Council of the
European Union

Brussels, 2 December 2015
(OR. en)

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NOTE

From:	EMCDDA
To:	Delegations
No. prev. doc.:	11558/15
Subject:	Risk assessment report on a new psychoactive substance: 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (**α**-pyrrolidinovalerophenone, **α**-PVP) In accordance with Article 6 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

Following the Council's request to conduct a Risk Assessment on a new psychoactive substance, 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (**α**-pyrrolidinovalerophenone, **α**-PVP), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.

Contents

10. Conclusion

The new psychoactive substance 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-PVP) is a potent psychostimulant. α-PVP is structurally related to cathinone, pyrovalerone, and MDPV, which are listed in the United Nations Convention on Psychotropic Substances of 1971.

α-PVP has been available on the drug market in the European Union since at least February 2011 and has been detected in all 28 Member States. α-PVP is typically administered by nasal insufflation, injection, and orally.

In vitro data suggests that α-PVP acts predominantly as an inhibitor of dopamine (DA) uptake at the dopamine transporter (DAT) and norepinephrine (NE) uptake at the norepinephrine transporter (NET). α-PVP has similar or even greater potency at DAT and NET but not the serotonin transporter (SERT) compared to cocaine and methamphetamine. This is a mode of action that is also known to occur with other psychostimulants with monoamine uptake properties, such as MDPV.

The effects of α-PVP in animals are in alignment with those observed with other psychostimulants such as MDPV, cocaine, and methamphetamine. The neurochemical features associated with α-PVP include detection of increased levels of extracellular dopamine levels in mice striatum using microdialysis, and behavioural features such as locomotor activation, and full substitution for the discriminative stimulus effects of cocaine and methamphetamine. Similar to MDPV, α-PVP was shown to act as a reinforcer when studied in animal models of reinforcement.

Data from non-clinical studies suggests that α-PVP may have an abuse liability and possibly a dependence potential in humans.

Limited information available from acute intoxications and deaths as well as from user websites suggests that the physiological and psychological effects of α-PVP might be similar to other psychostimulants such as MDPV.

The available data suggests that α-PVP is used by recreational drug users and problem drug users. In the latter case, this includes individuals who inject stimulant and opioid drugs. However, no further information on the size and demand and the characteristics of these groups of people is available. There is no specific information on the social risks that may be related to α-PVP.

One hundred and ninety one acute intoxications have been reported where α-PVP was detected in biological samples taken from the patients. Case level data was available for 29 of these cases. The adverse symptoms and signs were generally consistent with sympathomimetic toxicity.

One hundred and fifteen deaths have been reported where α-PVP was detected post-mortem. In 20% of these cases α-PVP was reported as either the cause of death or that it contributed to the death; in five (4%) of these cases α-PVP was the only substance detected.

There is limited information to suggest the potential involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. The chemical precursors and the synthetic routes used to manufacture the α-PVP detected within the European Union are unknown. Most of the α-PVP on the European drug market appears to originate from chemical companies based in China. However, two clandestine laboratories have also been seized within one Member State that were producing α-PVP in multi-kilogram amounts.

α-PVP has no recognized medical (human or veterinary) use in the European Union nor, it appears, elsewhere. There are no indications that α-PVP may be used for any other purpose aside from as an analytical reference standard and in scientific research.

α-PVP is not listed for control in the Single Convention on Narcotic Drugs of 1961 nor in the Convention on Psychotropic Substances of 1971. α-PVP is currently under assessment by the United Nations system.

Sixteen Member States control α-PVP under drug control legislation and five Member States control α-PVP under other legislation.

As for any new psychoactive substance, many of the questions related to α-PVP that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including targeted studies that examine user groups, increased risks of infectious diseases and other risk behaviours); the market; chemical profiling; receptor binding and functional activity; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between α-PVP and other substances; the dependence and abuse potential; and, the public health risks associated with its use.

The Committee notes that a decision to control α-PVP has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of α-PVP. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Although there is limited information on the human (psycho)pharmacological effects, chemically analogous substances that may replace α-PVP are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Finally, control measures should not inhibit the gathering

and dissemination of accurate information on α-PVP to users, practitioners, policy makers, and, decision makers.

11. List of annexes

Annex 1: Technical report on 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (**α**-pyrrolidinovalerophenone, **α**-PVP).

Annex 2: List of participants at the risk assessment meeting of 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (**α**-pyrrolidinovalerophenone, **α**-PVP).

European Monitoring Centre
for Drugs and Drug Addiction

Technical report on 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-pyrrolidinovalerophenone, α-PVP)

Annex 1 to the *Risk assessment report on a new psychoactive substance: 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (**α**-pyrrolidinovalerophenone, **α**-PVP)*

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EMCDDA contract: CT.15.SAT.0072.1.0

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EMCDDA contract: CT.15.SAT.0073.1.0

Suggested citation: EMCDDA. (2015), Technical report on 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-pyrrolidinovalerophenone, α-PVP). EMCDDA, Lisbon.

Data sources

The information in this technical report is derived from:

- data reported by the Member States to the EMCDDA and Europol in accordance with Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances ([1]); and,

- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, Internet drug discussion forums and related websites, and, online vendors selling α-PVP.

Note

It is important to note that when interpreting the data on self-reported user experiences that is provided in this report, it is not possible to confirm the specific substance(s) used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. In addition, the information provided on user websites and from specific user groups may not necessarily be representative of other users of α-PVP and should be regarded as illustrative only.

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

Contents

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-PVP) is a synthetic derivative of the naturally occurring stimulant cathinone, which is one of the psychoactive principles of the khat plant (*Catha edulis* Forsk). Cathinone is controlled under the United Nations Convention on Psychotropic Substances, 1971 (Schedule I).

Pyrrolidine cathinone derivatives such as α-PVP — where the nitrogen atom is part of a pyrrolidine ring — share the same structural skeleton as pyrovalerone and MDPV (Figure 1). The desmethyl analogue of α-PVP gives rise to pyrovalerone (1-(4-methylphenyl)-2-(1-pyrrolidinyl)pentan-1-one), which is controlled under the United Nations Convention on Psychotropic Substances, 1971 (Schedule IV). α-PVP is also structurally related to MDPV (3,4-methylenedioxypyrovalerone) ([2]) that was risk-assessed by the Scientific Committee of the EMCDDA in April 2014 (EMCDDA (2014)). In March 2015, it was decided that MDPV should be controlled under the Convention on Psychotropic Substances, 1971 (Schedule II) (Commission on Narcotic Drugs, 2015). The control entered into force in November 2015.

α-PVP contains a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*S*)-α-PVP and (*R*)-α-PVP.

Lower and higher homologues of α-PVP currently monitored by the EMCDDA are: α-pyrrolidinopropiophenone (α-PPP), α-pyrrolidinobutyrophenone (α-PBP), alpha-pyrrolidinohexanophenone (α-PHP), α-pyrrolidinoenanthophenone (α-PEP or α-PHPP or PV8), α-pyrrolidinooctanophenone (α-POP or PV9) and α-PNP (alpha-pyrrolidinononaphenone), respectively. Substituted derivatives of α-PVP which are being monitored by the EMCDDA are: 4-Br-α-PVP, 4-Cl-α-PVP, 4-F-α-PVP, 4-MeO-α-PVP and 3,4-DMeO-α-PVP ([3]). Substituted derivatives of lower and higher homologues of α-PVP which are being monitored by the EMCDDA are: 4-Cl-α-PPP, MPPP (4-Me-α-PPP), MOPPP (4-MeO-α-PPP), 4F-PBP, MPBP (4-Me-α-PBP), 4-MeO-α-PBP, 4-F-α-PHP, MPHP (4-Me-α-PHP), 3,4-DMeO-α-PHP, 4-MeO-α-PEP and 4-MeO-α-POP (4-MeO-α-PV9).

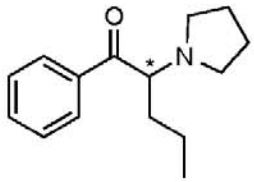
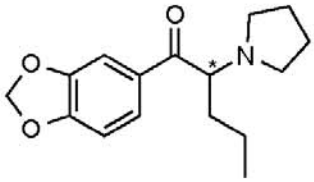
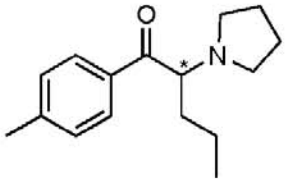
On 1 October 2015, the People's Republic of China placed α-PVP under national drug control legislation. α-PBP, α-PHP, α-PEP, 4-F-α-PVP, 4-MeO-α-PVP, α-

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

([3]) Derivatives substituted with a cycle on the phenyl ring, such as naphyrone, 1-naphyrone, 5-DBFPV (5-dihydrobenzofuranpyrovalerone), MDPV and TH-PVP have been excluded from the list. The number indicates the position(s) of the phenyl ring which are substituted with the substituents: bromo (Br), chloro (Cl), fluoro (F), methyl (M and Me) and methoxy (MeO) or dimethoxy (DMeO).

pyrrolidinovalerothiophenone (α-PVT) were also controlled. All of these substances are monitored by the EMCDDA.

Figure 1. The molecular structure, molecular formula, molecular weight, and monoisotopic mass of α-PVP. The molecular structure, molecular formula, molecular weight and monoisotopic mass of MDPV and pyrovalerone are provided for comparison. Chiral centres are denoted by an asterisk on the molecular structures.

		
α-PVP	**MDPV**	**Pyrovalerone**
Molecular formula: $C_{15}H_{21}NO$ Molecular weight: 231.34 Monoisotopic mass: 231.16231	Molecular formula: $C_{16}H_{21}NO_3$ Molecular weight: 275.35 Monoisotopic mass: 275.15214	Molecular formula: $C_{16}H_{23}NO$ Molecular weight: 245.37 Monoisotopic mass: 245.17796

The common name for α-PVP is alpha-pyrrolidinovalerophenone.

The systematic IUPAC name for α-PVP is 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one.

Chemical Abstract Service (CAS) registry numbers are given in Table 1. Commonly encountered names and codenames used for α-PVP are given in Table 2.

Table 1. Chemical Abstract Service (CAS) registry numbers for α-PVP.

CAS Registry Numbers	Variant
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 salt
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

Table 2. Chemical names, common names and codenames reported for **α**-PVP.

1-Phenyl-2-(1-pyrrolidinyl)-1-pentanone
1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-on (German)
1-Fenyyli-2-(1-pyrrolidinyyli)-1-pentanoni (Finnish)
2-(1-Pyrrolidinyl)-valerophenone
2-Pyrrolidinovalerophenone
2-(1-Pyrrolidinyl)-valerophenone
2-(Pyrrolidin-1-yl)phenylpentan-1-one
2-Pyrrolidin-1-yl-1-phenylpentan-1-one
α-Pyrrolidinopentiophenone
α-Pyrrolidinovalerophenone
α-Pyrrolidiinivalerofenoni (Finnish)
α-Pyrrolidinovalerophenon (German)
Desmethyl pyrovalerone
Prolintanone
β-keto-Prolintane
Pyrodilyl ketone
α-Pyrrolidino ketone
alpha-PVP, alfa-PVP, a-PVP, A PVP, PVP
α-2
CHEMBL205082
MFCD24386810
O-2387

Reported street names for α-PVP include: '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).

The following labelled 'legal high' products 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' (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 3', 'Ivory' and 'Vanila [sic] 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' (United Kingdom). Some of these products are marketed as 'research chemicals', 'bath salts', 'plant food' or 'insect repellents' in order to circumvent legislation.

Identification and analytical profile

α-PVP was first identified in Germany in 2005 (Westphal et al., 2011). Mass spectral data for α-PVP obtained from metabolism studies were published in 2009 (Sauer et al., 2009). Since 2011, the increased availability of α-PVP has facilitated the development of a range of analytical methods that are routinely used for its characterisation and detection in sample matrices commonly encountered in forensic and clinical investigations (Table 3). The Marquis and Mecke tests were reported to give a 'clear' and 'grey/black' reaction, respectively (Reagent-base.net, 2015).

Table 3. Representative examples of analytical methods applied to the detection and/or characterisation of α-PVP which have been published in the scientific literature ([4]).

GC-MS	**Reference**
Metabolism studies *in vivo* (male Wistar rats) and *in vitro*	Sauer, et al. (2009)
Analysis of a branded product	Elie et al. (2013)
Detection in biofluids	Saito et al. (2013)
Characterisation of synthesized material	Tsujikawa et al. (2013)
Detection in authentic urine specimens	Namera et al. (2014)

([4]) GC: gas chromatography; MS: mass spectrometry; LC: liquid chromatography (various forms); NMR: nuclear magnetic resonance spectroscopy; FTIR: Fourier transform infrared spectroscopy; ESI: electrospray ionisation; CID: collision-induced dissociation; UV: ultraviolet spectroscopy; MALDI: matrix-assisted laser desorption/ionisation; TOF: time-of-flight; MS/MS: tandem mass spectrometry.

Detection in authentic urine specimens	Uralets et al. (2014)
Method development using supplied samples	Fujii et al. (2015)
GC-MS and LC-MS	
Detection in biofluids	Namera et al. (2013b)
Detection in biofluids	Hasegawa et al. (2014)
Analysis of branded products	Leffler et al. (2014)
Detection in authentic urine specimens	Shima et al. (2014)
Metabolism studies *in vitro* and application to authentic biofluids samples	Friscia et al. (2015)
Detection in biofluids and powdered material	Sykutera et al. (2015)
GC-MS and other methods of analysis	
Characterisation of synthesized material (incl. NMR and FTIR)	Casale and Hays (2012)
Characterisation of supplied samples (incl. LC-UV, FTIR and IMS)	Armenta et al. (2015)
LC-MS	
Analysis of branded products	Shanks et al. (2012)
Method development for oral fluid analysis and application to test samples obtained from subjects	Amaratunga et al. (2013)
Method development for urine analysis and application to authentic urine specimens	Concheiro et al. (2013)
Detection in biofluids and powdered sample by FTIR and GC-MS	Eiden et al. (2013)
Detection in biofluids	Marinetti and Antonides (2013)
Method development for hair analysis and application to authentic hair specimens	Namera et al. (2013a)
Detection in biofluids	Shanks et al. (2013)

Metabolism studies *in-silico* and *in vitro* and application to authentic urine specimens	Tyrkkö et al. (2013)
Characterisation of supplied standards	Fornal (2014)
Detection in biofluids	Knoy et al. (2014)
Analysis of products purchased from shops	Schneir et al. (2014)
Use as internal standard for analyses of biofluids	Wurita et al. (2014)
Detection in wastewater samples	Borova et al. (2015)
Method development for urine analysis and application to authentic urine specimens	Concheiro et al. (2015)
In vitro metabolism studies	Negreira et al. (2015)
Detection in biofluids	Yap and Drummer (2015)
Miscellaneous methods of analysis	
Characterisation of synthesized material (ESI-in-source CID-MS)	Power et al. (2012)
Method development for blood and application to authentic blood specimens (MALDI-TOF-MS and Q-TOF-MS/MS)	Minakata et al. (2014)
Chiral analysis of products obtained from Internet retailers (LC-UV)	Taschwer et al. (2014)
Analysis of reference material (^{13}C-NMR)	Uchiyama et al. (2014)
Characterisation of synthesized samples (FTIR and NMR)	Guha et al. (2015)

Physical description

The hydrochloride salt of **α**-PVP is described as a white, crystalline powder. Its solubility is reported as: ~10 mg/mL in PBS (pH 7.2); ~20 mg/mL in EtOH; ~10 mg/mL in DMSO and ~3 mg/mL in DMF, respectively (Cayman Chemical Company, 2015). Earlier work carried out in the 1960s reported a number of melting points (Table 4). The boiling point was determined at 113 °C at 0.15 mm/Hg (Dr. Karl Thomae GmbH, 1963; Seeger, 1966, 1967).

Table 4. Melting points reported for **α**-PVP

Salt	Melting point	Reference
Hydrochloride	173 °C (ethanol/diethyl ether)	Madras et al. (2005), Meltzer et al. (2006)
Hydrochloride	162 °C	Seeger (1966), Seeger (1967)
Hydrochloride	162 °C (acetone)	Dr. Karl Thomae GmbH (1963)
Hydrochloride	104–106 °C / 169–170 °C[a]	Heffe (1966a)
Acid sulfate	140 °C (isopropanol)	Dr. Karl Thomae GmbH (1963)
Tartrate	148–149 °C	Seeger (1966)
Tartrate	148–149 °C (isopropanol)	Dr. Karl Thomae GmbH (1963)
Maleate	131 °C	Seeger (1966)
Maleate	131 °C (acetone)	Dr. Karl Thomae GmbH (1963)
Hydrogen maleate	131 °C	Seeger (1967)
Hydrogen maleate	131 °C (acetone)	Dr. Karl Thomae GmbH (1963)
Citrate	88 °C	Seeger (1966)
Citrate	88 °C (acetone)	Dr. Karl Thomae GmbH (1963)
[a] Described as anhydrous salt form.		

Racemic **α**-PVP is commercially available as analytical reference material.

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

Methods and chemical precursors used for the manufacture of α-PVP

No information was reported to the EMCDDA about the chemical precursors or manufacturing methods used to make the **α**-PVP which has been detected on the drug market in Europe.

Methods for the production of **α**-PVP are documented in the scientific literature and include **α**-halogenation of 1-phenylpentan-1-one (valerophenone) followed by amination with pyrrolidine (Dr. A. Wander S.A, 1963), (Dr. Karl Thomae GmbH, 1963). This particular route

is particularly useful for the preparation of cathinone derivatives in general. Other routes have also been reported and include the use of Grignard conditions (Casale and Hays, 2012), (Dr. A. Wander S.A, 1963), or reaction of an epoxide intermediate with pyrrolidine (Dr. A. Wander S.A, 1963; Heffe, 1966b; Heffe, 1966c), or involvement of the ephedrine-type precursor (Dr. A. Wander S.A, 1963; Guha, et al., 2015; Heffe, 1966a).

Typical impurities encountered in seized and collected samples

Detailed information available with regards to route-specific by-products produced during the synthesis of α-PVP is currently not available.

There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA.

Information on purity, which was available from 17 seizures reported to the EMCDDA, ranged from 23 % (2 seizures) to over 95 % (8 seizures).

In around 35 % of the seizures reported to the EMCDDA, α-PVP was found in combination with other substances (Section D3.1).

Most of the powder seizures detected were described as white or off-white in colour; in one case from Spain the powder was described as 'black rock powder'.

A1.2. Physical/pharmaceutical form

Reports of seizures and collected samples have noted that α-PVP has typically been detected in the form of powders as well as tablets (Section C). α-PVP has also been detected in powder-filled capsules, vegetable material, liquids, blotters (small pieces of paper impregnated with α-PVP for sublingual/buccal administration) and in jelly gums.

It is worth noting that α-PVP and a number of ring-substituted derivatives were featured in a number of patents in the early 1960s that investigated their potential use as central nervous stimulants and antihypotensive/vasopressor agents in humans. The suggested formulations for these substances included tablets (up to 60 mg), suppositories (1 – 60 mg), dragées (30 mg), ampules (10 mg/2 mL) and drops (60 mg/mL), respectively (Dr. A. Wander S.A, 1963; Dr. Karl Thomae GmbH, 1963; Seeger, 1966, 1967).

A1.3. Route of administration and dosage

Route of administration

Data reported to the EMCDDA as well as from user websites suggests that typical routes of administration of α-PVP are snorting (nasal insufflation), oral (ingestion), and injection (including intravenous route). Other reported routes, include sub-lingual, smoking/inhalation, and rectal.

Dosage

Self-reported user experiences have noted that in some individuals the 'threshold' level for α-PVP (that is the dose required to induce an effect) may occur with oral doses of 1–2 mg; 'strong' effects were reported with oral doses of 20–25 mg. Nasal insufflation was considered a more potent method of administration based on the doses needed to classify as 'threshold' levels and beyond (Psychonautwiki, 2015).

Data on the dose of α-PVP used was available in two analytically confirmed acute intoxications reported by Sweden. In one case, an oral dose of 15–20 mg was used; in another case, 330 mg was used (route unknown).

France reported a dose of 20–30 mg used by two individuals that had injected α-PVP intravenously.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

α-PVP and closely related 'α-pyrrolidino-valerophenones' have been studied to some extent as part of pharmaceutical investigations designed to explore their hypertensive and central nervous system stimulant effects. Published research studies were limited until the early 2000s when an extensive set of pyrovalerone derivatives were studied *in vitro* for their interactions with monoamine transporters (Madras, et al., 2005; Meltzer, et al., 2006).

Although there is no information about the action of the optical isomers of α-PVP, it is interesting to note that in the case of pyrovalerone — the 4-methylphenyl analogue of α-PVP — activity was reported to reside with the (*S*)-isomer (Meltzer, et al., 2006).

No studies were identified that have investigated the pharmacodynamics of α-PVP in humans.

In vitro pharmacology

Data suggests that α-PVP acts predominantly as an inhibitor of dopamine (DA) uptake at the dopamine transporter (DAT) and norepinephrine (NE) uptake at the norepinephrine transporter (NET). This mode of action is also known to occur with psychostimulants such as cocaine and MDPV, which are known to affect monoamine uptake (Table 5).

Table 5. *In vitro* uptake inhibition and binding data for α-PVP at the dopamine transporter (DAT), norepinephrine transporter (NET), and, serotonin transporter (SERT).

Uptake inhibition [a]			**Affinity** [b]			**Reference**
DAT IC_{50}/nM	NET IC_{50}/nM	SERT IC_{50}/nM	DAT K_i/nM	NET K_i/nM	SERT K_i/nM	
52.3	56.0	--	33.7	199	> 10,000	Madras, et al. (2005) [c], Meltzer, et al. (2006)

205 [d]	--	--	--	--	--	Kolanos et al. (2013) [e]
12.8	14.2	> 10,000	--	--	--	Marusich et al. (2014) [f]
17.5	--	> 10,000	--	--	--	Kolanos et al. (2015)
40	20	> 100,000	7	60	> 30,000	Rickli et al. (2015) [g]

[a] Meltzer, et al. (2006): HEK293-hDAT, HEK293-hNET, HEK293-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Kolanos, et al. (2013): HEK-hDAT ([^{3}H]DA); Marusich, et al. (2014): rat brain synaptosomes (5 nM [^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Kolanos, et al. (2015): rat brain synaptosomes (5 nM [^{3}H]DA, [^{3}H]5-HT); Rickli, et al. (2015): HEK293-hDAT, HEK293-hNET, HEK293-hSERT (5 nM [^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT).

[b] Meltzer, et al. (2006): HEK293-hDAT, HEK293-hNET, HEK293-hSERT ([^{125}I]RTI-55, 40 – 80 pM)); Rickli, et al. (2015): HEK293-hDAT, HEK293-hNET, HEK293-hSERT (*N*-methyl-[^{3}H]-nisoxetine and indatraline (NET), [^{3}H]citalopram and indatraline (SERT), [^{3}H]WIN35,428 and indatraline (DAT). A 'DAT affinity' value of 13 nM was also given in Madras, et al. (2005)

[c] Uptake data for cocaine (Meltzer, et al., 2006) (IC_{50}/nM): DAT = 461; NET = 378; SERT = 494. Affinity data for cocaine (Meltzer, et al., 2006) (K_i/nM): DAT = 432; NET = 2,150; SERT = 358.

[d] Additional experiments (two-electrode voltage clamp; −60 mV using *Xenopus* oocytes expressing hDAT to illustrate inhibitor-like behaviour. Following α-PVP exposure (10 µM), DA (5 µM) elicited hDAT-mediated inward current 25.4% relative to amplitude obtained from first DA application (5 µM).

[e] Affinity data for MDPV (Kolanos, et al., 2013): DAT K_i = 135 nM.

[f] Marusich, et al. (2014): Uptake data (IC_{50}/nM). MDPV: DAT = 4.1; NET = 25.9; SERT > 10,000; cocaine: DAT = 211; NET = 292; SERT = 313; amphetamine; DAT = 93; NET = 67; SERT = 3,418.

[g] Rickli, et al. (2015): Uptake data (IC_{50}/nM). MDPV: DAT = 50; NET = 40; SERT = 9,600; methamphetamine: DAT = 1,100; NET = 140; SERT = 18,000; amphetamine: DAT = 1,300; NET = 70; SERT = 35,000.

Affinity data (Rickli, et al., 2015) (K_i/nM). MDPV: DAT = 10; NET = 8; SERT = 2,900; methamphetamine: DAT = 1,800; NET = 3,000; SERT = 24,600.

[h] Receptor binding profiles:

K_i (µM): 5-HT_{1A} = 5.2; 5-HT_{2A} > 13; 5-HT_{2C} > 13; α_{1A} > 15; α_{2A} >20; D_1 > 12; D_2 > 10; D_3 > 17; H_1 > 13; TA_{1rat} = 16.3; TA_{1mouse} > 20; TA_{1human} > 20. 5-HT_{2B} Activation potency (EC_{50}) using HEK293-h5-HT_{2B} and FLIPR assay > 20 µM and no activation.

[h] [^{3}H]-8-OH-DPAT and indatraline (5-HT_{1A}), [^{3}H]ketanserin and spiperone (5-HT_{2A}), [^{3}H]mesulergine and mianserin (5-HT_{2C}), [^{3}H]prazosin and risperidone (α1 adrenergic receptor), [^{3}H]rauwolscine and phentolamine (α2 adrenergic receptor), [^{3}H]SCH 23390 and butaclamol (DA_{D1}), [^{3}H]spiperone and spiperone (DA_{D2} and DA_{D3}), [^{3}H]pyrilamine and clozapine (H_1) and [^{3}H]-RO5166017 and RO5166017 (TA_1).

In vivo pharmacology

Information available from animal studies suggests that the effects of α-PVP are in alignment with those observed with other psychostimulants such as MDPV, cocaine and

methamphetamine where the role of catecholaminergic mechanisms are well established. As summarised in Table 6, the neurochemical and behavioural features associated with **α**-PVP include locomotor activation, detection of increased levels of extracellular dopamine levels in mice striatum using microdialysis, and full substitution for the discriminative stimulus effects of cocaine and methamphetamine. Similar to MDPV, **α**-PVP was shown to act as a reinforcer when studied by intravenous self-administration in rats (Table 7). Stereotypy and bizarre behaviour have been observed in animals, especially at higher doses. This finding is consistent with a range of other psychostimulants.

Table 6. *In vivo* neurochemistry data for **α**-PVP

***In vivo* pharmacology (neurochemistry / physiology)**	**Reference**
DAT occupancy (rhesus monkeys): [a] 64% based on positron emission tomography imaging; intravenous injection following pre-treatment with [^{11}C]WIN 35,428 ([^{11}C]CFT).	Madras, et al. (2005)
Microdialysis: [b] oral administration of **α**-PVP (25 mg/kg) and methamphetamine (5 mg/kg) led to significant increase in dopamine levels in dialysate samples (striatum). **α**-PVP showed shorter onset than methamphetamine but less pronounced concentration levels: ~600% DA increase for methamphetamine vs. ~ 350% DA increase at 20 min post-administration.	Kaizaki et al. (2014)
Thermoregulation: [c] modest, but consistent; dose-dependent hypothermic alteration ~0.75 °C up to 3 hours after dosing.	Aarde et al. (2015)
[a] Comparison of positron emission tomography imaging pre- and post-drug session (cerebellum) based on reduced [^{11}C]WIN 35,428 binding one hour or longer after administration. [b] Balb/c male mice (8 weeks old). Extracellular dopamine levels determined in dialysate and collected for 120 min (12 measurements) following oral administration of **α**-PVP (25 mg/kg), methamphetamine (5 mg/kg) or water (10 mL/kg). [c] Male Wistar rats; room conditions 21 °C, single housing; radiotelemetry, data collection for 180 min following **α**-PVP administration (1, 5.6 and 10 mg/kg, i.p.).	

Table 7. *In vivo* behavioural data for **α**-PVP

***Behavioural* pharmacology**	**Reference**
Locomotor activity	

Oral administration of **α**-PVP (25 mg/kg) and methamphetamine (5 mg/kg) as a positive control. [a] Earlier and more pronounced onset observed with **α**-PVP (10 min) and considered "stronger"; effects also considered "more profound" than those observed for methamphetamine. Both substances displayed significant increases in locomotor activity based on distance travelled in metres. Administration of D_1 receptor antagonist or a D_2 receptor antagonist before **α**-PVP treatment led to attenuated distance travelled. Mean reduction (0−30 min) to 43% (D_1) and 54% (D_2); attenuation also observed in the 30−60 min time slot although less pronounced.	Kaizaki, et al. (2014)
Significant increases in activity over entire 60 min session at 3.0−10.0 mg/kg) and 20−50 min at 1 mg/kg following **α**-PVP injection. [b] Increases of cumulative beam breaks considered significant at 3.0 and 10 mg/kg. Administration of D_1 receptor antagonist before **α**-PVP treatment led to significant reduction in total beam breaks with a main effect of pre-treatment at 3.0 mg/kg **α**-PVP. Doses needed to significantly increase locomotor activity during the first 10-min bin were lower than those for cocaine. Pre-treatment with a D_1 receptor antagonist attenuated locomotor activity.	Marusich, et al. (2014)
Peak locomotor responses observed at 1.0 mg/kg and lasted ~2 h. Locomotor stimulant effects very similar to MDPV; **α**-PVP showed rebound of activity 2 h after injection of 5.6 mg/kg dose. [c]	Aarde, et al. (2015)
Time- and dose-dependent effects from 2.5 to 25 mg/kg; stimulant effects with 2.5, 5, and 10 mg/kg observed within 10 min lasting 240–290 min. Stimulant effects not observed in the first 60 min at 25 mg/kg and lasted 280 min. [d]	Gatch et al. (2015)
Drug discrimination	
Full substitution for discriminative stimulus effects of cocaine and methamphetamine; slope of **α**-PVP dose effect in cocaine-trained rats substantially shallower than dose-effect curve determined for methamphetamine-trained animals. [e]	Gatch, et al. (2015)
Full substitution observed for training dose of methamphetamine; total drug-lever responses reached 88.6% at 2.0 mg/kg; potency differences expressed as ED50 values: methamphetamine = 0.3 mg/kg; **α**-PVP = 0.7 mg/kg; cocaine = 3.3 mg/kg; control response rates were significantly reduced at doses of 1.0 mg/kg (methamphetamine), 2.0 mg/kg (**α**-PVP) and 8.0 mg/kg (cocaine). [f]	Naylor et al. (2015)
Miscellaneous	

Functional observational battery (FOB): Significant increases in some observational measures (male ICR mice) consistent with psychomotor stimulant properties (ranging between 3−10 mg/kg and 10−17 mg/kg): locomotion (first 10 min), exploration, circular ambulations, flattened body posture, hyperactivity, stereotyped head weaving, stereotyped head circling and stimulation. No significant increased noted for ataxia, retropulsion, bizarre behaviour and grooming.	Marusich, et al. (2014)
Intracranial self-stimulation (ICSS) thresholds: [g] Significant ICSS threshold reductions at 0.3 and 1 mg/kg (~19%) doses and comparable to methamphetamine. ED_{50}: α-PVP = 0.35 mg/kg; methamphetamine = 0.2 mg/kg); at 5 mg/kg (or 3 mg/kg for methamphetamine) aversive effects observed and increase of ICSS thresholds.	Watterson et al. (2014)
Intravenous self-administration: [h] α-PVP considered similar to MDPV in potency and efficacy as a reinforcer; intake and lever discrimination of α-PVP higher than MDPV.	Aarde, et al. (2015)
Conditioned place preference (CPP): [i] CPP was produced (0.3−10 mg/kg) with U-shaped dose−effect curve, i.e. no CPP at high (30 mg/kg) and low doses (0.1 mg/kg).	Gatch, et al. (2015)

[a] Balb/c male mice (8 weeks old) and comparison with saline. Locomotor activity measured for 120 min after administration using a video tracking system. Antagonism experiment: D_1 receptor antagonist (+)-SCH23390 (50 µg/kg, i.p.), D_2 receptor antagonist sulpiride (50 mg/kg, i.m.); antagonists administered 30 min before α-PVP (25 mg/kg) treatment. Locomotor activity measured for 60 min.

[b] Locomotor activity studies: male ICR mice; monitoring horizontal movements (two 4-beam infrared arrays) / beam breaks for 60 min following α-PVP administration (1, 3 and 10 mg/kg, i.p.); D_1 receptor antagonist (+)-SCH23390 (30 µg/kg, s.c.) given 30 min before drug administration; FOB studies: Male ICR mice.

[c] Male Wistar rats; activity rate determined by radiotelemetry for 180 min following α-PVP administration (1, 5.6 and 10 mg/kg, i.p.).

[d] Male Swiss Webster mice in temperature environment of 22−24 °C; panel of 16 infrared beams; α-PVP doses 1, 2.5, 5, 10 and 25 mg/kg (i.p.); horizontal activity measured for 8 h.

[e] Male Sprague-Dawley rats; α-PVP doses 0.1, 0.25, 0.5, 1, 2.5, 5 and 10 mg/kg (i.p.); rats trained to discriminate cocaine (10 mg/kg, i.p.) or methamphetamine (1 mg/kg i.p.) from vehicle (saline) using two-lever choice methodology.

[f] Male Sprague-Dawley rats; trained to discriminate methamphetamine (1.0 mg/kg) from saline using fixed-ratio (FR) 20 schedule; α-PVP doses 0.25–2.0 mg/kg (i.p.); cocaine (1.0–8.0 mg/kg) used as positive control.

[g] Male Sprague-Dawley rats, unilaterally implanted stainless steel bipolar electrode into medial forebrain bundle; α-PVP in comparison with methamphetamine (both 0.1, 0.3, 1, and 3 mg/kg; i.p.); training: nose-poke responses on FR1 schedule.

[h] Male Wistar rats; fixed-ratio 1 dose-response testing (1 h) (trained on 0.1 mg/kg/infusion) and progressive-ratio (3 h), dose-response testing (dose-response: 0.018–0.56 mg/kg/infusion).

[i] Male Swiss Webster mice; α-PVP place conditioning doses of 0.1, 0.3, 1, 3, 10, 30 mg/kg (i.p.).

Pharmacokinetics

Detailed data on the metabolic transformation of α-PVP in humans is not available, however a number of *in vitro* studies have recently been published that provide some initial data. In addition, some information became available from casework samples related to acute intoxications and deaths (Table 8). From what has been reported so far it would appear that the parent molecule is frequently detectable in a variety of biofluids (see also Section C). Other metabolites that may be suitable for the implementation of targeted investigations include the reduced β-hydroxy (HO-PVP) species and a range of additional analytes associated with modifications at the pyrrolidine ring, phenyl ring and α-alkyl group.

Table 8. Biotransformation data associated with α-PVP.

Comments	Reference
Rat urine: detected biotransformation products included PVP, *N*,*N*-bis-dealkyl-PVP, the pyrrolidin-2-one derivative 2''-oxo-PVP, hydroxyalkyl-PVP, hydroxyphenyl-*N*,*N*-bis-dealkyl-PVP, hydroxyphenyl-PVP, hydroxyalkyl-2''-oxo-PVP, carboxy-4-oxo-PVP, hydroxy- phenyl-2''-oxo-PVP, di-hydroxy-PVP, hydroxyphenyl-carboxy-4-oxo-PVP, and hydroxyphenyl-carboxy-4-oxo-PVP. Side chain hydroxylation of **α**-PVP catalyzed following exposure to human hepatic cytochrome-P450 (CYP) enzymes CYP2B6, CYP2C19, CYP2D6, and CYP1A2, respectively. [a]	Sauer et al. (2009), Meyer & Maurer (2010)
Identification of seven Phase I metabolites in authentic human urine samples; transformation steps included as reduction, hydroxylation, hydroxylation + dehydrogenation, reduction + hydroxylation + dehydrogenation, degradation of pyrrolidine ring, hydroxylation + dehydrogenation + ring opening + oxidation, and hydroxylation + oxidation, respectively. The reduced ketone, i.e. 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-ol (HO-**α**-PVP), was found to be the most abundant species in the analyzed human urine samples and in samples derived from *in vitro* experiments with human liver microsomes.	Tyrkkö et al. (2013)
Death: detection of **α**-PVP and HO-**α**-PVP in various biofluids and solid tissues.	Hasegawa et al. (2014)
Detection of the hydroxyalkyl-PVP species was observed in samples obtained in casework and *in vitro* studies.	Friscia et al. (2015)
Urine samples obtained from a substance user following intravenous administration of a drug mixture; urinary elimination half-live was estimated as 22 h for **α**-PVP based on the first five days of urinary analysis. Elimination half-live of **α**-PVP estimated for the second half period 6-10 days after injection was 40 h.	Namera et al. (2014)
Authentic human urine samples revealed the detection of HO-**α**-PVP diastereomers, 2''-oxo-**α**-PVP, 2''-HO-**α**-PVP and HO-**α**-PVP glucuronide.	Shima et al. (2014)
Large-scale investigation of submitted urine samples; detection of the unchanged molecule, metabolites derived from pyrrolidine degradation and primary amine formation followed by reduction to alcohols. The suggestion was made that direct reduction to HO-**α**-PVP without pyrrolidine degradation may be less pronounced in PVP-type substances.	Uralets et al. (2014)

In vitro Phase I and Phase II metabolism study; detection of six Phase I and two glucuronidated metabolites. Phase I metabolites were formed following reduction, hydroxylation, and pyrrolidine ring transformation. The main metabolite formed under the investigated conditions was the reduced **β**-hydroxy-2''-oxo-PVP species that was associated predominantly with recombinant human CYP2C19, CYP2B6 and CYP2C9 activity as determined by separate *in vitro* studies.	Negreira et al. (2015)
Death: in addition to the detection of pentedrone, the presence of **α**-PVP and OH-**α**-PVP was noted in various biofluids and solid tissues.	Sykutera et al. (2015)
[a] Screening of rat urine (male Wistar, **α**-PVP administration by gastric intubation, 20 mg/kg and 1 mg/kg) following analysis by gas chromatography mass spectrometry and chemical derivatisation.	

Interactions with other drugs or medicines

No studies were identified that have examined the interaction of **α**-PVP with other substances, including medicinal products. Table 8 provides details of some of the enzymes that have been identified from animal studies and *in vitro* studies using recombinant human enzymes and that are thought to be involved in the metabolism of **α**-PVP.

A3. Psychological and behavioural effects

No clinical studies were identified that have investigated the psychological and behavioural effects of **α**-PVP in humans. The limited information on the psychological and behavioural effects from self-reported user experiences is summarised in Section D.1.2.1; the limited information on the characteristics and behaviour of users is summarised in Section D3.3.

Behavioural studies in animals are summarised in Section A2, Table 7.

A4. Legitimate uses of the product

α-PVP and the corresponding enantiomers are used in scientific research as well as analytical reference materials in clinical and forensic case work/investigations. There are currently no other indications that **α**-PVP may be used for other legitimate purposes.

There are no reported uses of **α**-PVP as a component in industrial, cosmetic or agricultural products. In addition, a search of the REACH registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Numbers listed in Table 1 returned no results.

There is no marketing authorisation (existing, ongoing or suspended) for **α**-PVP neither in the European Union nor in the Member States that responded to the request for information

from the European Medicines Agency which was undertaken as part of the Joint Report process (EMCDDA & Europol, 2015).

There is no information to suggest that **α**-PVP is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products it is not possible to confirm whether or not **α**-PVP is currently used in the manufacture of a medicinal product.

Section B. Dependence and abuse potential

B1. Animal data

Section A2 provides a summary of data obtained from *in vitro* and *in vivo* animal studies. Data summarised in Table 6 and Table 7 indicates that the physiological and behavioural responses associated with **α**-PVP administration were consistent with those frequently reported with other psychomotor stimulants such as MDPV, cocaine, and methamphetamine. For example, **α**-PVP was shown to increase extracellular dopamine levels in dialysates collected from mice striatum using *in vivo* microdialysis, and dopamine transporter occupancy have been traced in rhesus monkeys using neuroimaging (Table 6). Consistent with the psychostimulants mentioned above, **α**-PVP was able to induce locomotor activity and conditioned place preference. More specific functional assays included drug discrimination and self-administration studies, which confirmed that **α**-PVP showed functional similarities displayed by MDPV, cocaine, and methamphetamine used as training drugs (Table 7).

Taken together, the available data appear to show sufficient predictive validity to consider abuse liability of **α**-PVP. These data are suggestive of a possible dependence potential in humans. However, further research is needed in order to obtain a more detailed understanding of the mode and mechanism of action of **α**-PVP (including its two enantiomers), in respect to its abuse liability and dependence potential, and how the data obtained from animal studies relate to humans.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of **α**-PVP in humans.

Self-reported user experiences suggest that re-dosing occurs in some individuals ([5]).

([5]) Data from the online survey conducted by the I-Trend project which was completed by 1074 Polish citizens aged 16+, found that out of 36 respondents who reported **α**-PVP as the last new psychoactive substance they had used, 16.7% (n = 6) reported a 'strong craving to use more' **α**-PVP after the initial dose. Users on a Finnish discussion forum reported 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'. Finally, one user in an Italian internet forum cautioned against re-dosing, suggesting that doing it 2 or 3 times in a short period of time brings about impulsive behaviour which results in continuous re-dosing ('you can no longer stop').

Section C. Prevalence of use

Information from seizures, collected and biological samples

The formal notification of α-PVP to the European Union Early Warning System (EU EWS) was in April 2011. This was related to a seizure of over 5 kg of white powder made by French Customs authorities at Charles de Gaulle Airport, Paris. The powder also contained pentedrone. Since then, the substance has been detected in all 28 EU Member States, Turkey and Norway ([6]) (EMCDDA & Europol, 2015) ([7]).

Of note is that it appears that prior to the detection reported by France in 2011, α-PVP was also detected in Germany in 2005. No further details were available on this detection (Westphal *et al.*, 2005).

Information from seizures

At the time of writing the Joint Report, 26 Member States ([8]), Norway and Turkey had reported seizures ([9]) of α-PVP to the EMCDDA. More than 5,200 seizures were reported in total, with eight countries reporting more than 100 seizures each: the United Kingdom (1094), Poland (938), Finland (787), Slovakia (502), Sweden (451), Ireland (336), Hungary (313) and Turkey (256).

α-PVP has typically been seized in powder form. Until July 2015, more than 750 kg of powdered substance have been seized in Europe. To a lesser extent, tablets (12,400 units), vegetable material containing α-PVP (<150 grams), liquids (< 150 ml), blotters (68 units), powder-filled capsules (3 seizures) and jelly gums (2 units) have also been seized.

In around 35% of these seizures, α-PVP was found in combination with other substances (Section D3.1).

Countries reporting larger seizures of α-PVP in powder form were, in decreasing order: Spain (312 kg), Netherlands (140), France (81), Ireland (63), United Kingdom (62), Hungary and Finland (24 each) and Poland (17). The biggest single powder seizure occurred in April

([6]) '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 from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

([7]) Unless indicated otherwise, information provided in this section has been extracted from the EMCDDA–Europol Joint Report on α-PVP (EMCDDA–Europol, 2015). The data collection for the preparation of the Joint Report was finalised on 8 July 2015.

([8]) Bulgaria and Romania did not report seizures. Note, however, that the Bulgarian and Romanian Europol National Units reported the detection of α-PVP to Europol.

([9]) 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 is 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.

2015 in Spain, when the Spanish National Customs Surveillance Service seized almost 260 kg of α-PVP in 13 containers at Barcelona Airport shipped from China. Single powder seizures over 10 kg were reported in seven Member States and single seizures of over 1000 tablets were reported in three Member States: Slovakia (7157 units), Hungary (3768) and Finland (1136).

After 8 July 2015, updated information on detections of α-PVP has been collected by the EMCDDA. Updated information on seizures, that was not included in the Joint Report, has been provided by eight countries and amounts to over 260 individual seizures and more than 26 kg of the substance: United Kingdom (over 90 seizures: 12.1 kg in powder form and tablet), Sweden (87 seizures: 1.9 kg of powder, 25.5 ml of liquids and 2 tablets), Poland (72 seizures amounting to 2.4 kg of powder, liquids and herbal material), Ireland (4 seizures amounting to 62 grams of powder), Norway (3 seizures of powder amounting to 6 grams), Spain, Slovakia and the Czech Republic (one seizure of powder each, of 7.2 kg, 1.5 kg and 1 kg, respectively). In addition to Spain, Slovakia, and the Czech Republic, two countries reported single seizures over 1 kg: Poland (a seizure of 1.3 kg) and the United Kingdom (1 kg).

Information on the production, processing and distribution of α-PVP in Europe has been reported to Europol. This relates to two illicit production sites were seized in Poland and two processing sites were dismantled in Hungary (tableting plants where pentedrone was also being processed). In terms of trafficking and distribution, it was found that in general bulk quantities of α-PVP are mainly imported into the EU from China and then further distributed from the Member States, rather than produced within Europe (Section F).

Information from collected samples

Eleven countries reported fifty samples collected from users or purchased on the Internet, which contained α-PVP ([10]) (Austria, Belgium, 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 (7). In France, powders, capsules containing powder and pellets were sold either as methamphetamine, pentedrone and ethylphenidate or as branded 'legal high' products. In the United Kingdom a sample sold as 'NRG-3' was also reported. In Spain, a powder containing α-PVP was sold as ketamine in one case and a yellow jelly was collected from a user in another case.

After 8 July 2015, updated information on detections of α-PVP in collected samples has been provided by the Czech Republic and Spain. In the Czech Republic, three samples of powder were collected from clients in a harm reduction programme; two of the samples also contained MDPBP and the third one contained methamphetamine. In Spain, a sample of powder sold as ecstasy was collected from a user in a recreational setting.

([10]) Countries are listed in alphabetical order.

Information from biological samples

Nine Member States (Finland, France, Hungary, Ireland, Italy, Poland, Spain, Sweden and the United Kingdom) as well as Norway reported a total of more than 1800 detections where α-PVP was analytically confirmed in biological samples. These included 306 serious adverse events (191 acute intoxication and 115 deaths). The remaining detections related to: patients undergoing drug treatment; persons suspected of driving under the influence of drugs; persons suspected of having consumed drugs, committed minor offenses or crimes; and, criminal justice drug screening programs.

Availability, supply, price

According to searches conducted in English for 'α-PVP', a Wikipedia entry was created in September 2009 (Wikipedia, 2015). Self-reported user experiences appear to have been posted to user websites from 2011 (Flashback, 2015; Drugs Forum, 2015) and 2012 (Bluelight, 2015; Shroomery, 2015) onwards.

Data from seizures reported to the EMCDDA suggest that most of the bulk quantities of α-PVP in Europe are mainly imported from China. In addition, more than 50 kg of α-PVP has been seized from two production sites in Poland where the drug was synthesised (Section F).

Online vendors may be an important supply channel for wholesale and retail amounts of α-PVP. Bricks-and-mortar shops and street-level drug dealers have also supplied α-PVP.

α-PVP has been sold as a drug in its own right (including marketing as a 'research chemical'), as well as in branded 'legal high' products, and surreptitiously as other drugs. It appears that in the case of many of the 'legal high' products there is no indication on the marketing materials and product packaging that they contain α-PVP. These products include α-PVP in powder form, as tablets, and mixed with plant material. This includes 'legal high' products sold under the commonly used guises of 'bath salts', 'plant food', and 'insect repellents' in order to circumvent legislation (EMCDDA & Europol, 2015).

Availability from Internet vendors

A structured search of the surface web ([11]) conducted in English in July 2015 for Internet vendors ([12]) offering α-PVP identified 65 vendors that appeared to be based in, and/or claim to have presence in, the European Union (n=28 sites), United States (n=13 sites), China

([11]) 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. Information on physical location of the vendor, quantities and prices, and substance marketing was then recorded for each vendor URL.

([12]) This includes vendors that appear to be consumer-orientated as well as vendors, for example on B2B sites, which appear to be manufacturers and/or wholesalers. It excludes those selling α-PVP through online classified advertisements, social media, and user websites.

(n=32 sites), India (n=3 sites), or Russia (n=6 sites). α-PVP was typically marketed on these sites as a 'research chemical' (EMCDDA & Europol, 2015).

17 of the sites only provided quantities and prices for α-PVP on application. 11 of the sites listed prices but did not specify quantities. The remaining 37 sites listed quantities and prices. Prices were listed in EUR on 14 sites, in USD on 22 sites, and in GBP on 1 site ([13]). 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 17000. 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. 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 594.5 (EUR 270–1200) (EUR 5.94/g). The mean price for 1 kg (n=30 sites) was EUR 2490 (EUR 1260–3600) (EUR 2.49/g). The mean price for 5 kg (n=9 sites) was EUR 10500 (EUR 4545–12000) (EUR 2.10/g). The mean price for 10 kg (n=4 sites) was EUR 17000 (EUR 6705–23000) (EUR 1.70/g).

In addition to the structured search of the surface web, data reported to the EMCDDA noted that:

- In 3 out of the 4 acute intoxications reported to the EMCDDA where the source of the substance was known, α-PVP had been obtained online; in the remaining case, the source was reported as 'internet and drug dealer'.
- Data on collected samples reported by France, found that most the products containing α-PVP were originally sourced from the Internet directly by the user or indirectly through a dealer or a friend. Reported prices per capsule were 15 and 20 EUR and between 20 and 80 EUR per gram of powder.

Sale as other drugs

Data from seizures, collected samples, and acute intoxications reported to the EMCDDA as well as data from Sundström *et al.*, (2015) suggest that α-PVP is sold surreptitiously as other psychoactive substances, including controlled drugs. These include: MDPV (Sweden and Finland), methamphetamine (France and Ireland), ecstasy ([14]), pentedrone (France), ethylphenidate (France), MDMA (Austria, Spain, and the United Kingdom), ketamine (Spain) and cocaine (United Kingdom and Ireland).

Prevalence of use

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

([13]) Prices listed in USD were converted to EUR according to Google exchange rate from the 27.07.2015 (USD 1 = EUR 0.90). Prices listed in GBP were converted to EUR according to Google exchange rate from the 28.07.2015 (GBP 1 = EUR 1.41).

([14]) Reports of seizures of tablets with markings such as 'Lacoste', 'Playboy', 'STADA1' and 'Homer Simpson'.

Along with the data on biological samples (see above), data on the prevalence of use of **α**-PVP appears to be limited to the following studies:

- an Internet-based survey of Polish citizens aged 16 and over, conducted by the I-Trend project during 2014;
- a study of fatal poisonings in people who use drugs in the Nordic countries based on 2012 data (Simonsen *et al.*, 2015);
- a study of patterns of drug abuse among drug users attending two different drug treatment centres in Finland, conducted in 2013 and 2014 (Sundström *et al.*, 2015); and,
- data provided by Ireland in respect to clients attending a methadone maintenance program.

Poland reported that the I-Trend project undertook an Internet survey of Polish citizens 16+, who were recruited mainly through adverts on Facebook during 2014. Respondents (n=1,385) appeared, on the whole, to be relatively experienced drug users ([15]), mostly young people (mean 21 years old, median 19, mode 17) and male (68.5%). The lifetime prevalence for **α**-PVP in this population was 10.0% (138 users, n=1,385). **α**-PVP was the last new psychoactive substance to be used by 3.4% (n=36) of the respondents (n=1074). Of these, 38.9% (n=14) had taken it at least 20 times in the previous year.

Simonsen *et al.*, (2015) reported that in Finland in 2012, **α**-PVP was detected in 4.9% of deaths (n=8/162) of individuals 'who according to information from the police and/or autopsy report [were] known to have abused drugs intravenously and/or abused drugs'. In Sweden, **α**-PVP was detected in 0.4% of deaths (n=1/255).

Sundström *et al.*, (2015) studied patterns of drug use among two groups who either:

a) irregularly attended a harm reduction unit providing social and healthcare counselling to individuals using intravenous drug (n=32); or,

b) regularly attended a rehabilitation clinic, such as patients undergoing opioid maintenance therapy or drug withdrawal therapy (n=36).

α-PVP was the most frequently detected new psychoactive substance in biological samples in clients attending the harm reduction unit (38% of all analytical findings, n=34 urine samples) than for those who regularly attended a rehabilitation clinic (1% of all analytical findings, n=67 urine samples). The authors suggest that while 10 of the users from the harm reduction unit self-reported using MDPV, data from urinalysis suggests that they were actually using **α**-PVP. The authors suggest that this is an indication that **α**-PVP has been replacing MDPV in the market in Finland.

([15]) For example, life time prevalence was: 97.8% for alcohol; 94.9% for tobacco; 93.1% for cannabis, 57.1% for amphetamine/methamphetamine, 42.5% for new psychoactive substances, 32.4% for ecstasy pill or MDMA powder, 25.9% for LSD or psilocybin mushrooms, 20.9% for cocaine, etc.

Ireland reported that between 2011 and the end of June 2015 there had been 112 urine samples mainly provided by patients in a methadone maintenance program where α-PVP was detected ([16]). Testing for new psychoactive substances was performed on request where use of these substances was suspected; some patients provided multiple samples (Table 9).

Table 9. Number of urine samples where α-PVP was detected that were mainly provided by patients in a methadone maintenance program in Ireland.

Year	Total number of urine samples tested	Number of urine samples where α-PVP was detected (% of total)
2011	151	11 (7.3%)
2012	412	21 (5.1%)
2013	486	18 (3.7%)
2014	418	33 (7.9%)
2015 (Jan–June)	371	29 (7.8%)

Overall, the available data suggest that α-PVP is being used by recreational stimulant users as well as high risk drug users. In the latter case this includes people who inject opioids and stimulants, some of whom are accessing low-threshold harm reduction services and/or receiving opioid substitution treatment. The extent of the possible appeal of α-PVP to these groups of users in general is unknown.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

The median lethal dose (LD_{50}) of α-PVP hydrochloride administered by intravenous injection to mice is 38.5 mg/kg (Seeger, 1964). While LD_{50} data on other relevant substances is not available in the report by Seeger (1964), data from other studies have reported the following:

- an LD_{50} of 43 mg/kg for pyrovalerone when administered by intravenous injection to mice (Usdin & Efron, 1972);

([16]) See also McNamara et al., (2015) for further details.

- an LD_{50} of 12.5 mg/kg for amphetamine when administered by intravenous injection to mice (Haas & Forth, 1956);
- an LD_{50} of 75 mg/kg for cocaine when administered by intraperitoneal injection to mice (Hayase et al., 1996); and,
- an LD_{50} 97 mg/kg for MDMA when administered by intraperitoneal injection to mice (Davis et al., 1987).

No other studies were identified that investigated the acute health effects of α-PVP and/or its metabolites in animals.

Data from an *in vitro* cytotoxicity bioassay (ToxiLight™ bioassay kit) found that α-PVP (100 µM, 4 h of incubation at 37°C) did not cause cytolysis under the conditions studied (Rickli, et al., 2015).

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of α-PVP and/or its metabolites in humans.

D1.2.1. User reports

Data reported by the Member States ([17]) and identified from open source information (e.g. Simonsen, et al. (2015) and Sundström et al. (2015)) suggests that α-PVP is used by recreational stimulant users and high risk drug users, including those who inject opioids and stimulants.

In respect to psychological and behavioural effects, data from the online survey conducted by the I-Trend project which was completed by 1074 Polish citizens aged 16+, found that out of 36 respondents who reported α-PVP as the last new psychoactive substance they had used: (multiple responses allowed):

- 38.9% (n=14) experienced aggression;
- 36.1% (n=13) experienced fatigue, exhaustion, sleepiness;
- 33.3% (n=12) experienced seizures;
- 30.6% (n=11) experienced shaking;

([17]) This includes data from: serious adverse events reported to the EMCDDA; questionnaire responses from 6 users providing information to drug testing organisation (SINTES, France); an online survey completed by 1385 people in Poland (I-Trend); reports from representatives of the Finnish Drug Users Union (FDUU); and, monitoring of self-reported user experiences posted on user websites. In the latter respect this included data from: France, which was obtained from systematic monitoring of 3 forums (902 discussions threads, 4 of which specifically related to i-PVP) and from a special project in French and English speaking forums (8 forums, 2 discussion threads on α-PVP); Finland, where 2 online discussion forums were monitored (www.paihdelinkki.fi and http://psyvault.net); and, in Italy where 2 cases were reported from discussion threads (in Italian) on www.psychonaut.com

- 30.6% (n=11) experienced depression, dejection;
- 30.6% (n=11) experienced strong paranoia, fear, anxiety;
- 19.4% (n=7) experienced muscle aches, cramps, jaw clenching;
- 16.7% (n=6) experienced strong craving to use more;
- 11.1% (n=4) experienced extreme agitation and excitement, sleeplessness;

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'. A user in an Italian internet forum cautioned against re-dosing, suggesting that doing it 2 or 3 times in a short period of time brings about impulsive behaviour which results in continuous re-dosing ('you can no longer stop').

Self-reported user experiences provided in the 'Erowid Experience Vaults' suggest that users may experience a range of adverse effects (Erowid, 2015).

D1.2.2. α-PVP associated acute toxicity

Acute intoxications reported by the Member States

205 acute intoxications associated with **α**-PVP were reported by 8 Member States: France (10 cases), Germany (2), Ireland (5), Italy (1), Poland (2), Slovakia (1), Spain (2), and Sweden (182) ([18]). These typically related to acute presentations at hospital emergency departments. The acute intoxications occurred between 2011 and 2015.

Case-level data was provided for 43 of these cases: France (10 cases), Germany (2), Ireland (5), Italy (1), Poland (2), Slovakia (1), Spain (2), and Sweden (20). In order to minimise the potential for confounding caused by other psychoactive substances, case-level data from Sweden was limited to 20 of the 182 reported cases where either **α**-PVP was the only substance that was analytically confirmed or where **α**-PVP was analytically confirmed along with ethanol and/or benzodiazepines and metabolites of benzodiazepines.

35 of the 43 cases were classified as non-fatal intoxications; in the remaining 8 cases the outcome of the intoxication was unknown: Germany (1 case), Poland (1), and Sweden (6).

In 29 of the 43 cases, **α**-PVP was analytically confirmed in one or more biological samples taken from the patient at or around the time of intoxication: France (4 cases), Italy (1),

([18]) The United Kingdom reported that the National Poisons Information Service (NPIS), which provide information on the number of accesses to information held on its online poisons information database TOXBASE® and details of telephone enquiries made to the service by health professionals, reported that in the financial year 2014 through to March 2015, NPIS did not receive any telephone enquiries relating to **α**-PVP or the common names 'Flakka' or 'Gravel'. There were 2 accesses to the **α**-PVP page on TOXBASE® during that year. For the period 1 April to 30 September 2015, three accesses to the **α**-PVP page were noted and one telephone enquiry concerning a case of recreational use of 'gravel' (a name sometimes associated with **α**-PVP) was recorded. No other enquiries were found using the search terms 'alpha-PVP' OR 'alpha PVP' OR 'alphaPVP' OR 'pyrrolidinovalerophenone' OR 'pyrrolidinopentiophenone' OR 'O-2387' OR 'O2387' OR '0-2387' OR '02387' OR 'Flakka'.

Poland (2), Spain (2), and Sweden (20). In the remaining 14 cases, α-PVP was not analytically confirmed: France (6 cases), Germany (2), Ireland (5), and, Slovakia (1); these latter cases have been excluded from the analysis below.

Thus of the 29 analytically confirmed cases, 23 related to non-fatal intoxications and 6 related to cases where the outcome is unknown.

Demographics

Of the 29 analytically confirmed acute intoxications, 24 were male and 4 were female; data on sex was missing for one case. The mean age of the male cases was 33.9 years (n = 21; median 32 years); data on age was missing for four male cases. The mean age of the female cases was 24.3 years (n = 4; median 24.5 years).

Substances analytically identified in biological samples

In 14 of the 29 analytically confirmed acute intoxications α-PVP was the only substance that was detected. In 5 cases, α-PVP and ethanol were the only substances detected; in 2 cases α-PVP, benzodiazepines and metabolites of benzodiazepines were the only substances detected; in 4 cases it is not known or not reported if α-PVP was the only substance detected; in 1 case α-PVP, ethanol, benzodiazepines and metabolites of benzodiazepines were the only substances detected; in 1 case α-PVP, pentedrone, and ethanol were the only substances detected; in 2 cases α-PVP and THC were the only substances detected.

Seriousness of the intoxications

Data on the seriousness of the intoxication were reported for 26 of the 29 analytically confirmed acute intoxications:

- in 10 cases the seriousness of the intoxication was classified as life threatening, requiring treatment in hospital. Of these cases: in 5 cases α-PVP was the only substance that was identified; in 2 cases α-PVP and benzodiazepines and metabolites of benzodiazepines were the only substances identified; in 1 case α-PVP, ethanol, benzodiazepines and metabolites of benzodiazepines were the only substances identified; in 2 cases it was not known if other substances were identified;
- in 15 cases the intoxication was classified as non-life threatening; and,
- in 1 case the intoxication was classified as involving persistent or significant disability or incapacity. No further details were reported.

Clinical features

Data on clinical features ([19]) were reported for 27 of the 29 analytically confirmed acute intoxications. These were generally consistent with sympathomimetic toxicity. They included: tachycardia (17 cases); mydriasis (8); agitation (7) or anxiety (3); tremor (5) or fasciculation (1) or tetany (1); hyperthermia (6); hallucinations (6); hypertension (4); diaphoresis (4); restlessness (3); chest pain (2); convulsions (3) or seizures (2); reduced consciousness (2); somnolence (4); numbness (2); distorted perception (1) or temporal/spatial disorientation (2); rhabdomyolysis (2); delirium (1); aggression (1); cardiac arrhythmia (1); hypotension (1), low oxygen saturation (1), impaired liver function (1); impaired coagulation (1); difficulty in talking (1); paranoia (1); hyperventilation (1); hypoventilation (1); respiratory distress (1); muscular symptoms (1); and, malaise (1).

In one case excited delirium was reported.

Route of administration

Data on the route of administration was available for 15 of the 29 analytically confirmed acute intoxications.

- in 6 cases the route of administration was reported as snorting (nasal insufflation);
- in 5 cases the route of administration was reported as injection. In 1 of these cases it was reported that the substance was injected intravenously. The specific route of injection for the other 4 cases is not known;
- in 3 cases the route of administration was reported as oral administration;
- in 1 case the route of administration were reported as oral administration and injection; the specific route of injection was not reported.

Name of the substance/product used

Data on the name of the substance/product used was available for 23 of the 29 analytically confirmed acute intoxications. These were: 'MDPV' (9 cases), 'alpha-PHP' (3), 'NRG3' or 'energy 3' (2), 'flakka' (2), 'crystal(s)' (2), 'penta' or 'pentadrone' (1), 'APP' (1), '3-MEC' (1), 'PV8' (1), 'internet drug' (1).

Acute intoxications identified from open source information

Examples of case reports of acute intoxications published in the scientific literature that involved the detection of α-PVP are shown in Table 10. In cases where details were available, some of the clinical features described were consistent with sympathomimetic toxicity. However, the data also show that α-PVP was not always the only detected substance, which adds challenges in the attempt to identify causal relationships in all cases.

Table 10. Analytically confirmed acute intoxications associated with α-PVP that were

([19]) Including abnormal laboratory findings.

identified from open source information.

Year of publication	No. of cases	Sex, age	Comments	Reference
2013	1	M, 27	Admission to emergency department following nasal insufflation: heart rate was 128 beats/min, blood pressure 160/90 mmHg, respiratory rate 30 breaths/min, oxygen saturation 97% and temperature 37.1°C, bilateral mydriasis; relevant initial laboratory data indicated rhabdomyolysis without renal failure: creatine kinase 1841 IU/L, myoglobin 275 µg/L, C-reactive protein 33.5 mg/L and normal lactic acid. Hepatic and pancreatic parameters normal; patient confirmed occasional consumption of 'NRG-3' (a few days every 2 months for 6 months) by nasal route, also cannabis and alcohol. Twelve hours after last 'NRG-3' intake (10 h after emergency admission), visual hallucinations were mentioned. Diazepam (20 mg, i.v.) and olanzapine (20 mg, i.v.) given to treat persistent anxiety, agitation, temporo-spatial disorientation and distorted perceptions. Urine positive for cannabis. Purchase of product 'NRG-3' on Internet; α-PVP plasma 235 ng/mL; urine > 5 µg/mL; THC positive This case report is included in the data reported to the EMCDDA by France (see above).	Eiden, et al. (2013)

2013	4	NR[a]	The clinical features of the four cases were not reported; analytical method applied to analysis of hair. Case 1: hair collected one month after most recent use; drug was injected several times with the aim to commit suicide. **α**-PVP (9.4 ng/mg) and **α**-PBP (3.1 ng/mg) detected 10-30 mm from scalp (2nd segment); 7.5 and 3.1 ng/mg in 3rd segment. Case 2: patient was arrested and hospitalized; **α**-PVP detected 10-30 mm and 40-90 mm from scalp, e.g. 40+ ng/mg and ~50 ng/mg in segments 2 and 3. Case 3: Concentrations of **α**-PVP, **α**-PBP and MDPV decreased in hair segments > 20mm from the scalp; hair was dyed brown 20-30 mm from scalp; significant differences noted in MDPV and **α**-PVP concentrations between bleached and unbleached hair segments. **α**-PVP (320+ ng/mg), MDPV (300+ ng/mg) detected in first segment; **α**-PVP, **α**-PBP and MDPV detected in segment 2. Case 4: Patient consulted hospital. **α**-PVP detected (4.5+ ng/mg) in pubic hair in segments 2 and 3 (20-40 mm from skin).	Namera, et al. (2013a)
2014	1	M, 46	Admission to emergency department (in 2013) following ingestion of zolpidem with suicidal intent; no recorded history of psychiatric disorders but active chronic hepatitis C and Gilbert's syndrome. Patient's condition diagnosed as persistent substance-induced psychosis, secondary to prolonged intake of MDPV, mephedrone, butylone and **α**-PVP. Continuous use (from one to three times a week) of a non-specified recreational drug since July 2012 was mentioned. Powdered material analysed to confirm the four substances. Haloperidol decanoate (150 mg) administered every 4 weeks. Slight improvement noted about persecutory delusion but no change in insight. Traces of MDPV were detected in urine.	Dragogna et al. (2014)

2014	1	M, 34	Impaired driving and evaluation by drug recognition expert. Poor navigation observed; driver appeared confused, disoriented and agitated at times; involuntary muscle movements at various times; dilated pupils, elevated systolic blood pressure (150/82 mmHg). Blood analysis: α-PVP (63 ng/mL) and methylone (6.1 ng/mL); positive for ethylone.	Knoy, et al. (2014)
2014	1	M, 'in his 40s'	No clinical features reported. Several intravenous injections of 'unregulated drug' with intention to commit suicide and admission to hospital several hours afterwards. Urine was collected for analysis each morning for one month. Based on first five days of urinary analysis (below level of detection on day 10): urinary elimination half-lives 22 h and 11 h for α-PVP and α-PBP; elimination half-lives during second half period (6-10 days after injection) were 40 h and 30 h for α-PVP and α-PBP. Detection of α-PVP and α-PBP, plus their pyrrolidin-2-one-type metabolites. Highest concentration in first sample > 32 h after final injection: α-PVP 1.2 and α-PBP 1.6 µg/mL.	Namera, et al. (2014)
2014	19	NR[a]	No details reported. Urine samples collected at autopsy or represented clinical toxicology cases.	Shima, et al. (2014)
2014	8	NR[a]	No details reported. Urine samples collected at autopsy or represented clinical toxicology cases. α-PVP urine levels 0.08–13 mg/L but other substances (not specified) were also detected.	Tyrkkö, et al. (2013)
[a] NR: not reported.				

D1.2.3. α-PVP associated deaths

Deaths reported by the Member States

Case-level data for 116 deaths associated with the use of α-PVP were reported by 8 Member States: Finland (37 cases), France (2), Hungary (19), Ireland (5), Poland (26), Spain (1), Sweden (16) and the United Kingdom (10). These deaths occurred between 2012 and 2015.

In 115 cases, α-PVP was analytically confirmed in one or more biological samples taken from the decedents. In the remaining case α-PVP was not analytically confirmed, and this case has been excluded from the analysis below.

Demographics

Of the 115 deaths, 92 (80%) were male and 23 (20%) were female. The mean age of the male decedents was 35.6 years (n = 72; median 32 years); the mean age of the female decedents was 35.3 years (n = 22; median 34.5 years).

Number of deaths by year

18 deaths occurred in 2012; 24 occurred in 2013; 49 in 2014; and, 23 in 2015. The year of death was not known for 1 case.

Cause of death reported by the Member States

A review of the cause of death reported for the 115 deaths found that:

- in 23 (20%) cases, α-PVP was reported as the cause of death or was reported as a contributing factor (i.e. α-PVP was explicitly mentioned). This includes 5 cases where α-PVP was the only substance detected.
- In the remaining cases there was alternative cause of death recorded or the cause of death was not known at the time of reporting. Where an alternative cause of death was reported, the manners of death were varied and included: hanging, drowning, fall, road traffic accident, carbon monoxide, blood loss, as well as cited drug intoxication.

Toxicological significance of α-PVP

In an attempt to evaluate the toxicological significance of α-PVP in the deaths reported, an assessment of the following evidence was considered in each case: presence and concentration (and pharmacological nature) of α-PVP; presence and concentration (and pharmacological nature) of other drugs present (including alcohol); circumstances of death; pathological findings at post-mortem, and cited cause of death. This allowed categorisation of the significance of α-PVP in the deaths as being of low significance (i.e. alternative cause of death), medium significance (i.e. α-PVP may have contributed to toxicity/death but other

drugs present may have been more toxicologically significant) or high significance (i.e. α-PVP was cited as the cause of death or was assessed to have been likely to contribute to toxicity/death even in the presence of other drugs). In order to highlight potential interactions or contributing toxicology, the other substances found in the cases were characterised.

The results of this assessment concluded that in 21 deaths α-PVP was either the cause of death or is likely to have contributed to death even in the presence of other substances; in 7 of these deaths α-PVP was the sole drug present. In 55 deaths α-PVP may have contributed to toxicity but other substances were present that may have been more toxicologically significant. In 39 deaths α-PVP was assessed to be of low significance, including an alternative cause of death. In the cases where other drugs were detected in addition to α-PVP (the majority) a wide variety of drugs were detected (including benzodiazepines, alcohol, opiates, opioids, antidepressants and anticonvulsants). Of other stimulants detected these included amphetamines, pseudoephedrine and synthetic cathinones (e.g. MDPV, pentedrone, 4-MEC, 3-MMC). Synthetic cannabinoids were also detected in some cases.

In the deaths where α-PVP was quantified, concentrations ranging from 0.003 mg/L to 2 mg/L in blood have been found. In cases where α-PVP would be regarded as being of low significance, the median blood concentration was 0.07 mg/L (range 0.003–1.38 mg/L), where α-PVP was of medium significance the median blood concentration was 0.09 mg/L (range 0.006–0.65 mg/L) and in those cases where α-PVP was of high significance the median blood concentration was 0.47 mg/L (range 0.02–2 mg/L).

In all deaths there was a lack of information regarding any symptoms experienced by the deceased prior to death, largely due to the manner of death (e.g. 'found dead' was the only information reported). However, in those instances where symptoms have been described, confusion, agitation, aggression, bizarre behaviour, seizures, high body temperature, rhabdomyolysis, sweating and increased heart rate were reported. Although other drugs were associated with most of these cases, the symptoms are consistent with those seen in acute intoxications.

Deaths identified from open source information

31 deaths that involved the detection of α-PVP in one or more biological samples were identified from the scientific literature. These cases were published between 2013 and 2015 and were from Japan (Hasegawa, et al., 2014), (Minakata, et al., 2014), (Nagai et al., 2014), (Namera, et al., 2013b), (Saito, et al., 2013), United States of America (Marinetti and Antonides, 2013), (Richards-Waugh et al., 2013), (Shanks, et al., 2013), Poland (Sykutera, et al., 2015) and Australia (Sellors et al., 2014), (Yap and Drummer, 2015). The manners of death, any symptoms and prevalence of other drugs were similar to those cases reported by Member States (above). Two of the case reports were also reported to the EMCDDA by France and Poland (Eiden, *et al.*, 2013; Sykutera, *et al.*, 2015).

D2. Chronic health effects

D2.1. Animal data

No studies were identified that have investigated the chronic health effects of α-PVP in animals.

D2.2. Human data

No studies were identified that have investigated the chronic health effects of α-PVP in humans.

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market

Data from seizures reported to the EMCDDA suggest that, in general, bulk quantities of α-PVP in powder form are mainly imported into the EU from China. In this respect, it is important to note that on 1 October 2015 the People's Republic of China controlled α-PVP under national drug control legislation.

In addition to importation, two illicit production sites synthesising α-PVP have been seized in Poland. The α-PVP was intended for the domestic market and export (Section F).

α-PVP is offered for sale in small, retail quantities (1 gram upwards) and in bulk (kilogram) quantities by Internet retailers as a drug in its own right (Section C). The purity of these products may be claimed to be high but this has not been tested by forensic analysis.

Detailed information in respect to route-specific by-products produced during the synthesis of α-PVP is currently not available. In addition, there are no quantitative data currently available on the impurities detected in seized and collected samples.

Information on purity was only available for 17 seizures reported to the EMCDDA. Here the purity ranged from 23% (2 seizures) to over 95 % (8 seizures) (Section A1.1).

α-PVP is also sold surreptitiously as other psychoactive substances, including controlled drugs such as MDPV and methamphetamine, as well as 'ecstasy' ([20]) (Section C).

Seizure data and collected samples reported by the Member States suggests that products found to contain α-PVP also contained other types of psychoactive substances: in around 35% of the detections, α-PVP was found in combination with other substances including other cathinones (mainly MEC ([21]), MMC ([22]), pentedrone, MDPBP ([23]), ethylcathinone and

([20]) Seized street tablets found to contain α-PVP showed a range of markings and logos thus, raising the possibility that they may be sold as 'ecstasy' tablets on the illicit drug market.

([21]) Methylethcathinone (isomer not specified).

MDPV), synthetic cannabinoids, and a range of other new psychoactive substances (such as MPA ([24]), 5-MeO-MIPT ([25]), AMT ([26]) and 2-DPMP ([27])), substances that are internationally controlled and/or controlled at EU-level (ketamine, PMMA ([28]), 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.

Overall, the data suggests that while some individuals may be exposed to α-PVP intentionally, others may be exposed unintentionally after consuming a product (including 'legal high' products) with no indication that it contains α-PVP or following its ingestion as a component of a mixture of other active substances.

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

There is limited information on commonly used English-language user websites regarding the effects and potential health/adverse effects related to the use of α-PVP (Section D1.2.1). The users and forum discussion participants appear to be generally aware of the psychostimulant-like effects of α-PVP. This includes awareness of both desired and undesired effects.

Data from the online survey conducted by the I-Trend project which was completed by 1074 Polish citizens aged 16+, found that out of 36 respondents who reported α-PVP as the last new psychoactive substance they had used: (multiple responses allowed):

63.9% (n=23) used it to bond with others/to socialise;

58.3% (n=21) used it to get high;

44.4% (n=16) used it to modify perception;

44.4% (n=16) used it to relax;

27.8% (n=10) used it to fight tiredness;

25% (n=9) used it provide themselves with energy (not sex related);

([22]) Methylmethcathinone (isomer not specified).

([23]) 3',4'-Methylenedioxy-α-pyrrolidinobutyrophenone.

([24]) Methylthienylpropamine.

([25]) 5-Methoxy-N-methyl-N-isopropyltryptamine.

([26]) α-methyltryptamine.

([27]) 2-(Diphenylmethyl)piperidine.

([28]) *para*-Methoxymethamphetamine.

19.4% (n=7) used it to allay or alleviate anxiety;

19.4% (n=7) used it to stimulate brain activity for learning or work;

16.7% (n=6) used it to reduce the negative effects of another drug;

8.3% (n=3) used it to improve sexual intercourse;

8.3% (n=) used it for other reasons;

5.6% (n=2) used it to sooth pain;

2.8% (n=1) used it to increase the positive effects of another drug;

2.8% (n=1) used it to flight sleeplessness.

Other effects reported on user websites include 'euphoria' and 'increased libido' (Finland, France) ([1]).

D3.3. Characteristics and behaviour of users

Information on the characteristics and behaviour of users of **α**-PVP is limited.

The available data suggests that **α**-PVP is used by recreational stimulant users and high-risk drug users (Section C). In the latter case this includes people who inject opioids and stimulants, some of whom are attending low threshold harm reduction services and drug treatment services, including opioid substitution treatment services. The available data also suggests that polydrug use might be common in those using **α**-PVP.

Data from the online survey conducted by the I-Trend project which was completed by 1074 Polish citizens aged 16+, found that out of 36 respondents who reported **α**-PVP as the last new psychoactive substance they had used:

38.9% (n=14) had used **α**-PVP on 20 days or more in the last 12 months;

11.1% (n=4) had used **α**-PVP on between 10 and 19 days in the last 12 months;

16.7% (n=6) had used **α**-PVP on between 4 and 9 days in the last 12 months;

19.5% (n=7) had used **α**-PVP on between 1 and 3 days in the last 12 months;

13.9% (n=5) had not used **α**-PVP at all in the last 12 months.

A case-control study conducted in Dublin, Ireland, following an outbreak of recently acquired HIV infections among homeless people who inject drugs found that the injection of 'snow blow'—which the authors suggest is **α**-PVP—was strongly associated with HIV infection (adjusted odds ratio: 49; p=0.003) (Giese et al., 2015). It is important to note that the epidemiological link between 'snowblow' and **α**-PVP suggested by the authors is limited to the analytical detection of **α**-PVP in the urine of 5 of 12 HIV positive cases and the detection of **α**-PVP in the urine of patients some of whom are in opioid substitution treatment programs (See Section C and McNamara et al., 2015). Data are not provided on when the urine samples of the cases were taken. No urinalyses appear to have been conducted on controls.

An unequivocal epidemiological link between 'snowblow' and α-PVP was not reported in the study.

D3.4. Nature and extent of health consequences

The limited information available on the pharmacology, dependence and abuse potential, and acute health effects of α-PVP have been discussed above (Section A2, Section B, Section D1, Section D2).

Based on animal model experiments (Section A2) as well as on self-reports and acute intoxications (Section D1.2), the acute behavioural effects of α-PVP, including effects on the ability to operate machinery and drive, might bear some similarities to those induced by other psychostimulants such as MDPV, cocaine, and methamphetamine.

Aggregated data related to cases of suspected driving under the influence of drugs (DUID) were reported to the EMCDDA. There are insufficient data available to discuss the circumstances of these cases

D3.5. Long-term consequences of use

There is no data on the long term consequences of using α-PVP.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

It appears that α-PVP is sourced and used by individuals attempting to source the drug itself. Sources appear to include internet retailers, bricks-and-mortar shops, friends and other acquaintances, and street level drug dealers. In addition, the available data also supports the premise that some users are unaware that they have sourced and used α-PVP (Section C and Section D1.2).

Based on the available data, it seems reasonable to consider that α-PVP is used in the same environments as other psychostimulants. This would be typically (but not restricted to) home environments, pubs/bars and discotheques/nightclubs, and outdoor music festivals ([29]). In addition, α-PVP is likely to be used in some of the other environments used by high risk drug users who inject opioids and stimulants (Section D1.2.3 and Giese et al., 2015; Sundström et al., 2015).

([29]) Data from the online survey conducted by the I-Trend project which was completed by 1074 Polish citizens aged 16+, found that out of 36 respondents who reported α-PVP as the last new psychoactive substance they had used: 36.1% (n=13) had last used α-PVP with friends either in their home or their friends home; 30.6% (n=11) had last used α-PVP with friends outside/in the countryside; 16.7% (n=6) had last used α-PVP alone at home; 8.3% (n=3) had last used α-PVP with friends at a club, pub, or party; 5.6% (n=2) had last used α-PVP at school or work; 2.8% (n=1) had last used α-PVP in other circumstances.