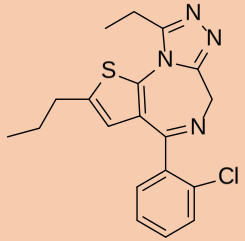
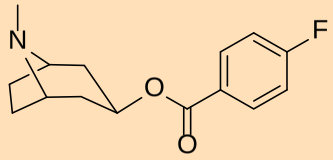
Common name	Chemical name	CAS number	R_1	R_2	R_α	R_4	R_5
4-AcO-DALT	4-Acetoxy-*N*,*N*-diallyltryptamine	-	$H_2C=CH-CH_2$	$H_2C=CH-CH_2$	H	$OC(O)CH_3$	H
4-AcO-DET	4-Acetoxy-*N*,*N*-diethyltryptamine	-	CH_2CH_3	CH_2CH_3	H	$OC(O)CH_3$	H
4-AcO-DiPT	4-Acetoxy-*N*,*N*-diisopropyltryptamine	936015-60-0	$CH(CH_3)_2$	$CH(CH_3)_2$	H	$OC(O)CH_3$	H
4-AcO-DMT	4-Acetoxy-*N*,*N*-dimethyltryptamine	92292-84-7	CH_3	CH_3	H	$OC(O)CH_3$	H
4-AcO-DPT	4-Acetoxy-*N*,*N*-dipropyltryptamine	-	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	$OC(O)CH_3$	H
4-AcO-MiPT	4-Acetoxy-*N*-isopropyl-*N*-methyltryptamine	96096-52-5	$CH(CH_3)_2$	CH_3	H	$OC(O)CH_3$	H
4-AcO-MET	4-Acetoxy-*N*-methyl-*N*-ethyltryptamine	-	CH_3	CH_2CH_3	H	$OC(O)CH_3$	H
4-HO-DET	4-Hydroxy-*N*,*N*-diethyltryptamine	22204-89-3	CH_2CH_3	CH_2CH_3	H	OH	H
4-HO-DiPT	4-Hydroxy-*N*,*N*-diisopropyltryptamine	63065-90-7	$CH(CH_3)_2$	$CH(CH_3)_2$	H	OH	H
4-HO-DPT	4-Hydroxy-dipropyltryptamine	63065-88-3	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	OH	H
5-HO-DMT, Bufotenine	5-Hydroxy-*N*,*N*-dimethyltryptamine	487-93-4	CH_3	CH_3	H	H	OH
4-HO-MiPT	4-Hydroxy-*N*-isopropyl-*N*-methyltryptamine	77872-43-6	$CH(CH_3)_2$	CH_3	-	OH	H
4-HO-MET	4-Hydroxy-*N*-methyl-*N*-ethyltryptamine	77872-41-4	CH_3	CH_2CH_3	H	OH	H

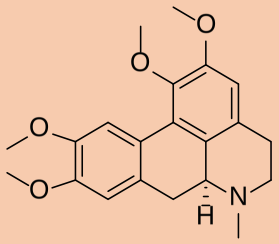
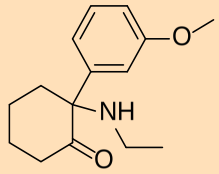
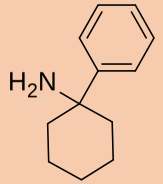
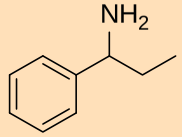
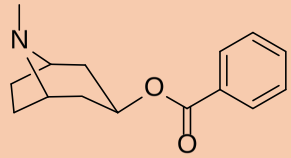
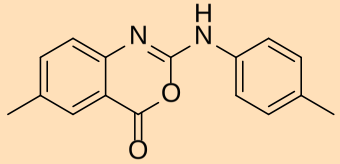
Common name	Chemical name	CAS number	R_1	R_2	R_α	R_4	R_5
4-OHT	4-Hydroxytryptamine	570-14-9	H	H	H	OH	H
5-HTP	5-Hydroxytryptophan	56-69-9	H	H	COOH	H	OH
5-MeO-DALT	5-Methoxy-*N*,*N*-diallyltryptamine	928822-98-4	H_2C=CH-CH_2	H_2C=CH-CH_2	H	H	OCH_3
5-MeO-DiPT	5-Methoxy-*N*,*N*-diisopropyltryptamine	4021-34-5	$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	OCH_3
5-MeO-DMT	5-Methoxy-*N*,*N*-dimethyltryptamine	1019-45-0	CH_3	CH_3	H	H	OCH_3
5-MeO-DPT	5-Methoxy-*N*,*N*-dipropyltryptamine	69496-75-9	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	OCH_3
5-MeO-MiPT	5-Methoxy-*N*-isopropyl-N-methyltryptamine	96096-55-8	$CH(CH_3)_2$	CH_3	H	H	OCH_3
5-MeO-MET	5-Methoxy-*N*-methyl-*N*-ethyltryptamine	1019-45-0	CH_3	CH_2CH_3	H	H	OCH_3
5-MeO- αMT	5-Methoxy-α-methyltryptamine	1137-04-8	H	H	CH_3	H	OCH_3
DiPT	*N*,*N*-Diisopropyltryptamine	14780-24-6	$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	H
DPT	*N*,*N*-Dipropyltryptamine	61-52-9	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	H
αMT	α-Methyltryptamine	879-36-7	H	H	CH_3	H	H

Annex 11. Others (24 substances)

Common name	Abbreviation	Chemical name	CAS number	Structure
1,4-Butanediol	1,4-BD	1,4-Butanediol	110-63-4	
2-(Diphenylmethyl)piperidine	2-DPMP	2-(Diphenylmethyl)piperidine	519-74-4	
3-Amino-1-phenylbutane	3-APB	3-Amino-1-phenylbutane	22374-89-6	
4-Benzylpiperidine	-	4-Benzylpiperidine	31252-42-3	
1,3-Dimethylamylamine	DMAA	4-Methylhexane -2-amine	105-41-9	
5-(2-Aminopropyl)indole	5-IT or 5-API	1-(1*H*-indol-5-yl)propan-2-amine	3784-30-3	
Arecoline	AREC	Methyl-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate	63-75-2	

Common name	Abbreviation	Chemical name	CAS number	Structure
Benzothiophenylcyclohexylpiperidine, Benocyclidine	BTCP, BCP	1-[1-(1-Benzothiophen-2-yl)cyclohexyl] piperidine	112726-66-6	
2-Bromo-*N*,*N*-diethyl-D-lysergamide	2-Bromo-LSD, BOL-148	(8β)-2-Bromo-N,N-diethyl-6-methyl-9,10-didehydroergoline-8-carboxamide	478-84-2	
O-Desmethyltramadol	O-DT	3-{2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl}phenol	73986-53-5	
Dimethocaine	-	3-(Diethylamino)2,2-dimethylpropyl4-aminobenzoate	94-15-5	
2-(Diphenylmethyl)pyrrolidine	Desoxy-D2PM	2-(Diphenylmethyl)pyrrolidine	119237-64-8	

Common name	Abbreviation	Chemical name	CAS number	Structure
Diphenylprolinol	D2PM	Diphenyl(pyrrolidin-2-yl)methanol	22348-32-9	
Etaqualone	-	3-(2-Ethylphenyl)-2-methyl-4-(3*H*)-quinazolinone	7432-25-9	
N-Ethyl-ketamine (*N*-ethyl-nor-ketamine)	NEK	2-(2-chlorophenyl)-2-(ethylamino)cyclohexanone	1354634-10-8	
Ethylphenidate	EP/EPH	Ethylphenyl (2-piperidinyl)acetate	57413-43-1	
Etizolam	-	4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine	40054-69-1	
Fluorotropacocaine	-	(3-oxo)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl4-fluorobenzoate	172883-97-5	

Common name	Abbreviation	Chemical name	CAS number	Structure
Glaucine	-	(*S*)-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-6-methyl-4H-dibenzo[de,g]quinoline	475-81-0	
Methoxetamine	MXE or 3-MeO-2-Oxo-PCE	(RS)2-(3-Methoxyphenyl)-2-(ethylamino) cyclohexanone	1239943-76-0	
1-Phenylcyclohexanamine	PCA	1-Phenylcyclohexylamine	2201-24-3	
1-Phenyl-1-propanamine	-	1-Phenylpropan-1-amine	2941-20-0	
Tropacocaine	-	8-Methyl-8-azabicyclo[3.2.1]oct-3-ylbenzoate	537-26-8	
URB754	-	6-Methyl-2-[(4-methylphenyl)amino]-1-benzoxazin-4-one	86672-58-4	

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