1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-PVP)

Critical Review Report

Agenda item 5.3

Expert Committee on Drug Dependence

Thirty-seventh Meeting

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World Health Organization

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Summary

1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one (α-PVP) is a psychomotor stimulant that has originally been explored in the 1960s. It is the desmethyl analogue of pyrovalerone, which is listed in Schedule IV of the 1971 United Nations Convention on Psychotropic Substances. A closely related derivative of α-PVP gives rise to 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (3,4-methylenedioxypyrovalerone, MDPV) that has recently been placed in Schedule II of the UN Convention on Psychotropic Substances (1971). The first official notification of α-PVP detection in the European Union was received in February 2011.

α-PVP is a synthetic cathinone derivative and commonly referred to as a new psychoactive substance (NPS), 'research chemical', 'bath salt' or 'designer drug'. α-PVP appears to act as a potent blocker at the dopamine and norepinephrine transporter and pre-clinical research into areas of abuse liability, psychomotor activity and drug discrimination suggests that the properties of α-PVP are reminiscent of MDPV, methamphetamine and cocaine.

Data indicate that α-PVP is most commonly encountered in powdered and tablet form. In addition to being available from Internet vendors in both wholesale and consumer amounts, α-PVP has also been encountered in products destined for the traditional illicit drugs market, for example, in form of 'ecstasy' tablets.

More than 130 deaths have been associated with α-PVP and among the non-fatal acute intoxications reported, hospitalizations were required. In cases where α-PVP use was established unambiguously, neurological and cardiovascular effects consistent with an extensive psychostimulant toxidrome have been observed and included cardiotoxicity, violent behavior and display of psychotic behavior. In addition to use by traditional recreational drug users it appears that α-PVP is also used by high-risk drug users including those who inject.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

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)

C. Other Names

α-Pyrrolidinopentiophenone, α-pyrrolidinovalerophenone, α-PVP, alpha-PVP, desmethyl pyrovalerone, prolintanone, β-keto-prolintane, pyrodilyl ketone, α-pyrrolidino ketone, 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, O-2387.

D. Trade Names

Not applicable.

E. Street Names

Street names encountered in European Member States and reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)[1] include 'grind', 'flakka', 'gravel', 'crystal love', 'Pure NRG', 'Snow Blow' and 'vanilla sky'. Prominent street names encountered in the United States of America include 'flakka' and 'gravel'. Product names reported to contain α-PVP include '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 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).

F. Physical properties

α-PVP HCl is a white crystalline powder.

G. WHO Review History

α-PVP was not previously pre-reviewed or critically reviewed. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.[1]

2. Chemistry

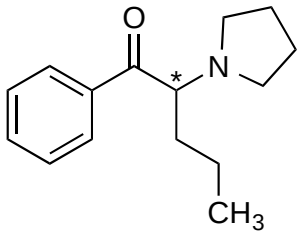
A. Chemical Name

IUPAC Name: 1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one

CA Index Name: 1-Phenyl-2-(1-pyrrolidinyl)-1-pentanone

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral center

Molecular Formula: $C_{15}H_{21}NO$ (free base)
Molecular Weight: 231.34 g/mol
Melting point:
Hydrochloride salt: 173 °C (ethanol/diethyl ether)[2, 3]
Hydrochloride salt: 162 °C[4, 5]
Hydrochloride salt: 162 °C (acetone)[6]
Hydrochloride salt: 104–106 °C followed by 169–170 °C (anhydrous)[7]
Acid sulfate salt: 140 °C (isopropanol)[6]
Tartrate salt: 148–149 °C[4]
Tartrate salt: 148–149 °C (isopropanol)[6]
Maleate salt: 131 °C[4]
Maleate salt: 131 °C (acetone)[6]
Hydrogen maleate salt: 131 °C[5]
Hydrogen maleate salt: 131 °C (acetone)[6]
Citrate salt: 88 °C[4]
Citrate salt: 88 °C (acetone)[6]

Boiling point:
Free base: 113 °C [4-6]

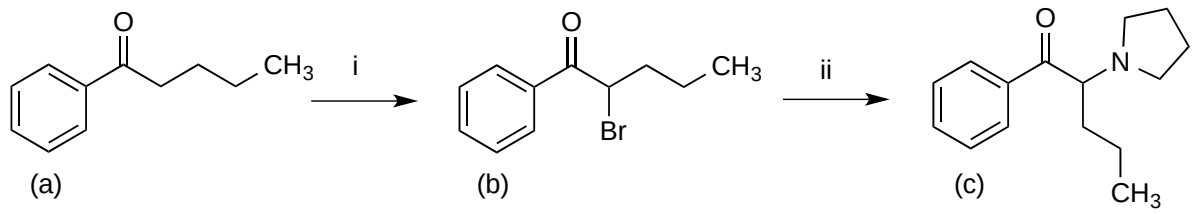
C. Stereoisomers

The presence of a chiral center at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-α-PVP and (*R*)-α-PVP, respectively. Currently, it appears that data about potentially distinguishable pharmacological properties have not been published. α-PVP is most likely to be available as the racemic mixture.

D. Synthesis

Methods of manufacturing:

One of the main procedures used for α-PVP synthesis includes the α-halogenation (e.g. using bromine) (step i) of the 1-phenylpentan-1-one (valerophenone) precursor (a) and formation of the 2-bromo-1-phenylpentan-1-one (b). Reaction with pyrrolidine (step ii) gives α-PVP (c) that can then be converted into a range of salts. Valerophenone (a) may also been obtained from a number of precursors including benzene or benzaldehyde. One of several alternatives may include the oxidation of the ephedrine-type 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-ol precursor[7-9] or reaction of 2-bromo-1-phenylpentan-1-one with alkoxide reagents to yield epoxide intermediates that can then be reacted with pyrrolidine.[8, 10, 11] A Grignard reaction between phenylmagnesium halide with 2-(pyrrolidin-1-yl)pentanamide has also been suggested.[8]



E. Chemical description

α-PVP is the desmethyl analogue of pyrovalerone, which is listed in Schedule IV of the 1971 United Nations Convention on Psychotropic Substances. A closely related derivative of α-PVP is 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (3,4-methylenedioxypyrovalerone, MDPV), a cathinone derivative that was subject to a critical review during the thirty-sixth meeting of the Expert Committee on Drug Dependence in 2014. The Committee recommended that MDPV be placed in Schedule II of the 1971 Convention.

F. Chemical properties

α-PVP hydrochloride is a white, crystalline powder. Its solubility was given 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.[12]

G. Chemical identification

The first thermal properties have been described in the early 1960s (Section B). The first NMR data have been published in 2005 and 2006, which followed a systematic investigation of pyrovalerone analogues that included the evaluation of monoamine transporter activities.[2, 3] Although α-PVP was reported to have been encountered in a German seizure in 2005,[13] mass spectral data derived from metabolism studies were only published in 2009.[14] Implementation of the Marquis test was reported to result in a 'clear' reaction whereas formation of a 'gray/black' result was obtained from the Mecke test.[15] α-PVP has been thoroughly employed for analytical purposes and featured in a range of routine methods of analysis associated with forensic and clinical investigations (Table 1).

Table 1. Representative examples of scientific literature associated with chemical analysis and α-PVP

Techniques [a]	**Comment**	**Reference**
GC-MS	Metabolism studies *in-vivo* (male Wistar rats) and *in-vitro.*	Sauer *et al.*[14]
NMR, GC-MS, FTIR,	Characterization of synthesized material.	Casale and Hays[16]
ESI-in-source CID-MS	Characterization of synthesized material.	Power *et al.*[17]
LC-TOF-MS	Analysis of branded products.	Shanks *et al.*[18]
LC-QqQ-MS/MS	Method development for oral fluid analysis and application to test samples obtained from subjects.	Amaratunga *et al.*[19]
LC-Q-MS/MS	Method development for urine analysis and application to authentic urine specimens.	Concheiro *et al.*[20]
LC-MS/MS	Detection in biofluids and powdered sample by FTIR and GC-MS.	Eiden *et al.*[21]
GC-MS	Analysis of a branded product.	Elie *et al.*[22]
LC-QqQ-MS/MS	Detection in biofluids.	Marinetti *et al.*[23]
LC-Q-MS	Method development for hair analysis and application to authentic hair specimens.	Namera *et al.*[24]
GC-MS, LC-Q-MS	Detection in biofluids.	Namera *et al.*[25]
GC-MS	Detection in biofluids.	Saito *et al.*[26]
LC-MS/MS	Detection in biofluids.	Shanks *et al.*[27]
GC-MS	Characterization of synthesized material.	Tsujikawa *et al.*[28]
LC-Q-TOF-MS/MS	Metabolism studies *in-silico* and *in-vitro* and application to authentic urine specimens.	Tyrkkö *et al.*[29]
LC-Q-TOF-MS/MS	Characterization of supplied standards.	Fornal[30]
GC-MS, LC-QqQ-MS/MS	Detection in biofluids.	Hasegawa *et al.*[31]
LC-TOF-MS	Detection in biofluids.	Knoy *et al.*[32]
GC-MS, LC, ion trap-Orbitrap-MS/MS	Analysis of branded products.	Leffler *et al.*[33]
MALDI-TOF-MS and Q-TOF-MS/MS	Method development for blood and application to authentic blood specimens.	Minakata *et al.*[34]
GC-MS	Detection in authentic urine specimens.	Namera *et al.*[35]
LC-TOF-MS	Analysis of products purchased from shops.	Schneir *et al.*[36]
GC-MS, LC-QqQ-LIT-MS/MS	Detection in authentic urine specimens.	Shima *et al.*[37]
LC-UV	Chiral analysis of products obtained from Internet retailers.	Taschwer *et al.*[38]
^{13}C-NMR	Analysis of reference material.	Uchiyama *et al.*[39]
GC-MS	Detection in authentic urine specimens.	Uralets *et al.*[40]
LC-QqQ-MS/MS	Use as internal standard for analyses of biofluids.	Wurita *et al.*[41]
GC-MS, LC-UV, FTIR, IMS	Characterization of supplied samples.	Armenta *et al.*[42]
LC-QqQ-MS/MS	Detection in wastewater samples.	Borova *et al.*[43]
LC-Q-Orbitrap-MS/MS	Method development for urine analysis and application to authentic urine specimens.	Concheiro *et al.*[44]
Several GC-MS and LC-MS	Metabolism studies *in-vitro* and application to authentic biofluids	Friscia *et al.*[45]

based methods.	samples	
SPME-GC-MS	Method development using supplied samples.	Fujii *et al*.[46]
FTIR, NMR	Characterization of synthesized samples	Guha *et al*.[9]
LC-Q-TOF-MS/MS	*In-vitro m*etabolism studies.	Negreira *et al*.[47]
GC-MS. LC-Q-MS	Detection in biofluids and powdered material.	Sykutera *et al*.[48]
LC-QqQ-MS/MS	Detection in biofluids.	Yap and Drummer[49]
[a] GC: gas chromatography; MS: mass spectrometry: MS/MS: tandem mass spectrometry; ESI: electrospray ionization; MALDI: matrix-assisted laser desorption/ionization; CID: collision-induced dissociation; TOF: time-of-flight; Q: quadrupole; QqQ: triple quadrupole; LIT: linear ion trap; LC: liquid chromatography (various forms); NMR: nuclear magnetic resonance spectroscopy; FTIR: Fourier transform infrared; UV: ultraviolet; SPME: solid-phase microextraction.		

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

One of the prominent features frequently encountered with cocaine and amphetamine-like psychostimulants includes the ability to increase extracellular levels of dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT), respectively. An important question related to the evaluation of psychostimulant properties on the molecular level includes the assessment of drug action at the dopamine (DAT), norepinephrine (NET) and serotonin (SERT) transporters. Evidence is mounting that α-PVP is potent blocker at DAT and NET with significantly reduced activity at SERT. So far, insights gained from investigations carried out *in vivo* also indicate the propensity of α-PVP to behave as a psychostimulant with potential for abuse liability under conditions explored in animal studies. It is anticipated that further studies will come to light given the emergence of this substance in recent years. Data obtained from systematic clinical studies in humans are currently unavailable.

A. Pharmacodynamics

The central nervous system stimulant and hypertensive properties of α-PVP and closely related 'α-pyrrolidino-valerophenones' have been recognized during earlier pharmaceutical explorations in the 1960s which led to a variety of suggested drug formulations (Section 4B).

<u>*In-vitro* pharmacology</u>

The first indication that α-PVP acted as a catecholamine-selective reuptake inhibitor appeared in the mid-2000s and was published by Meltzer *et al*. as part of comprehensive investigations on 38 analogues of pyrovalerone.[2,3] Indeed, more recent studies confirmed that the profile of α-PVP was consistent with DA and NE uptake blockage rather than substrate-type release, thus, behaving cocaine and MDPV-like rather than amphetamine-like.[50-53] Key data are summarized in Table 2 and it can be seen that transporter selectivity of α-PVP was comparable to MDPV as indicated as well by similar DAT/SERT ratios (α-PVP > 781; MDPV = 806). In comparison, non-selectivity of cocaine resulted in a DAT/SERT of 1.5 instead as shown, for example, by Marusich *et al*.[51] Radioligand binding data reported at this

stage (Table 2) indicate that α-PVP may show affinity in the micromolar range where highest affinity was observed at the 5-HT_{1A} receptor (K_i = 5.2 μM using [^{3}H]-8-OH-DPAT and indatraline). In contrast, K_i values determined for DAT and NET were 0.007 μM and 0.06 μM, respectively.[53] The extent to which these lower affinities might impact on the psychoactive properties of α-PVP in humans is unclear but may become relevant depending on dosage levels.

Table 2. *In vitro* assay data for α-PVP

Uptake [a]			**Affinity** [b]			**Ref**
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.*[2]; Meltzer *et al.* [c,3]
205 [d]	--	--	--	--	--	Kolanos *et al.* [e,50]
12.8	14.2	> 10,000	--	--	--	Marusich *et al.* [f,51]
17.5	--	> 10,000	--	--	--	Kolanos *et al.*[52]
40	20	> 100,000	7	60	> 30,000	Rickli *et al.* [g,53]
Additional *in-vitro* assay data for α-PVP						
Receptor binding profiles: [h] 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}): [i] > 20 μM and no activation. Cytotoxicity: None detected under conditions used (at 100 μM). [j]						Rickli *et al.*[g,53]

[a] Ref [3]: HEK293-hDAT, HEK293-hNET, HEK293-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Ref [50]: HEK-hDAT ([^{3}H]DA); Ref [51]: rat brain synaptosomes (5 nM [^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Ref [52]: rat brain synaptosomes (5 nM [^{3}H]DA, [^{3}H]5-HT); Ref [53]: HEK293-hDAT, HEK293-hNET, HEK293-hSERT (5 nM [^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT)

[b] Ref [3]: HEK293-hDAT, HEK293-hNET, HEK293-hSERT ([^{125}I]RTI-55, 40-80 pM)); Ref [53]: 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 ref. [2]

[c] Uptake data cocaine[3] (IC_{50}/nM): DAT = 461; NET = 378; SERT = 494. Affinity data for cocaine[3] (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[50]: DAT K_i = 135 nM.

[f] Uptake data MDPV[51] (IC_{50}/nM): DAT = 4.1; NET = 25.9; SERT > 10,000. Uptake data cocaine[51] (IC_{50}/nM): DAT = 211; NET = 292; SERT = 313. Uptake data amphetamine[51] (IC_{50}/nM): DAT = 93; NET = 67; SERT = 3,418.

[g] Uptake data MDPV[53] (IC_{50}/nM): DAT = 50; NET = 40; SERT = 9,600. Uptake data methamphetamine[53] (IC_{50}/nM): DAT = 1,100; NET = 140; SERT = 18,000. Uptake data amphetamine[53] (IC_{50}/nM): DAT = 1,300; NET = 70; SERT = 35,000. Affinity data for MDPV[53] (K_i/nM): DAT = 10; NET = 8; SERT = 2,900. Affinity data for methamphetamine[53] (K_i/nM): DAT = 1,800; NET = 3,000; SERT = 24,600. Affinity data for amphetamine[53] (K_i/nM): DAT = 5,700; NET = 1,000; SERT > 25,000.

[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).

[i] HEK293-h5-HT_{2B} and FLIPR assay.

[j] ToxiLight BioAssay (measurement of adenylate kinase release from damaged cells).

In-vivo pharmacology

The first indication that α-PVP interacted with the dopamine transporter in the animal brain came from Madras et al. who confirmed displacement of the high affinity probe [^{11}C]WIN 35,428 by positron emission tomography in rhesus monkeys. The occupancy was given as 64%.[2] Additional studies published since 2014 provided further evidence that effects induced by α-PVP might have been comparable to those induced by MDPV, cocaine and methamphetamine (Table 3), such as locomotor stimulation[51, 54-56] and elevation of extracellular dopamine levels in the striatum of 8 weeks old Balb/c male mice following microdialysis studies.[54] α-PVP also resulted in full substitution for the discriminative stimulus effects of cocaine and methamphetamine[56,57] and was shown to decrease intracranial self-stimulation thresholds in male Sprague-Dawley rats.[58] Conditioned place preference was observed at some doses[56] (Table 3) and both α-PVP and MDPV were determined to show similar potency and efficacy under a progressive-ratio schedule of reinforcement.[55] Consistent with the ability of a range of psychomotor stimulants to mediate hyperactive behavior via increased dopamine transmission, implementation of dopamine D_1 and D_2 receptors antagonism experiments resulted in attenuation of locomotor activation.[51, 54] Bizarre behavior and stereotypy have been observed in several studies, especially at higher dosage levels.

Table 3. *In vivo* assay data for α-PVP

Behaviour	Neurochemistry / Physiology etc.	Ref
--	Dopamine transporter (DAT) occupancy (rhesus monkeys): [a] 64% as determined by positron emission tomography imaging; intravenous injection following pre-treatment with [^{11}C]WIN 35,428 ([^{11}C]CFT).	Madras *et al.*[2]
Locomotor activity: [b] Oral administration of α-PVP (25 mg/kg) and methamphetamine (5 mg/kg) as a positive control. 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 and a D_2 receptor antagonists 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.	Microdialysis (striatum): [c] Oral administration of α-PVP (25 mg/kg) and methamphetamine (5 mg/kg) led to significant increase in dopamine levels in dialysate samples. α-PVP showed shorter onset than methamphetamine but less pronounced concentration levels, e.g. ~600% DA increase for methamphetamine vs. ~ 350% DA increase at 20 min post-administration).	Kaizaki *et al.*[54]
Locomotor activity: [d] 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. 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 D_1 receptor antagonist attenuated locomotor activity. Functional observational battery (FOB): [d] Significant increases in some observational measures 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.*[51]
Intracranial self-stimulation (ICSS) thresholds: [e] 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.*[58]
Locomotor activity: [f] 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	Thermoregulation: [f] Modest, but consistent; dose-dependent hypothermic alteration ~0.75 °C up to 3	Aarde *et al.*[55]

activity 2 h after injection of 5.6 mg/kg dose. Intravenous self-administration: [f] α-PVP considered similar to MDPV in potency and efficacy as a reinforcer; intake and lever discrimination of α-PVP higher than MDPV.	hours after dosing.	
Locomotor activity: [g] 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. Drug discrimination: [h] 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. 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.*[56]
Drug discrimination: [j] Full substitution of observed; total drug-lever responses reached 88.6% at 2.0 mg/kg; potency differences expressed as ED_{50} values: methamphetamine = 0.3 mg/kg; α-PVP = 0.7 mg/kg; cocaine = 3.3 mg/kg; control response rates were significantly reduced at does of 1.0 mg/kg (methamphetamine), 2.0 mg/kg (α-PVP) and 8.0 mg/kg (cocaine).		Naylor *et al.*[57]

[a] Comparison of positron emission tomography imaging pre- and post-drug session based on reduced [^{11}C]WIN 35,428 binding one hour or longer after administration.

[b] 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.

[c] 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).

[d] 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.

[e] 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.

[f] 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); activity rate determined by radiotelemetry transmitters for 180 min following α-PVP administration (1, 5.6 and 10 mg/kg, i.p.). Thermoregulation: room conditions 21 °C, single housing.

[g] 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.

[h] 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.

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

[j] 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.

B. Routes of administration and dosage

A number of drug formulations related to α-PVP have been suggested and published in the earlier patent literature and are summarized in Table 4. The claims made referred to its use as central nervous stimulants and hypertensive agents in humans. α-PVP, together with its *para*-substituted analogues (including chloro-, methyl- and methoxy-) was claimed to show 'good central-stimulating action without undesirable effects, such as circulatory effects'.[8]

Table 4. Suggested formulations encountered in the patent literature [a]

Formulation	Dosage unit	Ref
Tablets (240 mg, ø = 9 mm)	Production: 110 g product in 2606 g composition for tableting; suggested range 5 – 60 mg	8
Suppository	10 – 60 mg	8
Tablets (220 mg, ø = 9 mm)	20 mg	6
Dragees (350 mg, ø = 9 mm, convex)	30 mg	6
Ampoules (2 mL)	10 mg	6
Drops (1 mL)	15 mg	6
Tablets (220 mg)	20 mg	4, 5
Coated pills (~350 mg)	30 mg	4, 5
Ampoules (2 mL)	10 mg	4, 5
Drops (1 mL)	15 mg	4, 5

[a] Patents also capture several other *para*-ring-substituted analogues.

Reports submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), user reports on websites and case reports[1] indicate that routes of administration may include snorting, smoking/inhalation, injection, oral (ingestion), sub-lingual, rectal and mixed routes (oral and injection) of administration. Detailed information on common dosage levels may be difficult to obtain, especially if drug or product purities are not known, and it would appear that a particular route of administration might require varying dosage levels. Some tentative estimation pointed toward threshold levels around 1-2 mg to "strong" effects between 20-25 mg by oral ingestion. Nasal insufflation might result in more potent effects.[59] Dosage levels associated with α-PVP appear to be relatively similar to those reported for MDPV[60] but this has to remain speculative.

C. Pharmacokinetics

Information collected from systematic studies in humans is lacking but some data became available in recent years grounded in *in-vitro* studies and observations made in casework. Results obtained from casework analyses indicated that metabolically unchanged α-PVP was detectable and that other transformation products may be equally relevant for targeted analyses, such as 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.

The first investigation published in 2009 was based on the implementation of a screening procedure in 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 derivatization.[14] A range of biotransformation products were detected and 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 appeared to be catalyzed following exposure to human hepatic cytochrome-P450 (CYP) enzymes CYP2B6, CYP2C19, CYP2D6, and CYP1A2, respectively.[14,61] More recently, seven Phase I metabolites were identified in authentic human urine samples which confirmed a number of transformation steps such 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. giving rise to 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-ol (HO-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.[29] Similarly, the detection of the hydroxyalkyl-PVP species was also noted based on investigations in case work and *in vitro* studies.[45] Analyses of urine samples obtained from a substance user who administered a drug mixture intravenously led investigators to estimate an urinary elimination half-live of 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.[35] The analysis of authentic human urine samples also revealed the detection of HO-PVP diastereomers, 2''-oxo-PVP, 2''-HO-PVP and HO-PVP glucuronide.[37] A large-scale investigation of submitted urine samples confirmed the 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-PVP without pyrrolidine degradation may be less pronounced in PVP-type substances.[40] A recent investigation into in vitro Phase I and Phase II metabolism of α-PVP revealed the 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.[47]

5. Toxicology

The LD_{50} of α-PVP hydrochloride (mouse, intravenous) was given at 38.5 mg/kg.[62] A recently carried out cytolysis test that employed α-PVP and a variety of other pyrovalerone analogues did not lead to observations of cytotoxic effects under the conditions studied (after 4 h of incubation at 37°C, drug concentration 100 μM).[53] Data on the effects of α-PVP metabolites are currently not available.

6. Adverse reactions in humans

Tables 5-8 provide an overview of fatal and non-fatal intoxications obtained from the scientific literature and from reports received by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).[1] Representative, clinically relevant observations

have been added where available. It is worth noting that α-PVP was not always the only substance present in the analyzed biofluids and this can pose challenges when attempting to disentangle causal relationships, especially in the absence of detailed pharmacokinetic data obtained from human studies. A causal link could not be established in all cases and other confounders such as pre-existing history of poly-drug use and mental health problems might have been relevant as well. In cases where α-PVP use was established unambiguously, neurological and cardiovascular effects consistent with an extensive psychostimulant toxidrome have been observed and included cardiotoxicity, violent behavior and display of psychotic behavior.

Table 5. Fatal case reports associated with α-PVP published in the scientific literature

Year	Cases	Patient, age	Context/clinically related comments (examples)	Notes	Ref
2013	1	M, 32	Death (M, 32) following nasal insufflation; post-mortem: moderate obesity, pulmonary oedema, atherosclerotic heart disease with 70% narrowing of the right coronary artery and fatty liver changes with fibrosis.	Purchase of product "NRG-3" on Internet labelled with incorrect structure and chemical name; α-PVP confirmed by analysis; post-mortem plasma and urine concentrations of α-PVP 1500 ng/mL and 5 µg/mL; alcohol 3.65 g/L, THC, THC-COOH and 11-HO-THC = 3.3, 14.2 and 2 ng/mL.	Eiden *et al.*[a,21]
2013	6	2 x M, 34 and 51 4 x F, 32–50	Review of post-mortem cases confirming α-PVP detection; all cases included multiple drug intoxications; deaths concluded to include accidents and homicide.	Qualitative analyse of blood and urine samples.	Marinetti and Antonides[23]
2013	1	F, 35	Found unconscious and pronounced dead at hospital; signs of needle marks on left forearm and subcutaneous hemorrhage along left arm veins; multiple drug intoxication; presence of MDPV, α-PBP and α-PVP.	MDPV (1,200 ng/mL) and α-PBP (200 ng/mL) detected in cardiac blood; α-PVP detected in hair segments; range 0.2–1.2 ng/10 mm.	Namera *et al.*[25]
2013	3	3 x M, 31, 25, 51	Period March–May 2012; 51-yr case: found deceased on bathroom floor, powder residues within nostrils. 31-yr case: "seizure activity" noted before death. 25-yr case: firearm injuries and confrontation with law enforcement; aggressive, paranoid behaviour, and suicidal threats were mentioned.	51-yr case, blood: α-PVP 0.1 mg/L; THC and THC-COOH 2.6 and 25 ng/mL. 31-yr case, blood: α-PVP 0.52 mg/L; sertraline (0.16 mg/L), oxycodone (0.02 mg/L), and 7-aminoclonazepam (< 0.01 mg/L) also detected. 25-yr case, blood α-PVP 0.29 mg/L and pentedrone 0.48 mg/L.	Richards-Waugh *et al.*[63]
2013	1	M, 32	Violent behavior preceding death in hospital; autopsy findings unremarkable; route of administration unknown; small glass bottle with liquid found in pocket.	Whole blood from heart: α-PVP 486 ng/mL; α-PVP present in liquid sample.	Saito *et al.*[26]
2013	14	Not specified	Details not reported; various causes and manners of death; other substances always detected; most prevalent drug classes	Post-mortem blood samples α-PVP: 5-732 ng/mL (317 ± 227 ng/mL)	Shanks *et al.*[27]

			included cannabinoids (n = 7), opioids (n = 6), amphetamines (n = 5), and antidepressants (n = 4). Other substituted cathinones detected in 4 of the cases.		
2014	1	M, 41	Violent and agitated behaviour in apartment preceding death; no injuries related to death observed but external abrasions and subcutaneous hemorrhages; detection of caffeine, α-PVP and metabolite 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-ol (OH-α-PVP).	Detection of α-PVP and OH-α-PVP in various biofluids and solid tissues, e.g. femoral blood: 654 and 364 ng/mL; urine: 11.2 and 5.3 µg/mL; caffeine (100 ng/mL) in whole blood.	Hasegawa *et al.*[31]
2014	1	M, 'in his 40s'	Violent and suicidal behaviour in "rented room" preceding death; cardiopulmonary arrest.	Blood, right ventricle, left ventricle, and femoral vein; α-PVP levels: 597, 635 and 580 ng/mL.	Minakata *et al.*[34]
2014	1	M, 'mid-20s'	Sudden violent behaviour followed by sustained restraint for 2 hours by roommates; white powder found and confirmed to represent α-PVP; sudden death/cardiac arrest considered consequence of restraint and α-PVP intoxication.	α-PVP serum levels 411 ng/mL;	Nagai *et al.* [64]
2014	1	M, 44	History of substance; injection with product obtained from shop called "Smokin' Slurry Scrubba"; autonomic hyper-arousal, followed by cardiac arrest, rhabdomyolysis, renal failure, hepatic injury, anoxic brain injury 43 hours later and death.	α-PVP detected in coronial blood ante-mortem and post-mortem; qualitative analysis; immunoassay positive for benzodiazepines.	Sellors *et al.*[65]
2015	1	M, 28	History of "designer drugs" use; brought to hospital in asystole but died; white powder found labelled as "α-PVP"; autopsy revealed pulmonary oedema and moderately advanced atherosclerotic lesions of arteries. Chronic changes in the heart observed by microscopic observation.	Detection of pentedrone, α-PVP, OH-α-PVP in various biofluids and solid tissues, e.g. whole (femoral) blood: 8,794, 901 and 185 ng/mL.	Sykutera *et al.*[48]
2015	1	M, 40	Single vehicle collision against tree with high speed; also detected in blood: ethanol (0.05 g/100 mL), MDMA (~ 0.06 mg/L), diazepam (~ 0.2 mg/L), nordiazepam (~ 0.1 mg/L), oxycodone (~ 0.03 mg/L), paracetamol (trace), THC (~ 14 ng/mL).	MDPV (~60 ng/ mL) and α-PVP (~77 ng/ mL) detected in blood.	Yap and Drummer[49]
[a] Case also reported to the EMCDDA.					

Table 6. Case-level data for death cases reported to European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)[1]
Member States (number of cases): • Finland (37), France (2), Hungary (19), Ireland (5), Poland (21), Sweden (16) and United Kingdom (6).
Demographics: • Male: 81 (80.2%); female: 20 (19.8%) • Age (years): mean age of male decedents 36.3 (n = 66; median 33); mean age of female decedents 35.4 (n = 20; median 34.5).
Number of deaths by year: • 2012 (17); 2013 (24); 2014 (43); 2015 (Jan–July, 15)
Information about cause of death (preliminary review reported for 101 deaths): • α-PVP reported as the cause of death (3 cases) or as contributing factor (20). • Not known; investigations ongoing in some cases (26). • Cause of death reported as due to drug intoxication, no further details available (4). • Further investigation needed to confirm the role of α-PVP played in the deaths, if any (48).

Table 7. Non-fatal case reports associated with detection of α-PVP reported in the scientific literature

Year	Cases	Patient, age	Context/clinically related comments (examples)	Notes	Ref
2013	1	M, 27	Non-fatal (M, 27): admission to emergency department following nasal insufflation: heart rate was 128 betas/min, blood pressure 160/90 mmHg, respiratory rate 30 breaths/min, oxygen saturation 97% and temperature 37.1°C, bilateral mydriasis; pertinent 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 NRG3 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.	Non-fatal case: purchase of product "NRG3" on Internet; α-PVP plasma 235 ng/mL; urine > 5 µg/mL; THC positive	Eiden *et al.*[21]
2013	4	Not reported	Clinical features in four cases related to substance use 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. Case 2: patient was arrested and hospitalized. 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. Case 4: Patient consulted hospital.	Case 1: 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: α-PVP detected 10-30 mm and 40-90 mm from scalp, e.g. 40+ ng/mg and ~50 ng/m in segments 2 and 3. Case 3: α-PVP (320+ ng/mg), MDPV (300+ ng/mg) detected in first segment; α-PVP, α-PBP and MDPV detected in	Namera *et al.*[24]

				segment 2. Case 4: α-PVP detected (4.5+ ng/mg) in pubic hair in segments 2 and 3 (20-40 mm from skin).	
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 detected in urine.	Dragogna *et al.*[66]
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.*[32]
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 LOD 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 and α-PBP 1.6 μg/mL.	Namera *et al.*[35]
2014	19	Not reported	No clinical features reported. Urine sample obtained from 19 substance users.		Shima *et al.*[37]
2014	8	Not reported	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.*[29]

Table 8. Non-fatal, case-level data reported to European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)[1]

Member States (number of cases):

- France (10 cases), Germany (2), Ireland (5), Italy (1), Poland (1) and Sweden (15). Thirty-two of the 34 cases classified as non-fatal intoxications; in the remaining 2 cases the outcome of the intoxication was unknown (Germany, 1 case; Sweden, 1 case).
- Analytical confirmation was obtained from 21 of the 34 cases: France (4), Italy (1), Poland (1), Sweden (15) and further information from the remaining 13 cases were unavailable.

Demographics (21 analytically confirmed cases):

- Male: 19 (90.5%); female: 2 (9.5%)
- Age (years): mean age of male cases 33.2 (n = 18; median 28.5); mean age of female cases: 23 and 25 years (n = 2).

Substance identification (21 analytically confirmed cases):

Sweden:

- α-PVP was only substance identified (8 cases, biological matrices unknown).
- α-PVP and ethanol were the only substances identified (5 cases, biological matrices not reported).
- α-PVP and benzodiazepines (and metabolites of benzodiazepines) were the only substances identified (1 case, biological matrices not reported).
- α-PVP and benzodiazepines (and metabolites of benzodiazepines) and ethanol were the only substances identified (biological matrices not reported).

France:

- α-PVP was only substance identified in blood; urine drug screening identified 'cannabis' (1 case).
- In 1 case, it was not known if any other substances besides α-PVP were identified (biological matrices not reported).
- α-PVP was only substance identified (2 cases, biological matrices not reported).

Italy:

- α-PVP and THC were analytically identified in urine (1 case).

Poland:

- α-PVP only substance identified in blood; pentedrone and alcohol were identified in urine (1 case).

Seriousness of the intoxications (21 analytically confirmed acute intoxications):

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

Outcome of the non-fatal intoxications. Of the 20 analytically confirmed non-fatal intoxications:

- Outcome classified as recovered/resolved in 12 cases.
- Outcome classified as recovering/resolving in 2 cases.
- Outcome classified as not known in 4 cases.
- Outcome not reported in 2 cases.

EMCDDA definition:

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

7. Dependence potential

A. Animal Studies

An overview of animal studies carried out with α-PVP and representative data is summarized in Table 3 and Section 4A. The behavioral effects induced by α-PVP were observed to be comparable to other psychomotor stimulants such as cocaine, methamphetamine and MDPV but further studies are warranted to assess dependence potential in animals in more detail.

B. Human Studies

Data on systematic clinical studies in humans are currently not available.

8. Abuse potential

A. Animal Studies

As shown in Table 3 and Section 4A, the comparison with other psychomotor stimulants, such as cocaine, methamphetamine and MDPV, indicated that α-PVP displayed comparable potential for abuse under the conditions studied.

B. Human Studies

Data on systematic clinical studies in humans are currently not available.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Not applicable.

10. Listing on the WHO Model List of Essential Medicines

α-PVP is not listed.

11. Marketing authorizations (as a medicinal product)

α-PVP was never marketed as a medicinal product.

12. Industrial use

α-PVP has no recorded industrial use.

13. Non-medical use, abuse and dependence

As shown in previous sections, use of α-PVP appears to be limited to recreational substance users and attendees of drug treatment centers rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Dependence-producing properties in humans have not been studied.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Information obtained from sources described in earlier sections indicates that α-PVP appears to be associated with the purchase of 'research chemicals' or comparable products that may be obtained from Internet retailers. It has also been observed that α-PVP was encountered in tablets and related formulations sold as 'ecstasy' both in Europe and the Americas.[1, 67] It also appears that α-PVP is used by recreational and high-risk drug users, including those who inject drugs.[1, 68, 69] Surveys that systematically assess the prevalence of use are currently not available. Data from the Polish 'I-Trend' online questionnaire provided to the EMCDDA showed that out of 1074 respondents, α-PVP was the last new psychoactive substance to be used by 3.4% (n = 36) of the respondents (36 users, n = 1,074). Of these, 39% had taken it at least 20 times in the previous year.[1]

15. Licit production, consumption and international trade

In countries where α-PVP is not subject to legislative control, marketing efforts might include advertisement and sale as 'research chemical', 'bath salt', 'stain remover', 'plant food', 'plant fertilizer', 'insect repellant', and jewelry cleaner'. Information about agricultural, cosmetic or industrial use of α-PVP is not available. A structured search of online vendors of α-PVP carried out by the EMCDDA (surface web, using three search strings: 'buy a-PVP', 'buy alpha-PVP' and 'buy pyrrolidinopentiophenone' on www.google.co.uk) 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 (n = 32 sites), India (n = 3 sites), or Russia (n = 6 sites).[1]

16. Illicit manufacture and traffic and related information

Information provided to Europol and EMCDDA by 28 European Member States, Turkey and Norway is summarized in Table 9. Four EU Member States (Hungary, Latvia, Romania and Spain) provided information in relation to the involvement of organized crime in the manufacture or trafficking of α-PVP. For the period of January 2010 through to December 2013, the System to Retrieve Information from Drug Evidence (STRIDE) logged 689 exhibits for α-PVP whereas 4,536 reports were registered by the National Forensic Laboratory Information System (NFLIS) between January 2010 and December 2013.[70] The NFLIS 2014 Midyear Report, covering total drug reports submitted to laboratories from 1st January 2014 – 30th June 2014 (and analyzed by 30th September 2014), provides a national estimate of 2,244 reports. In comparison, methamphetamine and MDMA numbers were 121,109 and 2,347, respectively.[71] A number of 40 encounters were recorded by the United States Customs and Border Protection (CBP) between April 2010 and November 2013.[70]

Table 9. Information provided to Europol and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on seizures, levels of trafficking and manufacturing [a,1]

Information provided to Europol

Seizures

- First seizure reported in 2012.
- Over 295 seizures in powder or crystalline powder form totalling over 370 kg of α-PVP. Most of the seizures were described as white or off-white in colour, but in one case from Spain the powder was described as 'black rock powder'.
- Three Member States reported seizures of tablets containing α-PVP: Czech Republic (160 tablets), Hungary (454 tablets), Romania (2 tablets). Packages containing α-PVP were seized in Slovakia and in Spain. In 2015, Spain also reported a case with 2 jelly gums containing α-PVP.

Level of trafficking

- In one case, Poland was indicated as a country of origin and in the remaining 10 of the 11 cases (where trafficking route information was provided), China was noted as the source country for α-PVP. Mail shipments and courier services have also been reported to serve as routes for importation. Germany and France appear to serve as transit points in the EU and a large seizure from Spain (259 kg) indicates that this country might also serves as a distribution point.

Level of production

- Two tableting sites were encountered and dismantled in Hungary in 2013 and 2014. α-PVP was found in powdered form and suspected to be employed for tablet production.
- Two α-PVP production sites were seized in Poland in 2013 and 2014. Approximately 50 kg of α-PVP were produced in this site and destined both for the domestic market and to be exported. According to the Polish authorities, both cases were linked to a local group of 'football hooligans'. The synthesis was supervised by trained chemists, and the laboratories were operated by suppliers, producers and distributors of chemicals. The companies involved operated their own websites offering the sale and distribution of those substances across Poland.

Information provided to EMCDDA

Seizures

- First seizure reported in 2011 (France).
- α-PVP has been detected in more than 5200 seizures with eight countries reporting more than 100 seizures each: United Kingdom (1094), Poland (938), Finland (787), Slovakia (502), Sweden (451), Ireland (336), Hungary (313) and Turkey (256).
- α-PVP was commonly seized in powder form with total amount of powder over 750 kg. Seven countries reported seizures over 10 kg: Spain (312 kg), Netherlands (140), France (81), Ireland (63), United Kingdom (62), Hungary and Finland (24 each) and Poland (17).
- Thirteen countries reported seizures of tablets (Slovakia, Hungary, Finland, Czech Republic, Latvia, Turkey, Sweden, Norway, Spain, Poland, Belgium, Italy and France) amounting to over 12400 units. Of those, three countries reported seizures of over 1000 tablets: Slovakia (7157), Hungary (3768) and Finland (1136). The United Kingdom reported three seizures of powder-filled capsules.
- Seven countries (Lithuania, the United Kingdom, Hungary, Slovakia, France, Sweden and Poland) reported small seizures (< 150 grams) of vegetable material containing α-PVP, occasionally also containing synthetic cannabinoids.
- Three countries (Finland, Sweden and Poland) have seized small quantities of liquid (< 150 mL) containing α-PVP.
- Austria reported a single seizure of 68 paper doses (also known as a 'blotters') containing 2,5-dimethoxy-4-chloroamphetamine (DOC) and α-PVP. Finland reported 16 seizures amounting to over 700 units of tablets/blotters. Spain reported the seizure of 2 jelly gums, where α-PVP, amphetamine and caffeine were detected.
- In around 35% of the detections, α-PVP was found in combination with other substances including other synthetic ring-substituted cathinones, synthetic cannabinoids and a range of other new psychoactive substances. A number of them are internationally controlled and/or controlled at EU-level. Substances typically used as cutting agents and/or diluents included benzocaine, lidocaine and caffeine. Information on purity, which was available from 16 seizures, ranged from 23% (2 seizures) to over 95 % (8 seizures).
- Tablets containing α-PVP had the following markings: 'Lacoste', 'Playboy', 'STADA1' and 'Homer Simpson' (information available for 7 seizures) which suggested that α-PVP might have been sold as 'ecstasy'. Unmarked tablets in a variety of colors have been reported. Some of these products were obtained through online shops.
- Eleven countries reported fifty samples collected from users or purchased on the Internet, which contained α-PVP (Austria, Belgium, Czech Republic, Denmark, France, Hungary, the Netherlands, Slovenia, Spain, Turkey and the United Kingdom).

Level of production • The Reitox National Focal Point from the Slovak Republic reported the dismantling of a manufacturing and distribution site linked to new psychoactive substances intended to be marketed in Slovakia and Hungary. Fifteen kilograms of new psychoactive substances (3-methylmethcathinone, α-PVP and methiopropamine) were seized. The ingredients necessary for the production of these substances were imported from Hungary and, following their processing in Slovakia, were to be re- exported back to Hungary.[72]
[a] Some of the data reported to Europol and EMCDDA may overlap. Many 'seizures' related to individual case-level data, however, some data provided to the EMCDDA were aggregated at the country level. Some of the data from the United Kingdom were reported as 'records', where several records may come from the same case. Data were drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (EU EWS progress and final reports) and from individual Reporting forms submitted on an *ad hoc* basis.

17. Current international controls and their impact

Not applicable in terms of medical use.

18. Current and past national controls

The EMCDDA has received confirmation from fifteen Member States (Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Slovenia, Sweden and the United Kingdom) as well as Turkey and Norway and reported that α-PVP is controlled under drug control legislation:[1]

a. Estonia: listed in the Regulation No. 73 of the Minister of Social Affairs of 18 May 2005 since 2 June 2014.
b. Finland: listed in the Narcotics Act 373 of 2008 since 30 December 2013.
c. France: added to the controlled narcotic substance list since 2 August 2012.
d. Germany: placed under schedule II (narcotics eligible for trade but not for medical prescription) of the Narcotic Substance Act, effective as of 17 July 2013.
e. Greece: considered to be controlled under law 3459/2006 due to same molecular weight and molecular formula as metazocine, an opioid analgesic classified in Table C of this law.
f. Hungary: listed in Schedule A (psychotropic substances) of Act XXV of 1998 on human pharmaceuticals since 1 January 2015.
g. Ireland: covered by generic definition of controlled cathinones included in the Misuse of Drugs Act.
h. Italy: covered by generic definition under the Decree of the President of the Republic 309/90 since 29 December 2011.
i. Latvia: controlled generically according to Cabinet Regulation 847 'Regulations regarding narcotic substances, psychotropic substances and precursors to be controlled in Latvia'.
j. Lithuania: controlled as a cathinone derivative by an Amendment to the Law on the control of narcotic drugs and psychotropic substances adopted in 2010.
k. Poland: listed in Schedule IV of the Act of 24 June 2015 amending the Act of Counteracting Drug Addiction since 1 July 2015.
l. Romania: controlled by Law 143/2000 on preventing and combating trafficking and illicit drug use and listed in Table I of the law 339/2005 on the legal regime of plants, narcotic and psychotropic substances and preparations.
m. Slovenia: included by the Decree on amending the Decree on Classification of Illicit Drugs, Official Gazette of RS No. 45/2014 since July 2014.
n. Sweden: captured by the Narcotic Drugs Control Act since 1 February 2013.

o. United Kingdom: captured by generic definition of substituted cathinone derivatives placed under the Misuse of Drugs Act 1971 in April 2010 and it is controlled as a class B drug.
p. Turkey: listed in the Law on Control of Narcotics No.2313 adopted on 22 March 2012.
q. Norway: covered by generic definition of cathinones in the Norwegian list of narcotics.

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

a. Austria: categorized as member of the 'amino phenyl ethanone' (i.e. cathinone) generic group in the New Psychoactive Substances Act.
b. Cyprus: captured by generic definition of a cathinone under specific NPS legislation as of 24 June 2011.
c. Portugal: listed as controlled under Decree-Law 154/2013 of 17 April 2013.
d. Slovakia: listed as a 'hazardous substance' as of 1 October 2013.

The EMCDDA received reports that Belgium and Czech Republic started the process of controlling the substance using drug control legislation.

In the United States of America, α-PVP has been temporarily scheduled into schedule I pursuant to the temporary scheduling provisions of the Controlled Substances Act (CSA).[70] Other countries with legislative control include Japan ("Designated Substance") and other United Nation Member States.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Not applicable.

References

1. European Monitoring Centre for Drugs and Drug Addiction (2015), EMCDDA–Europol Joint Report on a new psychoactive substance: 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone (α-PVP), Joint Reports, Publications Office of the European Union, Luxembourg.
2. Madras BK, Meltzer PC, Butler D. Madras BK, Meltzer PC, Butler D (2005). Pyrovalerone analogs and therapeutic uses thereof. Patent No. WO 2005/034878 A2. President and Fellows of Harvard College, USA; Organix, Inc., 2005.
3. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-ylpentan-1-one (pyrovalerone) analogs: a promising class of monoamine uptake inhibitors. *J Med Chem* 2006;49:1420-32. doi:10.1021/jm050797a PMID:16480278
4. Seeger E. Compositions and methods for stimulating the central nervous system and increasing the blood pressure. Patent No. US 3287217. Boehringer Ingelheim GmbH, Biberach an der Riss, Germany, 1966.
5. Seeger E. α-Pyrrolidino ketones. Patent No. US 3314970. Boehringer Ingelheim GmbH, Biberach an der Riss, Germany, 1967.
6. Dr. Karl Thomae GmbH. α-Pyrrolidino-ketones. Patent No. GB 933507. Dr. Karl Thomae GmbH, Biberach an der Riss, Germany, 1963.
7. Heffe W. Verfahren zur Herstellung von α-Pyrrolidino-valerophenonen. Patent No. CH 395998. Dr. A. Wander A.G., Bern, Switzerland, 1966.
8. Dr. A. Wander S.A. α-Pyrrolidino-valerophenones. Patent No. GB 927475. Dr. A. Wander S.A, Bern, Switzerland, 1963.
9. Guha S, Rajeshkumar V, Kotha SS, Sekar G. A versatile and one-pot strategy to synthesize α-amino ketones from benzylic secondary alcohols using N-bromosuccinimide. *Org Lett* 2015;17:406-9. doi:10.1021/ol503683q PMID:25633934
10. Heffe W. Verfahren zur Herstellung von α-Pyrrolidino-valerophenonen. Patent No. CH 395999. Dr. A. Wander A.G., Bern, Switzerland, 1966.
11. Heffe W. Verfahren zur Herstellung von α-Pyrrolidino-valerophenonen. Patent No. CH 401054. Dr. A. Wander A.G., Bern, Switzerland, 1966.
12. Safety data sheet. alpha.-Pyrrolidinopentiophenone (hydrochloride). Revision: 02/01/2015. Cayman Chemical Company, Ann Arbor, MI, USA. Available at: http://www.caymanchem.com/msdss/9001083m.pdf [10 August 2015].
13. Westphal F, Junge T, Klein B, Fritschi G, Girreser U. Spectroscopic characterization of 3,4-methylenedioxypyrrolidinobutyrophenone: a new designer drug with α-pyrrolidinophenone structure. *Forensic Sci Int* 2011;209:126-32. doi:10.1016/j.forsciint.2011.01.016 PMID:21316166
14. Sauer C, Peters FT, Haas C, Meyer MR, Fritschi G, Maurer HH. New designer drug α-pyrrolidinovalerophenone (PVP): studies on its metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques. *J Mass Spectrom* 2009;44:952-64. doi:10.1002/jms.1571 PMID:19241365
15. Table of reagents. Available at: http://reagent-base.net/reagents-table/ [5th September 2015].
16. Casale JF, Hays PA. The characterization of α-pyrrolidinopentiophenone. *Microgram J* 2012;9:33-8.
17. Power JD, McDermott SD, Talbot B, O'Brien JE, Kavanagh P. The analysis of amphetamine-like cathinone derivatives using positive electrospray ionization with in-source collision-induced dissociation. *Rapid Commun Mass Spectrom* 2012;26:2601-11. doi:10.1002/rcm.6383 PMID:23059876

18. Shanks KG, Dahn T, Behonick G, Terrell A. Analysis of first and second generation legal highs for synthetic cannabinoids and synthetic stimulants by ultra-performance liquid chromatography and time of flight mass spectrometry. *J Anal Toxicol* 2012;36:360-71. doi:10.1093/jat/bks047 PMID:22586208
19. Amaratunga P, Lemberg BL, Lemberg D. Quantitative measurement of synthetic cathinones in oral fluid. *J Anal Toxicol* 2013;37:622-8. doi:10.1093/jat/bkt080 PMID:24123620
20. Concheiro M, Anizan S, Ellefsen K, Huestis MA. Simultaneous quantification of 28 synthetic cathinones and metabolites in urine by liquid chromatography-high resolution mass spectrometry. *Anal Bioanal Chem* 2013;405:9437-48. doi:10.1007/s00216-013-7386-z PMID:24196122
21. Eiden C, Mathieu O, Cathala P, Debruyne D, Baccino E, Petit P et al. Toxicity and death following recreational use of 2-pyrrolidino valerophenone. *Clin Toxicol* 2013;51:899-903. doi:10.3109/15563650.2013.847187 PMID:24111554
22. Elie MP, Elie LE, Baron MG. Keeping pace with NPS releases: fast GC-MS screening of legal high products. *Drug Test Anal* 2013;5:281-90. doi:10.1002/dta.1434 PMID:23297247
23. Marinetti LJ, Antonides HM. Analysis of synthetic cathinones commonly found in bath salts in human performance and postmortem toxicology: method development, drug distribution and interpretation of results. *J Anal Toxicol* 2013;37:135-46. doi:10.1093/jat/bks136 PMID: 23361867
24. Namera A, Konuma K, Saito T, Ota S, Oikawa H, Miyazaki S et al. Simple segmental hair analysis for α-pyrrolidinophenone-type designer drugs by MonoSpin extraction for evaluation of abuse history. *J Chromatogr B: Anal Technol Biomed Life Sci* 2013;942-943:15-20. doi:10.1016/j.jchromb.2013.10.021 PMID:24212139
25. Namera A, Urabe S, Saito T, Torikoshi-Hatano A, Shiraishi H, Arima Y et al. A fatal case of 3,4-methylenedioxypyrovalerone poisoning: coexistence of alpha-pyrrolidinobutiophenone and alpha-pyrrolidinovalerophenone in blood and/or hair. *Forensic Toxicol* 2013;31:338-43. doi:10.1007/s11419-013-0192-7
26. Saito T, Namera A, Osawa M, Aoki H, Inokuchi S. SPME-GC-MS analysis of alpha-pyrrolidinovaleorophenone in blood in a fatal poisoning case. *Forensic Toxicol* 2013;31:328-32. doi:10.1007/s11419-013-0183-8
27. Shanks KG, Behonick GS, R. TA. Detection of alpha-PVP in postmortem blood casework by UPLC/MS/MS. *P12, Proceedings of the Society of Forensic Toxicologists* 2013:Available at: http://soft-tox.org/files/meeting_abstracts/SOFT_2013_meeting_abstracts.pdf [12 August 5].
28. Tsujikawa K, Kuwayama K, Kanamori T, Iwata YT, Inoue H. Thermal degradation of α-pyrrolidinopentiophenone during injection in gas chromatography/mass spectrometry. *Forensic Sci Int* 2013;231:296-9. doi:10.1016/j.forsciint.2013.06.006 PMID:23890652
29. Tyrkkö E, Pelander A, Ketola RA, Ojanperä I. In silico and in vitro metabolism studies support identification of designer drugs in human urine by liquid chromatography/quadrupole-time-of-flight mass spectrometry. *Anal Bioanal Chem* 2013;405:6697-709. doi:10.1007/s00216-013-7137-1 PMID:23797910
30. Fornal E. Study of collision-induced dissociation of electrospray-generated protonated cathinones. *Drug Test Anal* 2014;6:705-15. doi:10.1002/dta.1573 PMID:24259394
31. Hasegawa K, Suzuki O, Wurita A, Minakata K, Yamagishi I, Nozawa H et al. Postmortem distribution of α-pyrrolidinovalerophenone and its metabolite in body fluids and solid tissues in a fatal poisoning case measured by LC-MS-MS with the standard addition method. *Forensic Toxicol* 2014;32:225-34. doi:10.1007/s11419-014-0227-8

32. Knoy JL, Peterson BL, Couper FJ. Suspected impaired driving case involving α-pyrrolidinovalerophenone, methylone and ethylone. *J Anal Toxicol* 2014;38:615-7. doi:10.1093/jat/bku073 PMID:25217556
33. Leffler AM, Smith PB, de Armas A, Dorman FL. The analytical investigation of synthetic street drugs containing cathinone analogs. *Forensic Sci Int* 2014;234:50-6. doi:10.1016/j.forsciint.2013.08.021 PMID:24378302
34. Minakata K, Yamagishi I, Nozawa H, Hasegawa K, Wurita A, Gonmori K et al. MALDI-TOF mass spectrometric determination of four pyrrolidino cathinones in human blood. *Forensic Toxicol* 2014;32:169-75. doi:10.1007/s11419-013-0212-7
35. Namera A, Konuma K, Kawamura M, Saito T, Nakamoto A, Yahata M et al. Time-course profile of urinary excretion of intravenously administered α-pyrrolidinovalerophenone and α-pyrrolidinobutiophenone in a human. *Forensic Toxicol* 2014;32:68-74. doi:10.1007/s11419-013-0203-8
36. Schneir A, Ly BT, Casagrande K, Darracq M, Offerman SR, Thornton S et al. Comprehensive analysis of "bath salts" purchased from California stores and the internet. *Clin Toxicol* 2014;52:651-8. doi:10.3109/15563650.2014.933231 PMID:25089721
37. Shima N, Katagi M, Kamata H, Matsuta S, Sasaki K, Kamata T et al. Metabolism of the newly encountered designer drug α-pyrrolidinovalerophenone in humans: identification and quantitation of urinary metabolites. *Forensic Toxicol* 2014;32:59-67. doi:10.1007/s11419-013-0202-9
38. Taschwer M, Seidl Y, Mohr S, Schmid MG. Chiral separation of cathinone and amphetamine derivatives by HPLC/UV using sulfated ß-cyclodextrin as chiral mobile phase additive. *Chirality* 2014;26:411-8. doi:10.1002/chir.22341 PMID:24909415
39. Uchiyama N, Matsuda S, Kawamura M, Shimokawa Y, Kikura-Hanajiri R, Aritake K et al. Characterization of four new designer drugs, 5-chloro-NNEI, NNEI indazole analog, alpha-PHPP and alpha-POP, with 11 newly distributed designer drugs in illegal products. *Forensic Sci Int* 2014;243:1-13. doi:10.1016/j.forsciint.2014.03.013 PMID:24769262
40. Uralets V, Rana S, Morgan S, Ross W. Testing for designer stimulants: metabolic profiles of 16 synthetic cathinones excreted free in human urine. *J Anal Toxicol* 2014;38:233-41. doi:10.1093/jat/bku021 PMID:24668489
41. Wurita A, Hasegawa K, Minakata K, Gonmori K, Nozawa H, Yamagishi I et al. Postmortem distribution of alpha-pyrrolidinobutiophenone in body fluids and solid tissues of a human cadaver. *Leg Med* 2014;16:241-6. doi:10.1016/j.legalmed.2014.05.001 PMID:24889409
42. Armenta S, Garrigues S, Guardia M, Brassier J, Alcala M, Blanco M et al. Detection and characterization of emerging psychoactive substances by ion mobility spectrometry. *Drug Test Anal* 2015;7:280-9. doi:10.1002/dta.1678 PMID:24935207
43. Borova VL, Gago-Ferrero P, Pistos C, Thomaidis NS. Multi-residue determination of 10 selected new psychoactive substances in wastewater samples by liquid chromatography-tandem mass spectrometry. *Talanta* 2015;144:592-603. doi:10.1016/j.talanta.2015.06.080
44. Concheiro M, Castaneto M, Kronstrand R, Huestis MA. Simultaneous determination of 40 novel psychoactive stimulants in urine by liquid chromatography-high resolution mass spectrometry and library matching. *J Chromatogr A* 2015;1397:32-42. doi:10.1016/j.chroma.2015.04.002 PMID:25931378
45. Friscia M, Wolf SE, Mohr ALA, Diamond FX, Yeakel JK, Logan BK. Identification of major metabolites in human blood and urine associated with the ingestion of alpha-pyrrolidinopentiophenone (Alpha PVP). *K55, 67th Proceedings of the American Academy of Forensic Sciences* 2015:1125-6. Available at: http://www.aafs.org/sites/default/files/2015/Proceedings.pdf [12 August].

46. Fujii H, Waters B, Hara K, Kashiwagi M, Matsusue A, Takayama M et al. Direct-heating headspace solid-phase microextraction for the screening of illicit drugs. *Forensic Toxicol* 2015;33:61-8. doi:10.1007/s11419-014-0252-7
47. Negreira N, Erratico C, Kosjek T, van Nuijs ALN, Heath E, Neels H et al. In vitro Phase I and Phase II metabolism of α-pyrrolidinovalerophenone (α-PVP), methylenedioxypyrovalerone (MDPV) and methedrone by human liver microsomes and human liver cytosol. *Anal Bioanal Chem* 2015;407:5803-16. doi:10.1007/s00216-015-8763-6 PMID:26014283
48. Sykutera M, Cychowska M, Bloch-Boguslawska E. A fatal case of pentedrone and α-pyrrolidinovalerophenone poisoning. *J Anal Toxicol* 2015;39:324-9. doi:10.1093/jat/bkv011 PMID:25737339
49. Yap S, Drummer OH. Prevalence of new psychoactive substances in Victorian fatally-injured drivers. *Aust J Forensic Sci* 2015:in press; doi: 10.1080/00450618.2015.1050066. doi:10.1080/00450618.2015.1050066
50. Kolanos R, Solis E, Sakloth F, De Felice LJ, Glennon RA. "Deconstruction" of the abused synthetic cathinone methylenedioxypyrovalerone (MDPV) and an examination of effects at the human dopamine transporter. *ACS Chem Neurosci* 2013;4:1524-9. doi:10.1021/cn4001236 PMID:24116392
51. Marusich JA, Antonazzo KR, Wiley JL, Blough BE, Partilla JS, Baumann MH. Pharmacology of novel synthetic stimulants structurally related to the "bath salts" constituent 3,4-methylenedioxypyrovalerone (MDPV). *Neuropharmacology* 2014;87:206-13. doi:10.1016/j.neuropharm.2014.02.016 PMID:24594476
52. Kolanos R, Sakloth F, Jain AD, Partilla JS, Baumann MH, Glennon RA. Structural modification of the designer stimulant α-pyrrolidinovalerophenone (α-PVP) influences potency at dopamine transporters. *ACS Chem Neurosci* 2015. doi:10.1021/acschemneuro.5b00160 PMID:26217965
53. Rickli A, Hoener MC, Liechti ME. Monoamine transporter and receptor interaction profiles of novel psychoactive substances: Para-halogenated amphetamines and pyrovalerone cathinones. *Eur Neuropsychopharmacol* 2015;25:365-76. doi:10.1016/j.euroneuro.2014.12.012 PMID:25624004
54. Kaizaki A, Tanaka S, Numazawa S. New recreational drug 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone (alpha-PVP) activates central nervous system via dopaminergic neuron. *J Toxicol Sci* 2014;39:1-6. doi:10.2131/jts.39.1 PMID:24418703
55. Aarde SM, Creehan KM, Vandewater SA, Dickerson TJ, Taffe MA. In vivo potency and efficacy of the novel cathinone α-pyrrolidinopentiophenone and 3,4-methylenedioxypyrovalerone: self-administration and locomotor stimulation in male rats. *Psychopharmacology* 2015;232:3045-55. doi:10.1007/s00213-015-3944-8 PMID:25925780
56. Gatch MB, Dolan SB, Forster MJ. Comparative behavioral pharmacology of three pyrrolidine-containing synthetic cathinone derivatives. *J Pharmacol Exp Ther* 2015;354:103-10. doi:10.1124/jpet.115.223586 PMID:25998047
57. Naylor JE, Freeman KB, Blough BE, Woolverton WL, Huskinson SL. Discriminative-stimulus effects of second generation synthetic cathinones in methamphetamine-trained rats. *Drug Alcohol Depend* 2015;149:280-4. doi:10.1016/j.drugalcdep.2015.02.002 PMID:25707704
58. Watterson LR, Burrows BT, Hernandez RD, Moore KN, Grabenauer M, Marusich JA et al. Effects of α-pyrrolidinopentiophenone and 4-methyl-N-ethylcathinone, two synthetic cathinones commonly found in second-generation "bath salts," on intracranial self-stimulation thresholds in rats. *Int J Neuropsychopharmacol* 2014;18:in press. doi:10.1093/ijnp/pyu014 PMID:25522379

59. Psychonautwiki. A-PVP. Available at: https://psychonautwiki.org/wiki/A-PVP [10 August 2015].
60. WHO Expert Committee on Drug Dependence. 3,4-Methylenedioxypyrovalerone (MDPV). Critical Review Report. Agenda item 4.13. Thirty-sixth meeting of the Expert Committee on Drug Dependence. Geneva, Switzerland, 16 - 20 June 2014. Available at: http://www.who.int/medicines/areas/quality_safety/4_13_Review.pdf [accessed 10 August 2015].
61. Meyer MR, Maurer HH. Metabolism of designer drugs of abuse: an updated review. *Curr Drug Metab* 2010;11:468-82. doi:10.2174/138920010791526042 PMID:20540700
62. Seeger E. Verfahren zur Herstellung von α-Pyrrolidinoketonen und deren Salzen. Patent No. DE 1161274. Dr. Karl Thomae GmbH, Biberach an der Riss, Germany, 1964.
63. Richards-Waugh LL, Bailey KM, Clay DJ, Gebhardt MA, Newsome-Sparks CL, E. MH et al. Deaths involving the recreational use of α-PVP (α-pyrrolidinopentiophenone). *K16, 65th Proceedings of the American Academy of Forensic Sciences* 2013:521-2. Available at: http://www.aafs.org/sites/default/files/pdf/ProceedingsWashingtonDC2013.pdf [10 August 5].
64. Nagai H, Saka K, Nakajima M, Maeda H, Kuroda R, Igarashi A et al. Sudden death after sustained restraint following self-administration of the designer drug α-pyrrolidinovalerophenone. *Int J Cardiol* 2014;172:263-5. doi:10.1016/j.ijcard.2013.12.262 PMID:24491861
65. Sellors K, Jones A, Chan B. Death due to intravenous use of α-pyrrolidinopentiophenone. *Medical Journal of Australia* 2014;201:601-3. doi:10.5694/mja13.00203 PMID:25390268
66. Dragogna F, Oldani L, Buoli M, Altamura AC. A case of severe psychosis induced by novel recreational drugs. *F1000Research* 2014;3:doi: 10.12688/f1000research.3-21.v1. doi:10.12688/f1000research.3-21.v1 PMID:25352977
67. UNODC. 2014 Global Synthetic Drugs Assessment. Amphetamine-type stimulants and new psychoactive substances. United Nations, New York. Available at: https://http://www.unodc.org/documents/southeastasiaandpacific/2014/05/gsda/2014_Global_Synthetic_Drugs_Assessment_embargoed_Tokyo_web.pdf [02 September 2015].
68. Simonsen KW, Edvardsen HME, Thelander G, Ojanperä I, Thordardottir S, Andersen LV et al. Fatal poisoning in drug addicts in the Nordic countries in 2012. *Forensic Sci Int* 2015;248:172-80. doi:10.1016/j.forsciint.2015.01.003 PMID:25645132
69. Sundström M, Pelander A, Simojoki K, Ojanperä I. Patterns of drug abuse among drug users with regular and irregular attendance for treatment as detected by comprehensive UHPLC-HR-TOF-MS. *Drug Test Anal* 2015:in press. doi:10.1002/dta.1818 PMID:26017246
70. DEA. Schedules of controlled substances: temporary placement of 10 synthetic cathinones into Schedule I. Final order. *Fed Reg* 2014;79:12938-43.
71. National Forensic Laboratory Information System (NFLIS). 2014 Midyear Report. US Department of Justice Drug Enforcement Administration Office of Diversion Control. Available at: https://http://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2014MY.pdf [5th September 2015].
72. Reitox National Focal Point Slovak Republic. 2014 National Report (2013 data) to the EMCDDA by the Reitox National Focal Point. New development, EMCDDA - European database on new drugs (EDND).