



9. PRECURSOR TRENDS AND MANUFACTURING METHODS

Amphetamine-type-stimulants (ATS) comprise a number of substances under international control, primarily amphetamine, methamphetamine, ecstasy-group substances (3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDE)) and methcathinone. There are numerous methods for the synthesis/manufacture of these substances and a wide range of precursor chemicals can be used. However, it is possible to identify the most commonly used chemicals which are listed in Table I and Table II of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

The majority of the precursor chemicals that can be used in the illicit manufacture of ATS and synthetic drugs have widespread licit use in the chemical and pharmaceutical industries. As such, their diversion from licit trade by drug trafficking organizations is the primary source of precursor chemicals used in the illicit manufacture of synthetic drugs. The 1988 United Nations Convention provides measures to assist Member States in preventing the diversion of these chemicals and the International Narcotics Control Board (INCB) has a number of resources to monitor the licit/illicit trade in precursor chemicals and developments/trends in the use of existing and novel precursor chemicals.

Data on the precursor chemicals and trends in their use is an invaluable source of information for law enforcement, forensic science and customs personnel in their respective roles in tackling the global trade in illicit drugs, the identification of the chemicals involved and prevention of their diversion. This chapter provides an overview of the recent trends with regard to the precursors used in the illicit manufacture of ATS and the responses of Member States and International Organizations in tackling the issue of the illicit manufacture of synthetic drugs

International responses to precursor trends in the manufacture of ATS

There have been a number of measures implemented by International Organisations and National Governments in recent years to tackle issues related to the diversion of precursor chemicals for use in the illicit manufacture of ATS. Precursor control initiatives initiated by the INCB including the establishment of the Precursor Incident Communication System (PICS) in 2012 revealed the continued emergence of phenylacetic acid as a precursor for the illicit manufacture of amphetamine and methamphetamine. The emergence of phenylacetic acid as an important

precursor led to its rescheduling from Table II to Table I of the 1988 UN Convention as of 2011. While many countries had existing legislation to monitor transactions and shipments of this chemical, a number of countries have recently amended their national legislation or adopted stricter measures. These included Canada, China, countries of the European Union and the South and Central American countries, El Salvador, Guatemala, Mexico, Nicaragua and Paraguay.

Previous INCB initiatives had revealed a shift from the use of pure ephedrine/pseudoephedrine to the use of pharmaceutical preparations containing these precursor chemicals. This trend follows the pattern of a response by drug traffickers to increased national awareness of and control measures on existing precursors. In recent years, a number of countries have also amended their legislation to more closely monitor pharmaceutical preparations containing ephedrine or pseudoephedrine. Over the 2010-2013 period, such amendments to legislation have been adopted by Australia, China, India New Zealand, the Republic of Korea, the Russian Federation, Thailand and Uruguay among others.^{412, 413} A direct consequence of the increased awareness of the use of alternate precursors and the introduction of new legislation is increased seizures of such substances in their various forms and thus a more clear picture of the methods used worldwide for the manufacture of ATS is made possible. Another consequence of increased precursor controls in countries with significant illicit ATS manufacture is that traffickers target countries with less established control systems and shift their manufacture and purchase of precursors to these countries. Thus, illicit manufacture continues to spread in African countries such as Nigeria and in South and Central America.⁴¹⁴

Trends in methamphetamine precursors: ephedrine and pseudoephedrine

Ephedrine and pseudoephedrine are attractive precursors as they are widely used in legitimate trade, and thus are more easily targeted for diversion. Also, their transforma-

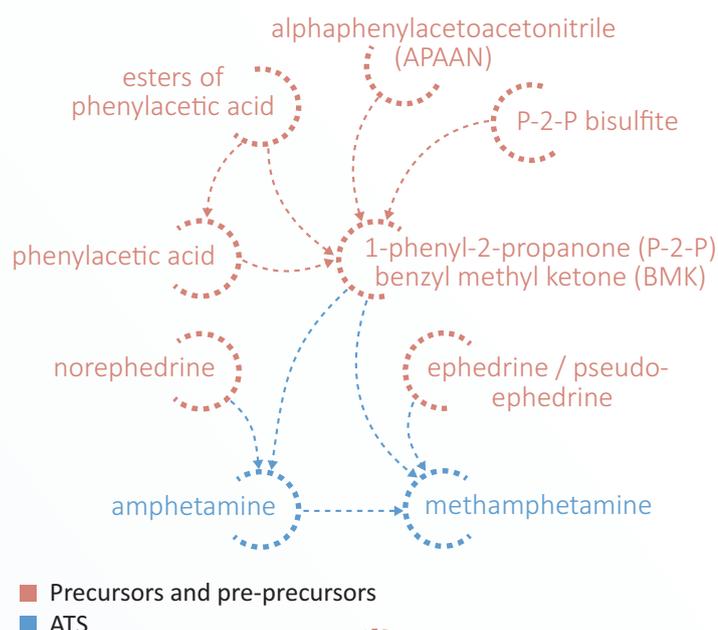
⁴¹² International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2013.

⁴¹³ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, 2014.

⁴¹⁴ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2013.

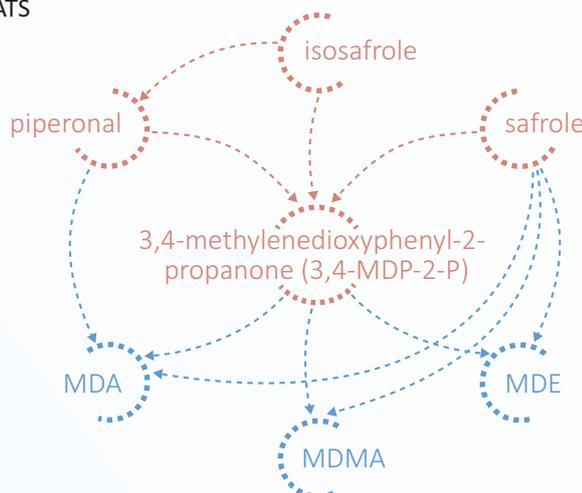
Precursors for amphetamine and methamphetamine

The primary precursor chemicals used in the manufacture of amphetamine and methamphetamine are ephedrine, pseudoephedrine and 1-phenyl-2-propanone (P-2-P). Ephedrine and pseudoephedrine are widely used in the manufacture of decongestants and bronchodilators, while the primary use of P-2-P is in the legitimate manufacture of amphetamine/methamphetamine by the pharmaceutical industry. Phenylacetic acid is also an important precursor of P-2-P and norephedrine is another precursor that can be used for the synthesis of amphetamine



Precursors for “ecstasy-type substances”

The primary precursor chemicals used in the manufacture of MDMA and its analogues, MDA and MDEA, are safrole (including in the form of safrole rich oils), isosafrole, piperonal and 3,4-methylenedioxyphenyl-2-propanone (3,4-MDP-2-P). Of these precursors, 3,4-MDP-2-P has little legitimate use, while safrole, isosafrole and piperonal are used worldwide in the chemical and pharmaceutical industries and thus are more prone to diversion from licit trade. As with other ATS, the manufacture of ecstasy-group substances is quite flexible given that the products themselves are analogues and also, that it is possible to convert MDA into both MDMA and MDE.



tion to methamphetamine is a relatively straightforward procedure that can be mediated by a variety of chemicals. Multi-ton amounts of these chemicals are seized every year and as a result of increased awareness, the number of countries now reporting seizures has doubled in 10 years according to the INCB.⁴¹⁵ In the years 2009-2012, 141 tons of bulk ephedrine/ pseudoephedrine were reported to the INCB as having been seized. In 2010 for example, China, India, Mexico and the United States all with multi-ton seizures accounted for 84% of global seizures.

Despite the continued seizures of precursors in bulk form, it has become evident in recent years that the use of alternate forms of these precursors also continues to increase in certain parts of the world. The first evidence of this is seen with the continued increase in use and seizures of

pharmaceutical preparations containing ephedrine/ pseudoephedrine. In the years 2009-2012, over 46 tons were reported seized by Member States in addition to the seizure of over 62 million tablets in this time period.

Within South and South East Asia, where there is considerable legitimate manufacture of pharmaceutical preparations containing ephedrine and pseudoephedrine, significant seizures of these preparations have been increasingly reported since 2010. Myanmar is one of the main destinations in the region for trafficked preparations which are primarily smuggled overland from China and India. According to a report presented at the Asia-Pacific Operational Drug Enforcement Conference (ADEC), 1.7 tons of pseudoephedrine primarily in the form of pharmaceutical preparations were seized in Myanmar in 2011 and over 6.9 tons were seized in 2012.⁴¹⁶ Seizures of pharmaceutical

⁴¹⁵ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2013.

⁴¹⁶ “Myanmar country report”, Central Committee for Drug Abuse Con-

Fig. 41: Global seizures of methamphetamine precursors (bulk), 2009-2012

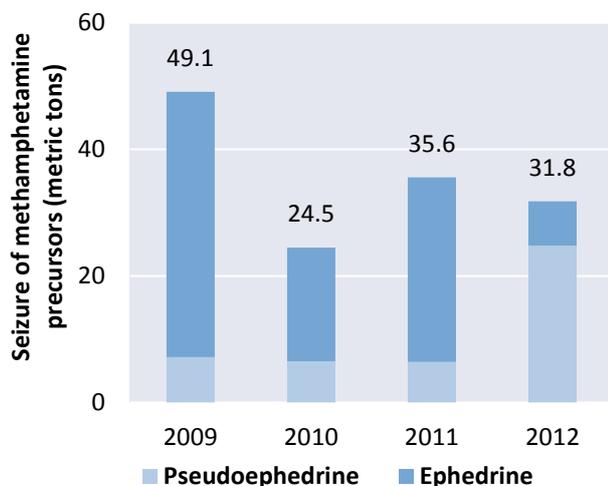


Fig. 42: Global seizures of pharmaceutical preparations of methamphetamine precursors, 2009-2012

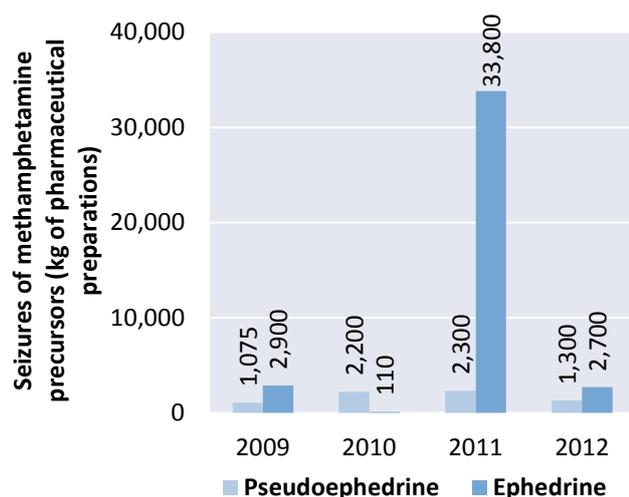
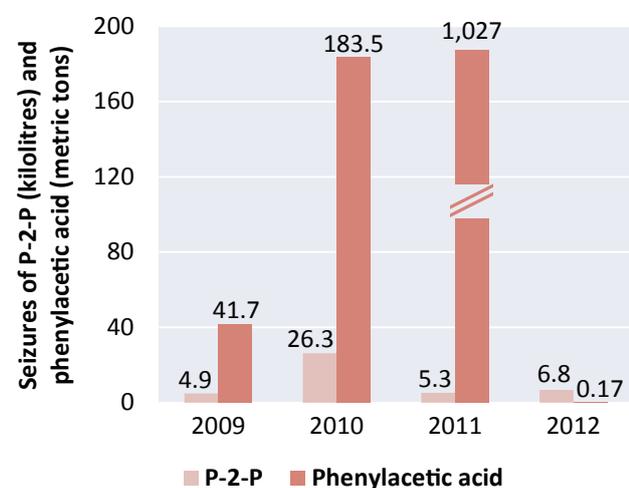


Fig. 43: Global seizures of 1-phenyl-2-propanone (P-2-P) and phenylacetic acid, 2009-2012



Source: International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, for 2010, 2011, 2012, 2013.

preparations containing pseudoephedrine and ephedrine preparations have also been on the increase in other countries in the region including China, the Republic of Korea, Lao People's Democratic Republic, Singapore and Thailand.⁴¹⁷ The seizures have in some cases been destined for locations with the region, but also to Central America, either directly or via Europe. Within the Oceanic region, in both Australia and New Zealand there have also been increased reports of seizures of pharmaceutical preparations in the form of ContacNT⁴¹⁸. New Zealand reported its highest seizure in 2010 (more than 0.9 tons) and a 1.3 ton seizure was made in Australia in 2012.⁴¹⁹ Also, in 2012, Australia reported its second highest detection weight of ATS precursors (excluding MDMA) in a decade, at approximately 1.8 tons.⁴²⁰ The majority of methamphetamine precursors seized in recent years in Australia, have been ephedrine and pseudoephedrine based, with P-2-P only accounting for 0.03 per cent of the total weight of precursors seized.⁴²¹ This statistic is in stark contrast to the situation in Europe, countries of Central America, Mexico and North America.

Trends in amphetamine and methamphetamine precursors: 1-phenyl-2-propanone (P-2-P) and phenylacetic acid

The flexibility of ATS manufacture is reflected in the number of precursor chemicals that can be used and indeed an even wider range of chemicals that can convert the precursors to the controlled drugs. The primary alternate precursor to pseudoephedrine and ephedrine in the manufacture of amphetamine and methamphetamine is 1-phenyl-2-propanone (P-2-P). The second most notable trend in recent years in the illicit manufacture of methamphetamine is the increasing shift towards P-2-P based routes involving precursors and derivatives of P-2-P in certain regions of the world. In particular, phenylacetic acid (a direct precursor to P-2-P) and its derivatives have been used in increasing amounts in the illicit manufacture

control (CCDAC), presented at the Eighteenth Asia-Pacific Operational Drug Enforcement Conference (ADEC), Tokyo, 26-27 February 2013.

⁴¹⁷ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2013.

⁴¹⁸ ContacNT is distinct granular pharmaceutical formulation containing pseudoephedrine; International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2013.

⁴¹⁹ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2011; International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, 2014.

⁴²⁰ "Illicit Drug Data Report 2011-12", Australian Crime Commission (ACC), Canberra, May 2013.

⁴²¹ "Illicit Drug Data Report 2011-12", Australian Crime Commission (ACC), Canberra, May 2013.

of amphetamine/methamphetamine. As a consequence, phenylacetic acid was rescheduled from Table II to Table I of the 1988 convention as of January 17, 2011. The use of such precursors has increased in recent years partly as a result of increased control measures and effective monitoring of ephedrine and pseudoephedrine. Manufacturing routes based on P-2-P are historically preferred in Europe, where this precursor is mainly used to manufacture amphetamine. In 2011, half of the 5,312 litres of P-2-P seized worldwide was reported by European countries, although this decreased to 12 % of global seizures of P-2-P in 2012, with Mexico accounting for 4,699 (69 %) of the total of 6,818 litres seized.

It is, however, the increase in the seizures of phenylacetic acid in recent years that is most notable, particularly in the United States, Mexico and Central America. There were significant seizures in Mexico (56.1 tons in 2010) and the United States (122.7 tons in 2010 and 997 tons in 2011) providing evidence of the shift away from ephedrine/pseudoephedrine based manufacturing methods in the region. Despite the fact that seizures of both P-2-P and phenylacetic acid decreased dramatically in 2012, forensic profiling of seized methamphetamine in the United States confirmed that currently, nearly all of the analysed methamphetamine is manufactured using phenylacetic acid or other P-2-P based methods (94 % of all samples tested in the second quarter of 2012, up from 69 % in 2010 and close to 1 % in 2007).⁴²² This shift in manufacturing methods is also showing signs of spreading to Central American countries and in Guatemala declining seizures of ephedrine and pseudoephedrine have been reported in 2013 coincident with the seizure of more than 1,000 litres of P-2-P in a clandestine laboratory in Tecun Uman, a border city between Guatemala and Mexico.⁴²³

Trends in ecstasy-group substance precursors

The main precursor chemicals used in the manufacture of ecstasy-group substances are included in Table 1 of the 1988 Convention and their licit trade and reported diversions to illicit manufacture are monitored by the INCB. Seizures of these precursors have increased in 2012- 2013 following a number of years where there was a considerable discrepancy in the volume of seizures compared to the worldwide availability of the drugs themselves, in particular MDMA. While the amounts of 3,4-MDP-2-P and piperonal seized continue to be low, safrole and safrole rich oil seizures have increased with Cambodia, Malaysia, Mexico

and the United States all reporting seizures greater than 2,000 litres in 2011, while Australian authorities reported a seizure of 3.5 tons of safrole in 2012.⁴²⁴ Within Cambodia, a further 4,000 litres of safrole rich oils were seized in a clandestine laboratory in 2012.⁴²⁶ Within Europe, the Belgian authorities seized almost 10,000 litres of safrole rich oils in 2011 and in August and October 2013, two industrial scale clandestine MDMA laboratories were dismantled in Belgium.⁴²⁷ In the first of these cases, several tons of safrole were seized and in the second 35 tons of as yet unidentified chemicals were found.

Non-controlled precursors used in the manufacture of amphetamine-type stimulants

Coincident with the increased use of phenylacetic acid in recent years, there has been a significant rise in the use of non-controlled precursor chemicals in the manufacture of amphetamine, methamphetamine and ecstasy-group substances. This development can also be attributed in part to increased control measures on listed precursor chemicals and successes in preventing their diversion to illicit manufacture forcing drug traffickers to seek alternative chemicals and/or masked precursors.

The use of such non-scheduled derivatives of known precursors is a continuing trend and Operation Phenylacetic Acid and its Derivatives (PAAD) initiated by the INCB in 2011 revealed the extent to which derivatives of phenylacetic acid were being used in Mexico and Central American countries. The initiative revealed a shift toward the use of non-controlled precursors in the region. The most commonly seized derivatives were the methyl and ethyl esters of phenylacetic acid and seizures of 526 tons and 430,000 litres of these pre-precursors were reported in 2011 by Mexico and El Salvador and in 2012 Guatemala reported the seizure of 16,000 kg of ethyl phenylacetate.⁴²⁸

A number of other phenylacetic acid derivatives or precursors were also reported including phenylacetamide, benzyl chloride and benzylcyanide. These non-controlled precursors can be converted to phenylacetic acid and/or P-2-P by straightforward transformations, and while ana-

⁴²² International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York 2013, p. 16.

⁴²³ United Nations Office on Drugs and Crime (UNODC), *Global SMART Update Volume 10*, Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) Programme, Vienna, September 2013.

⁴²⁴ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, January 2013.

⁴²⁵ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, 2014.

⁴²⁶ Official communication with the National Authority for Combating Drugs (NACD), October 2012.

⁴²⁷ Europol (European Police Office), "Police discover largest synthetic drugs production site ever found in the EU", the Hague, the Netherlands, 23 October 2013, at <https://www.europol.europa.eu/content/police-discover-largest-synthetic-drugs-production-site-ever-found-eu>.

⁴²⁸ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, 2014.

**Table 3:** Most commonly used ATS manufacturing methods and the yields of the stated methods

End Product	Precursor (1 kg or 1 lt.)	Synthesis Method (Method)	Practical Yield
Amphetamine	P-2-P (lt.)	Ammonium formate (Leuckart)	55%
Amphetamine	P-2-P (lt.)	Formamide (Leuckart)	67%
d,l-Methamphetamine	P-2-P (lt.)	Formic acid (Leuckart)	60%
d-Methamphetamine	Pseudo/ephedrine (kg)	Red phosphorus / iodine	47%
d-Methamphetamine	Pseudo/ephedrine (kg)	Red phosphorus / hydriodic acid	54%
d-Methamphetamine	Pseudo/ephedrine (kg)	Lithium / ammonia ('Birch')	55%
d-Methamphetamine	Pseudo/ephedrine (kg)	Hypophosphorous acid / iodine	76%
d-Methamphetamine	Pseudo/ephedrine (kg)	Thionyl chloride (Emde)	70%
Methcathinone	Pseudo/ephedrine (kg)	Potassium permanganate	50%
MDA	Sassafras oil* (lt.)	Hydrogen peroxide / sodium cyanoborohydride	12%
MDA	3,4-MDP-2-P (lt.)	Sodium cyanoborohydride	37%
MDA	Piperonal	Nitroethane	41%
MDMA	Sassafras oil* (lt.)	Hydrogen peroxide / aluminium amalgam	31%
MDMA	Sassafras oil* (lt.)	Hydrobromic acid	48%
MDMA	3,4-MDP-2-P (lt.)	Formic acid (Leuckart)	66%
MDMA	Sassafras oil* (lt.)	Methyl nitrite / aluminium amalgam (Wacker)	68%
MDMA	3,4-MDP-2-P (lt.)	Aluminium amalgam (reductive amination)	95%

* at 75% safrole.

Source: Drug Yield Calculator (V5.0), Royal Canadian Mounted Police and Health Canada; Suravina, L. G. and Voronenko, L. A. (1994). *Forensics Investigation of Narcotic and Drastic Substances Obtained from Ephedra Grass Using Home Production Methods*. Ministry of Justice of the Republic of Kazakhstan, Kazakhs Scientific Research Institute; DEA, *Methamphetamine Synthesis #7* (1997).

logue legislation in some countries can be used to control such derivatives, the relationship between the controlled precursor and its masked derivative is sometimes not easily identified.

Another non-controlled precursor of P-2-P, alphaphenylacetoacetonitrile (APAAN) has emerged since 2011 in a number of European countries in particular, where multi-ton seizures of shipments from China to the Netherlands were reported. Seizures of APAAN increased in 2012 when a total of 17.5 tons were seized in Europe. Significant seizures of APAAN has also been made in Canada in 2012, indicating the spread of its use to other ATS manufacturing regions. As a consequence of the increased use of APAAN in the manufacture of ATS and its limited use in legitimate trade,⁴²⁹ APAAN was on the agenda of the fifty-seventh session of the Commission on Narcotic Drugs (CND) for the inclusion in Table I of the United Nations

Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 at the time of writing this report.

Evidence of the use of non-controlled precursors in the manufacture of ecstasy-group substances has also increased in recent years, with seizures of 1,200 kg of the methyl glycidate derivative of 3,4-MDP-2-P in 2010. This trend continued in 2011 with the discovery of helional in several clandestine laboratories in Australia and the United States.⁴³⁰ This non-controlled precursor chemical, widely used in the chemical industry as a fragrance agent, can be used in the manufacture of MDA and thus also MDMA and MDE.

⁴²⁹ European Monitoring Centre for Drugs and Drug Addiction, "Perspectives on Drugs; Synthetic Drug Production in Europe", 2013.

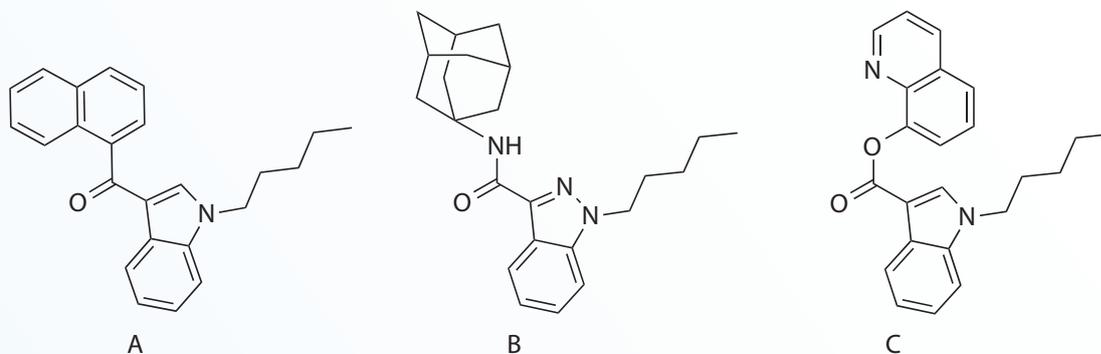
⁴³⁰ Trotter Brendan, et.al. "Manufacture of 3,4-Methylenedioxyamphetamine From Helional Encountered in Australia" *Journal of the Clandestine Laboratory Investigating Chemist Association* (23)(1) Jan. 2013: 4; Kovacs III, Edward J. and Dean A. Kirby, "Manufacture of 3,4-Methylenedioxyamphetamine From Helional Encountered in Australia" *Journal of the Clandestine Laboratory Investigating Chemist Association* (23)(1) Jan. 2013: 5-14.

Chemical structures of typical synthetic cannabinoids

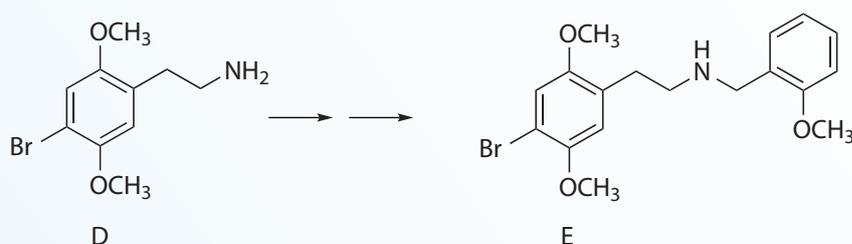
JWH-018 (1-pentyl-3-(1-naphthoyl)indole) (A),

APINACA (1-pentyl-N-tricyclo[3.3.1.1^{3,7}]dec-1-yl-1H-indazole-3-carboxamide) (B)

PB-22 (1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid ester) (C)



Manufacture of 2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25C-NBOMe) (E) using 2C-B (4-bromo-2,5-dimethoxyphenethylamine) (D)



Glycidic acid derivatives of both P-2-P and 3,4-MDP-2-P have also emerged as novel ATS pre-precursors in 2012.⁴³¹ The increasing use of non-controlled precursors reflects the increasing sophistication of ATS manufacture and the difficult challenges currently faced by Governments in their efforts to tackle the trafficking in precursor chemicals.

Manufacturing methods

The chemical transformations involved in the conversion of the precursor chemicals to illicit ATS products are mostly well known chemical reactions, described in the scientific literature and are also freely available on the internet. Due to the similarity of the products, many methods can be adapted for the manufacture of different products. One example of this is the use of P-2-P to make amphetamine or methamphetamine. The change in methamphetamine manufacturing methods in certain regions of the world to P-2-P based methods has resulted in dramatically increased seizures of methylamine (665 tons and 478,000 litres were seized in 2011). This chemical can be used in

methamphetamine manufacture using P-2-P (also used in MDMA manufacture with 3,4 MDP-2-P). One notable difference between methamphetamine produced by P-2-P based routes compared with ephedrine/pseudoephedrine based routes is the nature of the product. Both ephedrine and pseudoephedrine produce the more potent d-methamphetamine, whereas a mixture of d- and l-methamphetamine is produced from P-2-P. Therefore, in order to produce d-methamphetamine from P-2-P an extra step is required and certain other chemicals are required whose presence in a clandestine laboratory can indicate P-2-P based manufacture.

Manufacture methods using pre-precursors

Considering the recent developments in the increasing use of phenylacetic acid, its derivatives and other non-scheduled precursor chemicals for the manufacture of ATS, it should be noted that with such precursors, extra chemical steps can be required to manufacture the final ATS product. For example, chemicals such as acetic anhydride or lead acetate are used to convert phenylacetic acid to P-2-P and recently seizures of acetic anhydride, typically regarded as a precursor for the production of heroin, have increased

⁴³¹ International Narcotics Control Board (INCB), *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances*, New York, 2014.



in Mexico.⁴³² The conversion of phenylacetic acid esters to P-2-P can also require an intermediate step.

Similarly, the use of APAAN in the manufacture of amphetamine or methamphetamine requires its intermediary conversion to P-2-P. However, despite the extra steps that are required when using non-scheduled precursors, their eventual conversion to illicit drugs is relatively straightforward and the benefits of their use to traffickers are obvious compared to the more tightly controlled well known precursors. Another consequence of the increased sophistication of ATS manufacturing methods, is the improved efficiency of the manufacturers. For example, it was reported that the use of larger scale industrial equipment has enabled amphetamine manufacturing facilities in Belgium and the Netherlands to increase their yields per batch from 5-8 kg several years ago to a current 40 kg per batch.⁴³³

Manufacture of New Psychoactive Substances (NPS)

By December 2013, over 348 NPS had been reported to the UNODC early warning advisory⁴³⁴. It is possible to classify the majority of these molecules into the following substance groups based on structural similarities: aminoidanes, synthetic cannabinoids, synthetic cathinones, ketamine and phencyclidine-type substances, phenethylamines, piperazines, plant-based substances, tryptamines plus a group of miscellaneous substances. As a consequence of the number and diverse chemical structure of the new psychoactive substances, it has not been possible to comprehensively examine their methods of manufacture and identify and prioritise key precursor chemicals. However, within certain substance groups, it is possible to see common approaches to synthetic methods. Based on the recent trends in the appearance of new substances, it is also possible to understand what approaches are used in their manufacture to by-pass legislative responses of Member States to the emergence of NPS. Examples of the manufacture of selected NPS are provided in the following sections.

Synthetic cathinones

The synthetic cathinone most commonly reported to the UNODC is mephedrone (4-methylmethcathinone), which can be manufactured by a two-step process using 4-methylpropiofenone as one of the main precursors. This compound can be brominated and then reacted with another

precursor, methylamine to give mephedrone. This synthetic route is flexible and a number of cathinone derivatives can be manufactured by slight modifications to the precursors. For example, changing the position and/or identity of the alkyl group in 4-methylpropiofenone can produce a number of known cathinone compounds; e.g. 3-methylpropiofenone generates 3-methylmethcathinone and 4-ethylpropiofenone enables the manufacture of 4-ethylmethcathinone. In a similar manner, substituting methylamine with another amine such as ethylamine enables the manufacture of a series of ethcathinone derivatives.

Synthetic cannabinoids

The identification of methods/precursors for the manufacture of synthetic cannabinoids is complicated by the fact that this group of NPS contains a large number of structurally diverse substances. The synthetic cannabinoids can to some extent be subdivided into certain structural classes, however as new derivatives continue to appear on the market, new classifications are required. Naphthoylindoles are one of the main sub-groups of synthetic cannabinoids and JWH-018 (1-pentyl-3-(1-naphthoyl)indole) (see figure) is one of the most commonly reported substances. JWH-018 can be manufactured in two steps with indole as one of the primary precursors. Alkylation of indole with n-pentylbromide followed by reaction with 1-naphthoyl chloride produces JWH-018.⁴³⁵ Altering the precursors by adding/varying substituents can produce a wide variety of possible synthetic cannabinoids and other structural classes of synthetic cannabinoids can be obtained by changing the naphthoyl group to a benzoyl or a phenacetyl group.

Examination of synthetic cannabinoids that have appeared recently reveals some common approaches used to manufacture new compounds. These approaches have included: (see diagram)

- the replacement of a hydrogen in the terminal carbon of the alkyl chain with fluorine or chlorine.
- the use of indazole instead of indole as a starting material e.g. APINACA (1-pentyl-N-tricyclo[3.3.1.1.3,7]dec-1-yl-1H-indazole-3-carboxamide)
- the use of different linkages. JWH-018 has a ketone linkage, whereas PB-22 (1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid ester) has an ester linkage and MN-24 (N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide) has an amide linkage group.

⁴³² United Nations Office on Drugs and Crime (UNODC) and Organization of American States (OAS), *Amphetamine-Type Stimulants in Latin America*, February 2014.

⁴³³ European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), "Perspectives on drugs: Synthetic drug production in Europe", 2013.

⁴³⁴ For more information on the Early Warning Advisory (EWA) see www.unodc.org/nps.

⁴³⁵ Huffman, J.W., et al., "Structure-activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB1 and CB2 receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB2 receptor agonists", *Biorganic and Medicinal Chemistry* (13)(1) Jan. 2005: 89-112.

Phenethylamines

Phenethylamines are a group of NPS consisting of compounds that all contain the 2-phenyl-2-ethanamine group but also can have a variety of substituents in a number of different positions. As with the other NPS mentioned, the methods for the manufacture of phenethylamines are diverse and varied, thus it is difficult to identify key manufacturing methods or precursors. However, the approach of the manufacturers of NPS to the development of new substances can be illustrated with an example from the phenethylamine group of substances.

2C-B (4-bromo-2,5-dimethoxyphenethylamine), a substance controlled under schedule II of the United Nations convention on Psychotropic Substance 1971 is a member of the 2C class of phenethylamines of which there are approximately 27 members. 2C-B itself can be used as a precursor for manufacture of the hallucinogenic 2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25C-NBOMe) (see diagram). In a similar manner, reaction of any 2C drug with 2-methoxybenzaldehyde produces the corresponding NBOMe compound. In recent years, a number of NBOMe compounds have appeared in NPS markets and in the last 6 months more novel derivatives of NBOMe compounds have been reported to UNODC.