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α-PVP

EMCDDA–Europol Joint Report on a new psychoactive substance: 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone (α-PVP)

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

About this series

EMCDDA–Europol Joint Report publications examine the detailed information provided by the EU Member States on individual new psychoactive substances. Information is collected from the Reitox network, the Europol national units and the national competent authorities of the European Medicines Agency.

Each Joint Report serves as the basis upon which the decision to conduct a risk assessment of the new psychoactive substance is taken. It is part of the three-step procedure involving information exchange, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

EUROPOL

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joint publication

Contents

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- the Europol national units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway and Iceland;
- the European Medicines Agency (EMA) and the European Commission;
- the World Health Organization.

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1. Introduction

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

In May 2015 the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol examined the available information on the new psychoactive substance 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone, commonly known as α-pyrrolidinovalerophenone (α-PVP), through a joint assessment based upon the following criteria:

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

The EMCDDA and Europol agreed that the information collected on α-PVP satisfied all criteria (1 to 6). The two agencies therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on α-PVP as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 27 May 2015 the EMCDDA and Europol launched a procedure for the collection of information on α-PVP, in order to prepare the Joint Report. The information was collected mainly through the Reitox National Focal Points in the Member States, Turkey and Norway, and the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 8 July 2015; additional information and clarifications from some countries were received up to four weeks after this date.

Information provided to Europol

Europol asked the Europol National Units to provide information on:

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

Europol received responses from 19 Member States ([2]).

Information provided to the EMA

According to Article 5.3 of the Council Decision, the EMA requested that the national competent authorities responsible for human and veterinary medicinal products in the Member States and in Norway, Iceland and Liechtenstein provide information on whether:

- the new psychoactive substance α-PVP has obtained a marketing authorisation;
- the new psychoactive substance α-PVP is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance α-PVP has been suspended.

Twenty-one countries provided a response to the EMA's request regarding human and/or veterinary medicinal products ([3]). The EMA also provided information as relevant to the centralised procedure for authorising medicinal products.

([1]) OJ L 127, 20.5.2005, p. 32.

([2]) In alphabetical order: Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Estonia, France, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Poland, Romania, Slovakia, Slovenia and Spain.

([3]) Austria, Belgium, the Czech Republic, Estonia, Finland, Iceland, Ireland, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Greece and Italy provided a response in relation to human medicinal products. France, Germany, Hungary, Latvia, the Netherlands, Portugal and Slovenia provided a response in relation to veterinary medicinal products.

Furthermore, in anticipation of Article 7.3 of the Council Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested information on whether the new psychoactive substance α-PVP is used to manufacture a medicinal product:

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

Twenty-one countries ([4]) provided a response. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products.

Information provided to the EMCDDA

The EMCDDA collected data through:

1. a structured questionnaire to the Reitox National Focal Points. The EMCDDA received replies from the 28 Member States, Turkey and Norway;
2. information previously provided to the European Union (EU) Early Warning System, including EMCDDA–Europol Reporting Forms, Progress and Final Reports;
3. a specific information request to the World Health Organization on whether or not α-PVP is under assessment by the United Nations system; and,
4. a search of open source information that included: scientific and medical literature; official reports; grey literature; Internet drug discussion forums and related websites (hereafter, 'user websites'); and online vendors selling α-PVP.

Thus, the information included in sections 3.2.1, 3.3 and Annex of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusion of the Joint Report was prepared and agreed by the EMCDDA and Europol, the two agencies responsible for the report.

([4]) Austria, Belgium, the Czech Republic, Estonia, Finland, Iceland, Ireland, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Greece and Italy provided a response in relation to human medicinal products. France, Germany, Hungary, Latvia, the Netherlands, Portugal and Slovenia provided a response in relation to veterinary medicinal products.

3. Information required by Article 5.2 of the Council Decision

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

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

Chemical description and names

α-PVP is a synthetic derivative of the naturally occurring substance cathinone, which is internationally controlled ([5]), and one of the psychoactive principles in khat (*Catha edulis* Forsk). α-PVP was first described in 1963 in the patent literature on α-pyrrolidino valerophenones (Wander, 1963) and on α-pyrrolidino ketones (Thomae, 1963).

All synthetic cathinone derivatives monitored by the EMCDDA through the EU Early Warning System are either *N*-alkylated or the nitrogen atom is part of a pyrrolidine ring, which is the case with α-PVP. Unlike many cathinone derivatives, α-PVP is not substituted on the phenyl ring.

Pyrrolidine derivatives, such as α-PVP, can be regarded as a subset of cathinone derivatives that share the same structural skeleton as pyrovalerone, prolintane and MDPV (Figure 1).

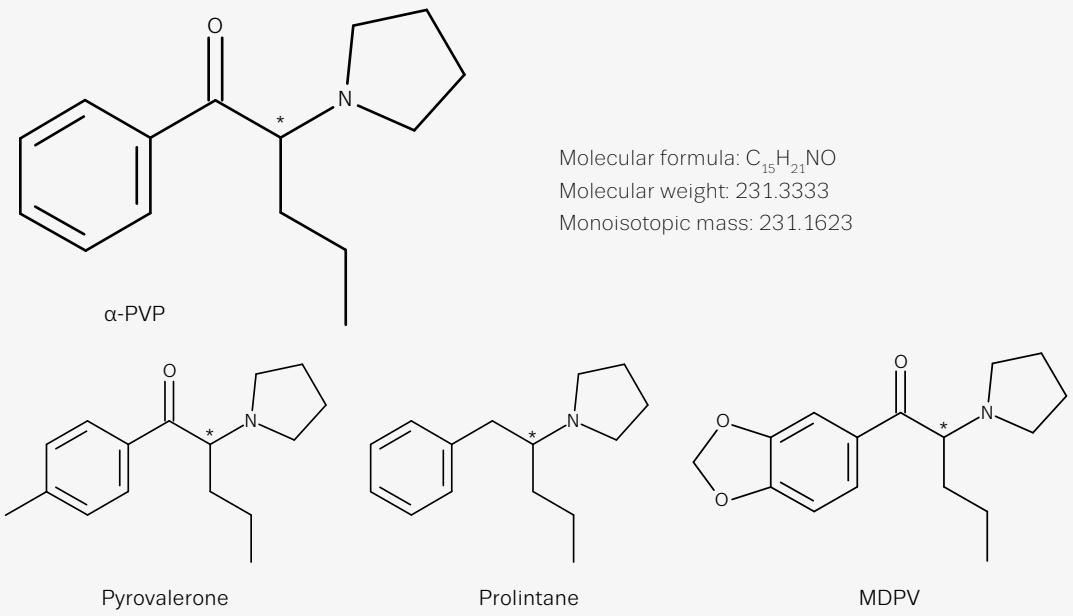
α-PVP is also a metabolite — the desmethylated analogue — of pyrovalerone (1-(4-methylphenyl)-2-(1-pyrrolidinyl) pentan-1-one), which is internationally controlled ([6]). α-PVP is the beta-keto derivative of prolintane (1-(1-benzylbutyl) pyrrolidine), a noradrenaline-dopamine reuptake inhibitor developed in the 1950s. The methylenedioxy derivative of α-PVP — MDPV ([7]) — was risk-assessed by the Scientific Committee of the EMCDDA in 2014 ([8]).

Pyrrolidino ketones such as α-PVP contain a stereogenic centre, thus allowing for the existence of a pair of

([5]) Listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances.
([6]) Listed in Schedule IV of the 1971 United Nations Convention on Psychotropic Substances.
([7]) 1-(1,3-Benzodioxol-5-yl)-2-pyrrolidin-1-yl-pentan-1-one or methylenedioxypyrovalerone.
([8]) EMCDDA (2014), *Report on the risk assessment of 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (MDPV) in the framework of the Council Decision on new psychoactive substances*, Publications Office of the European Union, Luxembourg, May 2014.

FIGURE 1.

The molecular structure, weight and monoisotopic mass of α-PVP. The molecular structure for pyrovalerone, prolintane and MDPV are provided for comparison. Chiral centres are denoted by an asterisk on the molecular structures below



enantiomers. There is no information on the isomeric composition of the samples of α-PVP detected within the EU, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories.

The most common substitution of alpha-pyrrolidinophenones is a side chain at the alpha carbon. Lower and higher homologues of α-PVP monitored by the EMCDDA are: alpha-pyrrolidinopropiophenone (α-PPP), alpha-pyrrolidinobutyrophenone (α-PBP), alpha-pyrrolidinohexanophenone (α-PHP), alpha-pyrrolidinoenanthophenone (α-PEP or PV8), alpha-pyrrolidinooctanophenone (α-POP or PV9) and alpha-pyrrolidinononaphenone (α-PNP) ([9]).

α-PVP is the common name for alpha-pyrrolidinovalerophenone. The systematic IUPAC name for α-PVP is (*RS*)-1-phenyl-2-(1-pyrrolidinyl)-1-pentanone.

Additional chemical synonyms reported are:

1-phenyl-2-(1-pyrrolidinyl)-1-pentanone
1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one
2-pyrrolidin-1-yl-1-phenylpentan-1-one
2-(pyrrolidin-1-yl)phenylpentan-1-one
2-pyrrolidinovalerophenone
α-pyrrolidinopentiophenone
2-(1-pyrrolidinyl)-valerophenone
1-fenyyli-2-(1-pyrrolidinyyli)-1-pentanoni (Finnish)
α-pyrrolidiinivalerofenoni (Finnish)
α-pyrrolidinovalerophenon (German)
1-phenyl-2-(pyrrolidin-1-yl)pentan-1-on (German)

Common names or code names for α-PVP have also been reported: alfa-PVP, a-PVP, A PVP, PVP (code name also used for polyvinylpyrrolidone, a polymer commonly called polyvidone or povidone), PV (code name used for pyrovalerone), alpha-2, α-2, β-ketone-prolintane, prolintanone, desmethyl pyrrolidinovalerophenone and O-2387. The code name O-2387 originated in research published by Meltzer et al., 2006.

The following street names have also been reported for α-PVP: 'grind' (Belgium), 'flakka' (Croatia, Cyprus, the United Kingdom and Turkey), 'gravel' (Cyprus and Turkey), 'crystal love' (Finland), 'Pure NRG' (Germany), 'Snow Blow' (Ireland) and 'vanilla sky' (Malta).

Finally, the following products labelled 'legal high' have been reported to contain α-PVP: 'Yayo soft', 'Yayo experimental' and '1NRG' (Belgium); 'Ocean Breath' (Cyprus); 'Guarana Coco jumbo', 'Cherry Coco jumbo', 'Iloveparade' and 'Sensation' (the Czech Republic); 'NRG3', 'Energy 3' and 'PV-11' (France); 'Pure NRG' (Germany); 'A-1 PUP' (Italy); 'E21', 'G-Y', 'S1 Turbo' and 'GIE-ES M' (Poland); 'Sextacy', 'Bloom', 'Quick Silver', 'Formula

([9]) The origin for the common name is indicated by underlining the relevant letters in the systematic chemical name.

3', 'Ivory' and 'Vanila Sky' (Portugal); 'Doves', 'Fire Ball', 'Green Speed', 'Knock out', 'Max', 'Speedway', 'Total speed' and 'Ultra Violet Exclusive' (Slovakia); and 'NRG-3', 'Energy-3 (NRG-3)' and 'Spellweaver' (the United Kingdom). Some of these products are marketed as 'research chemicals', 'bath salts', 'plant food' or 'insect repellents' in order to circumvent legislation.

Chemical Abstract Service (CAS) registry numbers:

14530-33-7	free base
5485-65-4	hydrochloride salt
14859-27-9	tartrate salt
14859-28-0	maleate salt
14995-79-0	citrate salt
100175-06-2	hydrogen maleate
16121-74-7	sulfate salt
13415-49-1	sulfate salt (1:1)
1346599-00-5	D_8-free base
1781744-06-6	D_8-hydrochloride salt

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed above. The searches returned no results.

Physical description

The hydrochloride salt of α-PVP is described as a white or off-white, odourless crystalline powder, with a melting point of 161.3°C ([10]). It is reported to be soluble in PBS (~10mg/ml, pH7.2), in EtOH (~20mg/ml), in DMSO (~10mg/ml) and in DMF (~3mg/ml).

Information provided from seizures and collected samples reported by the Member States have usually noted the presence of α-PVP in powder form. α-PVP has also been detected in: tablets, powder-filled capsules, vegetable material, liquids, blotters (small pieces of paper impregnated with α-PVP for sublingual/buccal administration) and jelly gums.

A more detailed description of α-PVP seizures and collected samples that have been reported can be found in sections 3.2.1 and 3.2.2.

([10]) Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG), 'Monograph on α-PVP'. Available at: www.swgdrug.org/Monographs/a-PVP.pdf

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

It is important to note that some of the data reported to Europol (section 3.2.1) may overlap with the data reported to the EMCDDA (section 3.2.2).

3.2.1. Information provided to Europol

Europol received replies from 19 Member States (Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Estonia, France, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Poland, Romania, Slovakia, Slovenia and Spain).

The level of production

Hungary reported that α-PVP was detected in two tableting sites that were dismantled in 2013 and 2014. It must be noted that the synthesis of α-PVP did not take place at those sites. The site dismantled in 2013 was a tableting unit where pentedrone ([11]) tablets were produced; 24 908 tablets containing pentedrone and 800 g of α-PVP in powder form were seized (Figure 1 of the Annex). In 2014 the Hungarian police dismantled a tableting site where pentedrone tablets were also produced. In the storage location linked to this site, 1.5 kg of α-PVP in powder form was seized (Figure 2 of the Annex). According to the Hungarian police, in both cases suspects intended to produce tablets using the α-PVP powder.

Poland reported the seizure of two illicit production sites synthesising α-PVP. The first production facility, where brephedrone ([12]) was also manufactured, was seized in July 2013 in Chorzow (Figure 3 of the Annex). Approximately 50 kg of α-PVP was produced in this site, which was destined both for the domestic market and to be exported. The second synthetic drug production facility, dismantled in October 2014 in Krakow, also produced brephedrone and NEB (*N*-ethylbuphedrone). The amount of α-PVP and brephedrone seized totalled 4.5 kg. According to the Polish authorities, both cases were linked to a local group of 'football hooligans'. The synthesis was supervised by trained chemists, and the laboratories were operated by suppliers, producers and distributors of chemicals. The companies involved operated their own websites offering the sale and distribution of those substances across Poland.

([11]) 2-Methylamino-1-phenyl-1-pentanone; another synthetic cathinone derivative.
([12]) 4-Bromomethcathinone; another synthetic cathinone derivative.

The level of distribution

Seizure data reported to Europol suggest that α-PVP has been present in the EU drug market since at least 2012. With the exception of the synthetic drug production in Poland noted above, bulk quantities of α-PVP are mainly imported to the EU from China and further distributed from the Member States. The Czech Republic reported a case where α-PVP was shipped from there to another country outside the EU.

The earliest reported seizures of α-PVP were in 2012 (Belgium, Cyprus, Finland and Latvia). Eleven Member States reported seizures for 2015 (Croatia, the Czech Republic, Finland, France, Germany, Hungary, Latvia, Lithuania, Luxembourg, Romania and Spain).

In total, over 295 seizures in powder or crystalline powder form were reported, totalling over 370 kg of α-PVP ([13]). Most of the seizures were described as white or off-white in colour, but in one case from Spain the powder was described as 'black rock powder'. Individual seizures ranged from low quantities of less than one gram up to quantities greater than one kilogram reported by seven Member States (Belgium, the Czech Republic, Finland, France, Hungary, Lithuania and Spain). The largest seizures were reported by Spain, where 259 kg of α-PVP was seized at Barcelona airport in one day, in April 2015.

Three Member States reported seizures of tablets containing α-PVP: the Czech Republic (160 tablets sold as MDMA, see Figure 4 of the Annex), Hungary (454 tablets in addition to the seizure conducted at the tableting site mentioned above) and Romania (two tablets). Packages containing α-PVP were seized in Slovakia (see Figure 5 of the Annex) and in Spain. In 2015 Spain also reported a case with two jelly gums containing α-PVP.

Croatia reported that α-PVP is imported for personal use by young people, especially foreign tourists, who travel to Croatia for music festivals and other similar activities.

The level of trafficking

Information related to trafficking routes was provided by seven Member States (Bulgaria, France, Germany, Latvia, Luxembourg, Slovakia and Spain). See Table 1 for information on trafficking routes.

Poland is indicated as a country of origin in one case, which may be linked to the synthetic drug production facilities dismantled by the Polish authorities. In 10 of the 11 cases where trafficking route information was provided, China was noted as the source country for α-PVP. Germany and France would appear to be transit points in the EU, possibly due to the location of air-freight hubs. The large quantities of α-PVP seized in or en route to Spain suggest that Spain may be an important point in the distribution chain of α-PVP.

TABLE 1

Summary of α-PVP trafficking routes. The asterisk indicates the place where the seizure was made

Origin	Transit	Destination	Comment
Poland	Slovakia*	Czech Republic	Weight not specified
China	Luxembourg*	Germany	54 g in postal parcel
China	–	Bulgaria*	2 g in postal parcel
China	–	Latvia*	Postal parcel (weight not specified)
China	France*	Spain	50 kg in transit at Roissy Airport, Paris
China	France*	Spain	1 kg in transit at Roissy Airport, Paris
China	Germany*	Austria	248 g in transit at Frankfurt Airport
China	Germany*	United Kingdom	171 g in transit at Munich Airport
China	Germany*	Sweden	10 g in transit at Frankfurt Airport
China	–	Germany*	4 g seized at Frankfurt Airport
China	–	Spain*	259 kg seized at Barcelona Airport

Romania reported that the main source country for importation of α-PVP is China, mainly via postal mail parcels.

The Czech Republic reported that α-PVP is imported using postal mail shipments and courier services.

3.2.2. Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States, Turkey and Norway. Of these, 26 Member States ([14]), Turkey and Norway reported detections of α-PVP ([15]).

According to reports to the EMCDDA, α-PVP has been present on the EU drugs market since 2011, although information published in the literature indicates that it was detected in Germany in 2005 (Westphal et al., 2005).

([13]) These figures do not include α-PVP seized by the Polish authorities on the two illicit drug production sites mentioned above.

([14]) All Member States with the exception of Bulgaria and Romania. Note that the Bulgarian and Romanian Europol National Units reported the detection of α-PVP to Europol (section 3.2.1).

([15]) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those collected from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

Seizures

Twenty-six Member States (all Member States with the exception of Bulgaria and Romania), Norway and Turkey reported seizures ([16]) of α-PVP to the EMCDDA.

Overall, in excess of 5 200 seizures have been reported, with eight countries reporting more than 100 seizures each: the United Kingdom (1 094), Poland (938), Finland (787), Slovakia (502), Sweden (451), Ireland (336), Hungary (313) and Turkey (256).

In 2011, after the first seizure of α-PVP was reported by France (see section 3.6), at least 38 additional seizures were reported in 17 countries: Austria, Belgium, the Czech Republic, Denmark, Estonia, Germany, Greece, Finland, Hungary, Ireland, Italy, Lithuania, Spain, Sweden, Slovakia, Turkey and the United Kingdom ([17]).

α-PVP has typically been seized in powder form (reported by all countries where α-PVP was detected). Over 750 kg of powder has been seized in total, with eight countries reporting seizures over 10 kg: Spain (312 kg), the Netherlands (140 kg), France (81 kg), Ireland (63 kg), the United Kingdom (62 kg), Hungary (24 kg), Finland (24 kg) and Poland (17 kg). Of these, the biggest single seizure occurred on 9 April 2015 in Spain, when the Spanish National Customs Surveillance Service seized almost 260 kg of α-PVP in 13 containers at Barcelona Airport, delivered from China. Two other single significant seizures also took place in Spain in 2015, with over 20 kg and 5 kg of powder seized.

Thirteen countries reported seizures of tablets (Slovakia, Hungary, Finland, the Czech Republic, Latvia, Turkey, Sweden, Norway, Spain, Poland, Belgium, Italy and France) ([18]) amounting to over 12 400 units. Of those, three countries reported seizures of over 1 000 tablets: Slovakia (7 157), Hungary (3 768) and Finland (1 136). The United Kingdom reported three seizures of powder-filled capsules.

Seven countries (Lithuania, the United Kingdom, Hungary, Slovakia, France, Sweden and Poland) ([19]) have reported small seizures (< 150 g) of vegetable material containing α-PVP, sometimes also containing synthetic cannabinoids. Three countries (Finland, Sweden and Poland) ([20]) have seized small quantities (< 150 ml) of liquids containing α-PVP. Austria reported a single seizure of 68 paper doses (also known as a 'blotters') containing DOC ([21]) and α-PVP, and Finland reported 16 seizures amounting to over 700 units of tablets/blotters. Spain reported the seizure of two jelly gums in which α-PVP, amphetamine and caffeine were detected.

In around 35 % of the detections α-PVP was found in combination with other substances, including other cathinones (mainly MEC ([22]), MMC ([23]), pentedrone, MDPBP ([24]), ethylcathinone and MDPV), synthetic cannabinoids and a range of other new psychoactive substances (such as MPA ([25]), 5-MeO-MIPT ([26]), AMT ([27]) and 2-DPMP ([28])), substances that are internationally controlled and/or controlled at EU level (ketamine, PMMA ([29]), methoxetamine, MDMA, cocaine, amphetamine and heroin), benzodiazepines (etizolam, flubromazolam), and substances typically used as cutting agents and/or diluents such as benzocaine, lidocaine and caffeine.

Information on purity, which was available from 16 seizures, ranged from 23 % (two seizures) to over 95 % (eight seizures).

Several countries reported α-PVP in powders contained in branded 'legal high' products with names such as: 'Fire Ball', 'Ultra Violet Exclusive', 'Pure NRG', 'Max', 'Total speed', 'Energy-3 (NRG-3)', 'Guarana Coco jumbo', 'Cherry Coco jumbo', 'Sensation', 'Iloveparade', 'Speedway' and 'A-1 PUP'. A full list of names is provided in section 3.1. In addition, the substance was found in two products branded 'Green Speed' and 'Knock out' containing plant material. Tablets containing α-PVP had the following markings: 'Lacoste', 'Playboy', 'STADA1' and 'Homer Simpson' (information available for seven seizures). These tablet findings may suggest that α-PVP is being sold as ecstasy. There were also unmarked tablets reported in a variety of colours. Some of these products were obtained through online shops (www.euphoriashop.sk, www.hypnotic.sk).

Collected samples

Eleven countries reported 50 samples collected from users or purchased on the Internet that contained α-PVP ([30]) (Austria, Belgium, the Czech Republic, Denmark, France, Hungary, the Netherlands, Slovenia, Spain, Turkey and the United Kingdom).

Three countries reported powders sold as MDMA: Austria and Spain (one case each) and the United Kingdom (seven). In France, powders, capsules containing powder and pellets were sold either as methamphetamine, pentedrone and

([16]) Many 'seizures' relate to individual case-level data, however, some data provided to the EMCDDA are aggregated at the country level. Some of the data from the United Kingdom are reported as 'records', where several records may come from the same case. Data are drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (EU EWS progress and final reports) and from individual Reporting forms submitted on an ad hoc basis.
([17]) Countries are listed in alphabetical order.
([18]) Countries are listed in decreasing order of number of tablets seized.
([19]) Countries are listed in decreasing order of quantity of plant material seized.
([20]) Countries are listed in decreasing order of quantity of liquids seized.
([21]) 2,5-Dimethoxy-4-chloroamphetamine.
([22]) Methylethcathinone (isomer not specified).
([23]) Methylmethcathinone (isomer not specified).
([24]) 3',4'-Methylenedioxy-α-pyrrolidinobutyrophenone.
([25]) Methylthienylpropamine.
([26]) 5-Methoxy-N-methyl-N-isopropyltryptamine.
([27]) α-methyltryptamine.
([28]) 2-(Diphenylmethyl)piperidine.
([29]) *para*-Methoxymethamphetamine.
([30]) Countries are listed in alphabetical order.

ethylphenidate or as branded 'legal high' products: 'NRG-3' (four samples), 'PV-11' (two) and 'Ivory Wave Extreme' (two). In the United Kingdom a sample sold as 'NRG-3' was also reported. In Spain a powder containing the substance was sold as ketamine in one case and a yellow jelly was collected from a user in another case. For more information on 'legal high' products that have been reported to contain α-PVP see section 3.1.

Biological samples

Eight Member States (Finland, France, Hungary, Ireland, Italy, Poland, Sweden and the United Kingdom) and Norway reported a total of 1 746 detections where α-PVP was analytically confirmed in biological samples.

These related to: 126 serious adverse events (105 deaths and 21 acute intoxications); 393 cases related to patients undergoing drug treatment; 389 cases of persons suspected of driving under the influence of drugs; and 590 cases where detection was made by the police in persons suspected of having consumed drugs, or committed minor offences or crimes. A further 105 cases were detected through criminal justice drug screening programmes and the remaining 143 were reported by the STRIDA project in respect to acute intoxications associated with new psychoactive substances.

In Finland α-PVP was analytically detected in 335 cases (including 37 deaths); in France six cases (two deaths and four non-fatal intoxications); in Hungary 352 cases (including 19 deaths); in Ireland 116 detections (including four deaths); in Italy one case consisting of a non-fatal intoxication; in Poland there were 34 detections (including 21 deaths and one non-fatal intoxications); in Sweden 883 cases (including 16 deaths, 14 non-fatal intoxications and one acute intoxication where the outcome is not known); in the United Kingdom eight detections (including six deaths); and finally in Norway 11 cases (all consisting of persons suspected of driving under the influence of drugs).

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

Four Member States (Hungary, Latvia, Romania and Spain) provided information in relation to the involvement of organised crime in the manufacture or trafficking of α-PVP.

According to Hungarian authorities there are no 'classical' organised crime groups involved in the manufacture or trafficking of α-PVP.

Latvian authorities reported that since 2014 a new trend has been observed in relation to the market in new psychoactive substances. A Latvian organised crime group was involved in the mixing and posterior distribution of new psychoactive substances with plant material.

Romania reported that criminal groups are not involved in the trafficking of α-PVP.

Spain reported that they do not have any intelligence about α-PVP being linked to criminal groups.

Money laundering aspects

No information was received on money laundering in connection with the production and/or trafficking of α-PVP.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of α-PVP.

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

3.4.1. Serious adverse events reported to the EMCDDA

Case-level data for 140 serious adverse events ([31]) associated with α-PVP were reported to the EMCDDA by nine Member States (Finland, France, Germany, Hungary, Ireland, Italy, Poland, Sweden and the United Kingdom). These cases comprised 34 acute intoxications (32 non-fatal intoxications and two intoxications where the outcome was unknown ([32]))

([31]) Serious adverse event means any adverse event, whether analytically confirmed or not, that is associated with the consumption of a new psychoactive substance in a human that: results in death; is life-threatening; requires intensive treatment in an emergency room and/or requires hospitalisation; results in persistent or significant disability or incapacity; results in substance dependency or substance abuse; consists of a congenital anomaly or birth defect; or is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. An example of such events is: convulsions that do not result in hospitalisation.

([32]) I.e. in two cases it was not known if the acute intoxication related to a non-fatal or fatal intoxication.

and 106 deaths ([33]). An overview of these data is presented below.

Acute intoxications

Case-level data for 34 acute intoxications associated with α-PVP were reported by six Member States: France (10 cases), Germany (two), Ireland (five), Italy (one), Poland (one) and Sweden (15). Thirty-two of the 34 cases were classified as non-fatal intoxications; in the remaining two cases the outcome of the intoxication was unknown (Germany, one case; Sweden, one case).

α-PVP was analytically confirmed in 21 of the 34 cases (section 3.2.2): France (four cases), Italy (one), Poland (one) and Sweden (15). In the remaining 13 cases α-PVP was not analytically confirmed: France (six cases), Germany (two) and Ireland (five); these latter cases have not been analysed further. Thus the overview below is based on data from the 21 analytically confirmed cases.

It is important to note that case-level data on intoxications in Sweden are limited to a subset of cases where:

1. α-PVP was the sole substance that was analytically identified (eight cases); or,
2. α-PVP and ethanol were the only substances that were analytically identified (five cases); or,
3. α-PVP and benzodiazepines (and metabolites of benzodiazepines) were the only substances that were analytically identified (one case); or,
4. α-PVP and benzodiazepines (and metabolites of benzodiazepines) and ethanol were the only substances that were analytically identified (one case).

Overview of the analytically confirmed acute intoxications

The overview below provides some of the characteristics for the 21 analytically confirmed acute intoxications associated with α-PVP. Of these, 20 cases relate to non-fatal intoxications and one case relates to an intoxication where the outcome is unknown.

Demographics

Of the 21 analytically confirmed acute intoxications, 19 were male and two were female. The mean age of the male cases was 33.2 years (n=18; median 28.5 years); the two female cases were aged 23 and 25 years (n=2).

Substances analytically identified

Of the 21 analytically confirmed acute intoxications:

- in eight cases reported by Sweden, α-PVP was the only substance that was identified (biological matrices unknown);
- in five cases reported by Sweden, α-PVP and ethanol were the only substances that were identified (biological matrices not reported);
- in one case reported by Sweden, α-PVP and benzodiazepines (and metabolites of benzodiazepines) were the only substances that were identified (biological matrices not reported);
- in one case reported by Sweden, α-PVP and benzodiazepines (and metabolites of benzodiazepines) and ethanol were the only substances that were identified (biological matrices not reported);
- in one case reported by France, α-PVP was the only substance that was identified in blood; urine drug screening identified 'cannabis';
- in one case reported by France, it was not known if any other substances besides α-PVP were identified (biological matrices not reported);
- in two cases reported by France, α-PVP was the only substance that was identified (biological matrices not reported);
- in one case reported by Italy, α-PVP and THC were analytically identified in urine; and,
- in one case reported by Poland, α-PVP was the only substance that was analytically identified in blood; pentedrone and alcohol were identified in urine.

Adverse symptoms and signs

Information on adverse symptoms and signs ([34]) reported from the 21 analytically confirmed acute intoxications were generally consistent with sympathomimetic toxicity.

Adverse symptoms and signs were reported for each case. They included: tachycardia (15 cases); mydriasis (eight); hallucinations (six); agitation (five) or anxiety (two); tremor (five) or fasciculation (one) or tetany (one); hypertension (four); diaphoresis (four); hyperthermia (four); restlessness (three); chest pain (two); convulsions (two) or seizures (two); reduced consciousness (two); somnolence (two); numbness (two); distorted perception (one) or temporal/spatial disorientation (two); rhabdomyolysis (two); impaired liver function (one); impaired coagulation (one); difficulty in talking (one); paranoia (one); hyperventilation (one); hypoventilation (one); respiratory distress (one); muscular symptoms (one); and malaise (one).

([33]) Cases that were believed by the EMCDDA to be duplicates (six deaths and three non-fatal intoxications) were not included in this total.

([34]) Adverse sign includes an abnormal laboratory finding.

Seriousness of the intoxications

Of the 21 analytically confirmed acute intoxications:

1. in five cases the seriousness of the intoxication was classified as life-threatening, requiring treatment in hospital. Of these cases: in three cases α-PVP was the only substance that was identified; in one case α-PVP and benzodiazepines (and metabolites of benzodiazepines) were the only substances identified; in one case α-PVP and benzodiazepines (and metabolites of benzodiazepines) and ethanol were the only substances identified;
2. in 11 cases the seriousness of the intoxication was classified as non-life-threatening but required treatment in hospital;
3. in one case the seriousness of the intoxication was classified as involving persistent or significant disability or incapacity;
4. in two cases the seriousness of the intoxication was classified as 'moderate' using an alternate national classification system ('moderate' is synonymous with pronounced or prolonged symptoms or signs); and,
5. in two cases the seriousness of the intoxication was not reported.

Outcome of the non-fatal intoxications

Of the 20 analytically confirmed non-fatal intoxications:

1. in 12 cases the outcome was classified as recovered/resolved;
2. in two cases the outcome was classified as recovering/resolving;
3. in four cases the outcome was classified not known; and,
4. in two cases the outcome was not reported.

Route of administration

Of the 21 analytically confirmed acute intoxications:

1. in six cases the route of administration was reported as snorting (nasal insufflation);
2. in three cases the route of administration was reported as injection. In one of these cases it was reported that the substance was injected intravenously. The specific route of injection for the other three cases is not known;
3. in two cases the route of administration was reported as oral administration;
4. in one case the route of administration was reported as oral administration and injection; the specific route of injection was not reported; and,
5. in nine cases the route of administration was not known.

Name of the substance/product used

Of the 21 analytically confirmed acute intoxications:

1. in seven cases the name of the substance/product reported to be consumed was 'MDPV' ([35]);
2. in three cases the name of the substance/product reported to be consumed was 'alpha-PHP';
3. in two cases the name of the substance/product reported to be consumed was 'NRG3' or 'energy 3';
4. in one case the name of the substance/product reported to be consumed was 'crystal';
5. in one case the name of the substance/product reported to be consumed was 'penta' or 'pentadrone';
6. in one case the name of the substance/product reported to be consumed was 'APP';
7. in one case the name of the substance/product reported to be consumed was '3-MEC';
8. in one case the name of the substance/product reported to be consumed was 'PV8'; and,
9. in four cases the name of the substance/product reported to be consumed was not known.

Source

Information on where the patients had sourced the α-PVP was available in four cases: in three cases it was sourced from the Internet; in one case it was sourced from the Internet and a drug dealer.

Physical form

Information on the physical form of α-PVP used by the patients was available in four cases: all four used a powder (other characteristics of the powder were not reported).

Amount or dose administered

Information on the amount of substance administered by the patients was only available in two cases:

- in one case the amount or dose administered was reported as '15–20 mg' (oral);
- in one case the amount or dose administered was reported as 'ca. 330 mg' (route not known).

Deaths

Case-level data for 106 deaths associated with the use of α-PVP were reported by seven Member States: Finland (37 cases), France (two), Hungary (19), Ireland (five), Poland (21), Sweden (16) and the United Kingdom (six).

([35]) This includes one case where the substance consumed was reported as 'MDPVP', which is a synonym of MDPV.

α-PVP was analytically confirmed in 105 deaths. One death reported by Ireland was excluded from further analysis as it was not analytically confirmed. In addition, four deaths reported by Poland were also excluded from further analysis, as, beyond the fact that they were analytically confirmed, no further information on the cases is currently available. Thus the overview below is based on data from 101 analytically confirmed deaths.

Demographics

Of the 101 deaths, 81 (80.2 %) were male and 20 (19.8 %) were female. The mean age of the male decedents was 36.3 years (n=66; median 33 years); the mean age of the female decedents was 35.4 years (n=20; median 34.5 years).

Number of deaths by year

Seventeen deaths occurred in 2012; 24 occurred in 2013; 43 in 2014; and 15 in 2015. The year of death was not known for two of the deaths.

Cause of death

Preliminary review of the cause of death reported for the 101 deaths suggests that:

- in 23 cases α-PVP was reported as the cause of death (three cases) or was reported as a contributing factor (20);
- in 26 cases the cause of death was reported as 'not known' — in some of these cases the investigation is ongoing;
- in four cases the cause of death was reported as due to drug intoxication (no further details available);
- further analysis of the data are required for the remaining 48 cases in order to determine what role, if any, α-PVP played in the deaths.

3.4.2. Serious adverse events identified in open source information

Case-level data for 33 serious adverse events associated with α-PVP were identified from searches of open source information (OSI) (Eiden et al., 2013; Dragogna et al., 2014; Hasegawa et al., 2014; Marinetti and Antonides, 2013; Minakata et al., 2014; Namera et al., 2013; Namera et al., 2014; Richards-Waugh et al., 2013; Saito et al., 2013; Sellors et al., 2014; Shanks et al., 2013; Sykutera et al., 2015; Yoshida et al., 2014) ([36]). These comprised three non-fatal intoxications and 30 deaths. One of the deaths is believed to be reported in two separate reports and so the total number of deaths is believed to be 29. Of these cases, one non-fatal intoxication (Eiden et al., 2013) and two of the deaths (Eiden et al., 2013; Sykutera et al., 2015) were also reported to the EMCDDA by the Member States and are excluded from the analysis below. Details of the two non-fatal intoxications are provided in Dragogna et al., 2014 and Namera et al., 2014. A total of 27 deaths that occurred outside the EU were identified.

Briefly, a cause of death has been reported for 13 of the 27 deaths that occurred outside the EU:

- in seven cases α-PVP was considered the cause of death or a contributing factor (no other substances were analytically identified in four of these cases). It is important to note that in two of the seven cases the deaths occurred following responses to the aggressive behaviour shown by the decedents. In one case the confrontation resulted in the decedent being shot by the police, in one other case the confrontation led to prolonged restraint, which was reported to have contributed to the death;
- in four cases polydrug intoxication or overdose where another substance was considered the primary cause of death was reported;
- in one case the cause of death was related to a shooting by police; and,
- in one case the cause of death was related to hanging.

3.4.3. Pharmacology

Mode of action

Overview

Published data on the pharmacological mode of action of α-PVP appear to be limited to eight non-clinical studies ([37]). All but one of these studies (Meltzer et al., 2006) ([38]) were undertaken as a result of α-PVP emerging on the drug market; notably, seven of them have been published since 2014 (Aarde et al., 2015; Gatch et al., 2015; Kaizaki et al., 2014; Marusich et al., 2014; Naylor et al., 2015; Rickli et al., 2015; Watterson et al., 2014a).

Taken together, the data from these studies are suggestive that α-PVP is likely to be a potent psychostimulant in humans, an observation that is consistent both with reports of serious adverse events and with subjective experiential reports from

([36]) In addition, Papsun (2015) reports 28 postmortem cases where α-PVP was analytically identified. No further details are available on these cases.

([37]) Non-clinical study means a scientific study that is conducted either in silico, in vitro, or *in vivo* in animals.

([38]) In respect to data on pharmacology of α-PVP, the study by Meltzer et al., 2006 was limited to investigating the *in vitro* characteristics as an inhibitor of the dopamine (DAT), norepinephrine (NET), and serotonin (SERT) transporters.

TABLE 2

Effects of MDPV, α-PVP, α-PBP, α-PPP, cocaine, and amphetamine on inhibition of [^{3}H] transmitter uptake at DAT, NET and SERT in rat brain synaptosomes. Data are expressed as nM concentrations (mean±SD) for n=3 experiments performed in triplicate

Test drug	[^{3}H]Dopamine uptake, IC_{50} at DAT (nM)	[^{3}H]Norepinephrine uptake, IC_{50} at NET (nM)	[^{3}H]Serotonin uptake, IC_{50} at SERT (nM)	DAT/SERT ratio
MDPV	4.1±0.6	25.9±5.6	3305±485	806
α-PVP	12.8±1.2	14.2±1.2	>10 000	>781
α –PBP	63.3±5.7	91.5±12.8	>10 000	>159
α –PPP	196.7±9.9	444.7±39.2	>10 000	>51
Cocaine ([a])	211±19	292±34	313±17	1.5
Amphetamine ([a])	93±17	67±16	3418±314	37

Note:
([a]) Data for cocaine and amphetamine were derived from Baumann et al., 2013. Reproduced from Marusich et al., 2014.

users on discussion forums. The data are also suggestive of abuse liability and dependence potential in humans.

Further research is required in order to have a more detailed understanding of the mode and mechanism of action of α-PVP (including its two enantiomers), including abuse liability and dependence potential, and how this relates to humans. This should also include the study of the pharmacological effects of α-PVP on other neurotransmitter systems and the pharmacological effects of the metabolites of α-PVP.

In vitro data

Data from *in vitro* transporter assays by Marusich et al., 2014 showed that α-PVP was a potent inhibitor of dopamine uptake at the dopamine transporter (DAT) (IC_{50} 12.8±1.2) and norepinephrine uptake at the norepinephrine transporter (NET) (IC_{50} 14.2±1.2), whereas it was a much weaker inhibitor of serotonin uptake at the serotonin transporter (SERT) (IC_{50} >10,000 nM) (Table 2). These data confirmed the findings reported by Meltzer et al., 2006 and Rickli et al., 2015. Interestingly, α-PVP appeared to share similar effects with 3,4-methylenedioxypyrovalerone (MDPV).

Overall, the data from the transporter assays show that:

1. α-PVP is a potent and selective inhibitor of the catecholamine uptake at DAT and NET;
2. α-PVP does not act as a transporter substrate, i.e. it does not cause neurotransmitter release;
3. α-PVP is a more potent inhibitor of DAT and NET than the classical stimulants cocaine and amphetamine; and,
4. α-PVP and MDPV both exhibit catecholamine-transporter selective activity and similar potencies in respect to inhibition of DAT and NET.

Animal data

Data from locomotor studies in mice conducted by Marusich et al., 2014 showed that α-PVP at 3.0 and 10.0 mg/kg given by intraperitoneal injection (IP) produced significant increases in locomotion compared to saline over a 60 minute test session; a dose of 1 mg/kg IP only produced a significant increases in locomotion between 20–50 minutes of the test session. While α-PVP was less potent than MDPV in stimulating locomotion, the two substances showed similar efficacy, as a higher dose of α-PVP was able to increase locomotion to at least the same level. Both α-PVP and MDPV were more potent at stimulating locomotion than cocaine ([39]).

Data from Marusich et al., 2014 also showed that pretreatment with 0.03 mg/kg IP ([40]) of the dopamine D1 receptor antagonist *SCH23390* significantly decreased locomotor activity in mice when given at a 3 mg/kg dose of α-PVP. This finding suggests that the D1 receptor may mediate at least some of the locomotor effects of α-PVP consistent with previous findings published by Kaizaki et al., 2014. Data from previous studies have shown that the activation of the D1 receptor is implicated in the psychomotor and/or behavioural effects of stimulants such as cocaine, amphetamine, cathinone, and mephedrone (Marusich et al., 2014). Data from locomotor studies in rats conducted by Aarde et al., 2015 also show that, compared to saline, peak locomotor responses to α-PVP occurred at 1.0 mg/kg IP and lasted for ~2 hours; similar findings were also reported for MDPV. Data from a functional observational battery in mice conducted by Marusich et al., 2014 showed that α-PVP produced psychostimulant effects similar to the classical stimulants cocaine and methamphetamine. In addition, α-PVP

([39]) Data for cocaine were derived from Baumann et al., 2013.
([40]) Intraperitoneal.

also induced exploration and flattened body posture. Studies in mice reported by Gatch et al., 2015 confirmed that α-PVP induced stimulant locomotor activity, conditioned place preference (inverted U-shaped dose effects), and fully substituted for discriminative stimulus effects in rats trained to discriminate between cocaine, methamphetamine and saline. An additional drug discrimination study confirmed that α-PVP fully substituted for methamphetamine (Naylor et al., 2015).

Metabolism

Data on the metabolism of α-PVP are presented in Hasegawa et al., 2014; Namera et al., 2014; Negreira et al., 2015; Sauer et al., 2009; Shima et al., 2014; Uralets et al., 2014; and Tyrkkö et al., 2013.

No studies were identified that have examined the pharmacological effects of the metabolites of α-PVP.

Abuse liability and dependence potential

Data on the dependence potential and abuse liability of α-PVP are limited to non-clinical studies.

Data from a discriminative-stimulus effect study conducted by Naylor et al., 2015 showed that in rats trained to discriminate 1.0 mg/kg of the classical stimulant methamphetamine from saline, α-PVP fully substituted for methamphetamine. α-PVP (ED_{50}=0.7 mg/kg) was approximately 2.5 times less potent than methamphetamine (ED_{50}=0.3 mg/kg) and 4.5 times more potent than cocaine (ED_{50} 3.3 mg/kg). These data were consistent with α-PVP producing behavioural effects similar to those of methamphetamine.

Data from a study conducted by Watterson *et al.*, 2014a that examined intracranial self-stimulation (ICSS) thresholds in rats showed that α-PVP at 1 mg/kg produced a significant maximal reduction in ICSS thresholds (~19 %) similar to methamphetamine (1 mg/kg ~20 %) and MDPV (0.5 mg/kg ~18 %) ([41]). It was suggested that α-PVP might show abuse liability in humans. Studies in mice reported by Gatch et al., 2015 confirmed that α-PVP exhibited induced conditioned place preference (inverted U-shaped dose effects), and that it fully substituted for discriminative stimulus effects in rats trained to discriminate between cocaine, methamphetamine and saline. Data from a study conducted by Aarde et al., 2015 that examined intravenous self-administration of α-PVP in rats showed that it was readily self-administered, and equally potent and effective to MDPV, which suggested potential for abuse liability in humans.

([41]) Data on MDPV from Watterson et al., 2014b.

3.4.4. Toxicology

No studies were identified that have examined the toxicology of α-PVP including its enantiomers; no studies were identified that have examined the toxicology of the metabolites of α-PVP. Data from serious adverse events associated with α-PVP are discussed above (see section 3.4.1).

3.4.5. Characteristics of users

Data on the characteristics of users of α-PVP are limited.

Data reported by the Member States ([42]) and identified from open source information (e.g. Sundström et al., 2015 and Simonsen et al., 2015) suggests that α-PVP is used by recreational and high-risk drug users, including those who inject drugs.

It is important to note that it is not possible to confirm the specific substance(s) used from self-reported user experiences, nor the purity, dose/amount, etc. Analyses of new psychoactive substances or products containing them that are sold on the drug market have shown that the composition can differ both from that claimed by the retailer and over geographical areas and time. In addition, the information provided on user websites may not necessarily be representative of users of α-PVP in general and should be regarded as illustrative only.

Route of administration, dose, drug regimens and settings of use

Routes of administration include snorting, smoking/inhalation, injection, oral (ingestion), sub-lingual, rectal and mixed routes (oral and injection).

Injection of α-PVP was stated in four of the acute intoxications reported by the Member States. Injection was also self-reported as a route of administration by the Finnish Drug Users' Union, three users presenting at a French drug testing unit, and by an undisclosed number of users in online forums. Data from France and Finland related to analysis of discussion forums suggest that intravenous injection was a common route of injection.

([42]) Including data from: serious adverse events reported to the EMCDDA, where details of the set or setting of administration were known; questionnaire responses from six users presenting at a drug testing organisation (SINTES, France); an online questionnaire completed by 1 385 people in Poland (I-Trend); reports from representatives of the Finnish Drug Users' Union (FDUU); monitoring of self-reported user experiences posted in Internet discussion forums. This information was captured by several countries, in their native tongue. Briefly, in France, data was obtained from the systematic monitoring of three forums (902 discussions threads, four of which specifically related to i-PVP) and from a special project in French- and English-speaking forums (eight forums, two discussion threads on α-PVP); for Finland, two online discussion forums were monitored (www.paihdelinkki.fi and psyvault.net); in Italy two cases were reported from discussion threads (in Italian, www.psychonaut.com).

Data from Sundström et al., 2015 and Simonsen et al., 2015 also suggest that α-PVP is being used by high-risk drug users. Simonsen et al., 2015 have shown that, in 2012, in eight of 162 deaths in Finland (4.9 %) and in one of 255 deaths in Sweden (0.4 %) α-PVP was analytically identified. Sundström et al., 2015 have shown that α-PVP was analytically identified in 13 out of 34 (38 %) attendees of a drug treatment centre specialising in supporting intravenous drug users. Data reported by Ireland suggest that injection under the skin ('skin-popping') might also be a feature since a substance called 'Snow Blow', suspected to contain α-PVP, has been used in this manner. This suggestion is based on α-PVP analytical findings in high-risk drug users reporting that they use 'Snow Blow'.

Snorting was the route used in seven of the serious adverse events reported to the EMCDDA and is the most frequently quoted route of administration in online discussion forums in France and Poland (89 % of 36 responders to the Polish I-Trend survey). Some users believe that smoking α-PVP (by vapourisation or using a pipe) increases 'side effects' (I-Trend, France).

Information from serious adverse events suggests that α-PVP may be used as part of polydrug regimens (data not shown).

Dose, re-dosing

The available data do not allow the identification of common/typical doses of α-PVP.

France reported a dose of 20–30 mg reported by two drug users that was injected intravenously. Data on the dose of α-PVP taken were available in two acute intoxications reported by the Member States. In one case a dose of 15–20 mg was orally taken, and in another case 330 mg was taken (route unknown).

Users in a Finnish discussion forum report re-dosing after 30–120 minutes, since 'the effects don›t last very long', being sometimes as short-lived as 15 minutes, 'so one has to take a new dose shortly after the previous one'. Interestingly, a user in an Italian Internet forum warns against re-dosing, suggesting that doing it two or three times in a short period of time brings about impulsive behaviour which results in continuous re-dosing ('you can no longer stop'). Survey data from the Polish I-Trend project found that 17 % of 36 α-PVP users (n=6) reported a 'strong craving to use more' α-PVP after the initial dose.

Settings of use

There is limited data on the settings of use for α-PVP.

Survey data from the Polish I-Trend project found that, out of 36 α-PVP users, 53 % took it at home (n=19) and 75 % with friends (n=27). Data from serious adverse events are suggestive of α-PVP being used in a range of settings including at home (seven deaths, Hungary and the United Kingdom) and in party contexts (two deaths, France and Hungary).

Subjective effects

Data on the subjective effects of α-PVP are limited.

Survey data from the Polish I-Trend project found that, out of 36 α-PVP users, the substance is used to 'get high' (72 %, n=19) and 'socialise/bond with others' (66 %, n=24). 'Euphoria' and 'increased libido' are mentioned in discussion forums (Finland, France).

There are several reports of adverse effects occurring following self-reported consumption of α-PVP. Survey data from the Polish I-Trend project found that out of 36 α-PVP users, 53 % (n=19) reports of negative effects. Negative effects can include paranoia, intensive hallucinations, aggression and insomnia. According to the respondents, these adverse effects can persist for several days.

Availability, supply, price

Online vendors

A structured search by the EMCDDA of online vendors ([43]) of α-PVP on the surface web ([44]) identified 65 vendors that appeared to be based in, and/or claim to have a presence in, the EU (n=28 sites), the United States (n=13 sites), China (n=32 sites), India (n=3 sites) or Russia (n=6 sites).

Seventeen of the sites only provided quantities and prices for α-PVP on application. Eleven of the sites listed prices but did not specify quantities. The remaining 37 sites listed quantities and prices. Briefly:

- On these sites α-PVP was typically sold as a 'research chemical'.
- The minimum quantity offered was 1 g (n=16 sites) with a mean price of EUR 17.50 (EUR 12–24).
- The maximum quantity offered was 10 kg (n=4 sites) with a mean price of EUR 17 000.
- Most of the 37 sites offered quantities ranging from 1 g (n=16 sites) to 1 kg (n=21 sites).
- The mean price for 1 g was EUR 17.50.

([43]) This includes vendors that appear to be consumer-orientated as well as vendors, for example on business-to-business sites, that appear to be manufacturers and/or wholesalers. It excludes those selling α-PVP through online classified advertisements, social media and user websites.

([44]) The search of online vendors of α-PVP was performed on google.co.uk using three search strings: 'buy a-PVP', 'buy alpha-PVP' and 'buy pyrrolidinopentiophenone'. For each of the search strings the first 100 results were recorded and the sites reviewed. The results of the three searches partially overlapped; duplicate sites were removed from the analysis. Each identified vendor site was then scored for information on warehouse location, quantities and prices, and substance marketing.

- The mean price for 10 g (n=26 sites) was EUR 134.50 (EUR 63–180) (EUR 13.45/g).
- The mean price for 100 g (n=33 sites) was EUR 594.50 (EUR 270–1 200) (EUR 5.94/g).
- The mean price for 1 kg (n=30 sites) was EUR 2 490 (EUR 1 260–3 600) (EUR 2.49/g).
- The mean price for 5 kg (n=9 sites) was EUR 10 500 (EUR 4 545–12 000) (EUR 2.10/g).
- The mean price for 10 kg (n=4 sites) was EUR 17 000 (EUR 6 705–23 000) (EUR 1.70/g).

Prices were listed in Euros (EUR) on 14 sites, in United States Dollars (USD) on 22 sites, and in Great British Pounds (GBP) on one site ([45]).

Other information

Information reported by France suggests that *α-PVP* may not be as easily obtainable in France 'by name' as it might have been during 2013 when sales were made through Internet retailers that were accessible only by invitation.

In France it was reported that *α-PVP was sold as MDMA, cocaine and amphetamine. In Ireland it is sold as cocaine or methamphetamine. It has also* been reported as being sold by its own name.

France provided detailed information on the source and price of some samples collected from users. Reported prices per capsule were EUR 15 and EUR 20, and between EUR 20–80 per gram of powder (for more details see sections 3.4.2 and 3.8.2). In most of the cases the products had been originally sourced from the Internet by the user, a dealer or a friend.

Prevalence of use

No prevalence surveys were identified that have examined the use of α-PVP in the general population.

Data reported from the Polish I-Trend online questionnaire indicate that, among 1 074 respondents, α-PVP was the most recently used new psychoactive substance to be used by 3.4 % (n=36) of the respondents (36 users, n=1 074). Of these, 39 % had taken it at least 20 times in the previous year.

One study has analysed the frequency of α-PVP analytical findings in deaths of high-risk drug users in Nordic countries (Denmark, Finland, Norway, Sweden and Iceland) in 2012, and found it to be 4.9 % in Finland and 0.4 % in Sweden (Simonsen et al., 2015).

([45]) Prices listed in USD were converted to EUR according to the Google exchange rate on 27 July 2015 (USD 1 = EUR 0.90). Prices listed in GBP were converted to EUR according to the Google exchange rate on 28 July 2015 (GBP 1 = EUR 1.41).

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

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. On 27 June 2015 the World Health Organization informed the EMCDDA that α-PVP is currently not under assessment and has not been under assessment by the United Nations system.

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

The first official notification of α-PVP to the EMCDDA–Europol dates from April 2011, from the French National Focal Point. The Reporting Form details a seizure of 5 114 g of white powder, also containing pentedrone, that was seized on 22 February 2011 by the French Customs authorities at Charles de Gaulle Airport in Paris. The identification and analytical characterisation was based on GC-MS ([46]) at the SCL laboratory of Paris ([47]).

α-PVP was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the EU Early Warning System and a profile of the substance was created on the European Database on New Drugs (EDND). Since then, analytical details and other information have been exchanged between the EMCDDA, Europol and the Member States on an *ad hoc* basis; the European Commission and the EMA have been kept duly informed.

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

Fifteen Member States (Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Slovenia, Sweden and the United Kingdom), Turkey and Norway reported that α-PVP is controlled under drug control legislation.

([46]) Gas chromatography-mass spectrometry.
([47]) Service commun des laboratoires (SCL).

- In Estonia α-PVP was listed in Regulation No. 73 of the Minister of Social Affairs of 18 May 2005 on 2 June 2014.
- In Finland α-PVP was listed in the Narcotics Act 373 of 2008 on 30 December 2013.
- In France α-PVP was added to the controlled narcotic substance list on 2 August 2012.
- In Germany α-PVP was placed under schedule II (narcotics eligible for trade but not for medical prescription) of the Narcotic Substance Act, effective as of 17 July 2013.
- In Greece α-PVP is considered to be controlled under law 3459/2006 due to the fact that it has the same molecular weight and molecular formula as Metazocine, an opioid analgesic classified in Table C of this law.
- In Hungary α-PVP is listed in Schedule A (psychotropic substances) of Act XXV of 1998 on human pharmaceuticals on 1 January 2015.
- In Ireland α-PVP is covered by the generic definition of controlled cathinones included in the Misuse of Drugs Act.
- In Italy α-PVP is also controlled generically, as a derivative of 2-amino-1-phenyl-1-propanone, under the Decree of the President of the Republic 309/90 of 29 December 2011.
- In Latvia α-PVP is controlled generically according to Cabinet Regulation 847, 'Regulations regarding narcotic substances, psychotropic substances and precursors to be controlled in Latvia'.
- In Lithuania α-PVP is controlled as a cathinone derivative by an Amendment to the Law on the Control of Narcotic Drugs and Psychotropic Substances adopted in 2010.
- In Poland α-PVP was listed in Schedule IV of the Act of 24 June 2015 amending the Act of Counteracting Drug Addiction on 1 July 2015.
- In Romania α-PVP is controlled by Law 143/2000 on preventing and combating trafficking and illicit drug use and it is listed in Table I of the law 339/2005 on the legal regime of plants, narcotic and psychotropic substances and preparations.
- In Slovenia α-PVP was included by the Decree on amending the Decree on Classification of Illicit Drugs, Official Gazette of RS No. 45/2014 in July 2014.
- In Sweden α-PVP came under the Narcotic Drugs Control Act on 1 February 2013.
- In the United Kingdom α-PVP was included in the generic definition of substituted cathinone derivatives placed under the Misuse of Drugs Act 1971 in April 2010 and it is controlled as a class B drug.
- In Turkey α-PVP is listed in the Law on Control of Narcotics No.2313 adopted on 22 March 2012.
- In Norway α-PVP is covered by the generic definition of cathinones in the Norwegian list of narcotics.

Four Member States (Austria, Cyprus, Portugal and Slovakia) reported that α-PVP is controlled under legislation prohibiting the unauthorised supply of defined or qualifying new psychoactive substances.

- In Austria α-PVP is categorised as a member of the 'amino phenyl ethanone' (i.e. cathinone) generic group in the new psychoactive substances act.
- In Cyprus α-PVP also falls under the generic definition of a cathinone under specific new psychoactive substances legislation as of 24 June 2011.
- In Portugal α-PVP is listed as controlled under Decree-Law 154/2013 of 17 April 2013.
- In Slovakia α-PVP was listed as a 'hazardous substance' on 1 October 2013.

In the Netherlands the sale of α-PVP in consumer amounts is treated as being a medicinal product and must comply with medicines legislation.

Eight Member States (Belgium, Bulgaria, Croatia, the Czech Republic, Denmark, Luxembourg, Malta and Spain) reported that α-PVP is not subject to control measures at the national level. Belgium and the Czech Republic reported that they have started the process to control the substance under drug control legislation.

3.8. Further information (Article 5.2(h) of the Council Decision)

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

No information was reported by the Member States, Turkey or Norway about the chemical precursors or manufacturing methods used to make the α-PVP that has been detected within the EU. Methods for the production of α-PVP are documented in the scientific literature.

The synthesis of pyrovalerone and its derivatives was initially published by Wander (1963) and Thomae (1963).

The synthesis of α-PVP was also described in 1967 in a patent on α-pyrrolidino ketones by Boehringer Ingelheim (1967). In that patent, α-PVP was prepared by adding pyrrolidine to a solution of α-chloro-valerophenone in benzene, accompanied by stirring. Synthesis of α-PVP by Meltzer et al., 2006 was achieved through the α-bromination of the intermediate ketone with the addition of pyrrolidine to yield α-PVP as a colourless solid. Casale et al., 2012 employed a similar synthetic method, reacting valeronitrinile with phenylmagnesium bromide to form 1-phenyl-1-pentanone, which was then brominated to form the intermediate alpha-bromo ketone.

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

No studies were identified that have examined the mode and scope of established or expected use of α-PVP. Given the limited information currently available, the relevant information has been included in the previous sections.

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

No information was provided by any Member State that indicated that α-PVP had any other use apart from in legitimate scientific research and in analytical reference materials.

From the available information, it does not appear that α-PVP is used in the manufacture of a medicinal product in the EU; however, the data collection is incomplete and some countries indicated that this information is not known.

Seven Member States (Austria, the Czech Republic, Estonia, Finland, Greece, Poland and Spain) provided information that α-PVP is not used to manufacture a medicinal product for human use. Six Member States (Belgium, Croatia, Ireland, Italy, Sweden and the United Kingdom) and Iceland replied that they did not know this information. Ten Member States (Austria, the Czech Republic, Estonia, Finland, France, Hungary, Latvia, Poland, Spain and the United Kingdom) provided information that α-PVP is not used to manufacture a medicinal product for veterinary use. Seven Member States (Belgium, Germany, Ireland, the Netherlands, Portugal, Slovenia and Sweden) and Iceland replied that they did not know this information.

In addition, the EMA reported that it is not known if α-PVP is used in the manufacture of medicinal products for human or veterinary use in the EU. It is understood that the collection of such information is a challenge in the absence of an EU database on the synthetic routes of all medicinal products.

4. Information from the EMA (Article 5.3 of the Council Decision)

4.1. Marketing authorisation

Twenty-one Member States responded to the EMA's information request (section 2). They reported that the new psychoactive substance α-PVP has not obtained a marketing authorisation ([48]). The EMA also reported that the new psychoactive substance α-PVP has not obtained a marketing authorisation through the centralised procedure for authorising medicinal products.

4.2. Application for a marketing authorisation

Twenty-one Member States responded to the EMA's information request (section 2). They reported that the new psychoactive substance α-PVP is not the subject of an application for a marketing authorisation ([48]). The EMA also reported that the new psychoactive substance α-PVP is not the subject of an application for a marketing authorisation through the centralised procedure.

4.3. Suspended marketing authorisation

Twenty-one Member States responded to the EMA's information request (section 2). They reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance α-PVP ([48]). The EMA also reported that the new psychoactive substance α-PVP is not the subject of a suspended marketing authorisation through the centralised procedure.

5. Conclusion

α-PVP is a synthetic cathinone derivative closely related to pyrovalerone and MDPV, both of which are synthetic stimulants that are controlled under the 1971 United Nations Convention on Psychotropic Substances.

([48]) Austria, Belgium, the Czech Republic, Estonia, Finland, Iceland, Ireland, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Greece and Italy provided a response in relation to human medicinal products. France, Germany, Hungary, Latvia, the Netherlands, Portugal and Slovenia provided a response in relation to veterinary medicinal products.

Data suggest that α-PVP is likely to be a potent psychostimulant with abuse liability and dependence potential in humans; these effects may be similar to MDPV.

α-PVP has been available in the European Union since at least February 2011 and has been detected in 28 Member States, Turkey and Norway. In most cases it has been seized as a powder, but other forms including tablets have been detected. Multi-kilogram quantities of α-PVP have been seized at European borders, which usually originate from China. This includes the seizure of more than 280 kg in 2015. Illicit production and tableting sites within the EU have also been seized. α-PVP is sold as a 'research chemical' online and is available in wholesale and consumer amounts.

One hundred and forty serious adverse events associated with α-PVP have been reported by nine Member States. This includes acute intoxications requiring hospitalisation and more than 100 deaths; in at least 23 of these deaths α-PVP was the cause of death or contributed to the death. Of concern is that α-PVP is being used by high-risk drug users, including those who inject.

We conclude that the health and social risks caused by the manufacture, trafficking and use of α-PVP, and the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

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Annex

Pictures of dismantled tableting and production facilities of α-PVP and of seizures containing α-PVP. Provided by Europol

FIGURE A1

Tableting site dismantled by the Hungarian police in Érd in 2013. Tablets containing pentedrone and 800 g of α-PVP were seized

FIGURE A2

Tableting site dismantled by the Hungarian police in 2014. Tablets containing pentedrone and 1.5 kg of α-PVP in powder form were seized in the storage location linked to this tableting site

FIGURE A3

Production facility seized in Chorzow, Poland in 2013

FIGURE A4

Tablets containing α-PVP and other new psychoactive substances seized by Czech authorities. Sold as MDMA

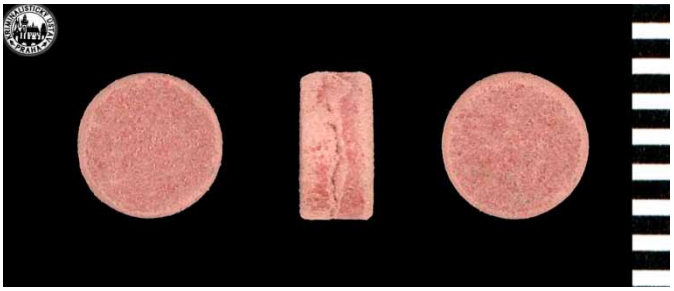

FIGURE A5

Package containing 109 g of α-PVP seized in Slovakia

TD-AS-15-001-EN-N

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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

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