Pentedrone

Critical Review Report

Agenda item 4.6

Expert Committee on Drug Dependence

Thirty-eighth Meeting

Geneva, 14-18 November 2016

World Health Organization

Contents

Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Policy Access and Use team. The WHO Secretariat would like to thank the following people for their contribution in producing this critical review report: Dr. Jan van Amsterdam and Dr. Ed Pennings, The Netherlands (literature search, review and drafting) and Dr. Stephanie Kershaw, Geneva, Switzerland (editing and questionnaire report drafting).

Summary

Pentedrone is a substituted phenethylamine derivative, first identified in 2010 as one of the varieties of bath salts throughout the US and UK. Pentedrone belongs to the class of cathinones, and users of pentedrone have reported MDMA-like stimulating effects, such as euphoria, openness and increased sociability, and sexual drive. As a pure transporter blocker, pentedrone preferentially inhibits the uptake of dopamine and noradrenaline with minimal effects on the uptake of serotonin, but does not evoke monoamine release.

Pentedrone (10 mg/kg i.p.) significantly increased apomorphine-induced climbing behaviour in mice and dose-dependently (3-10 mg/kg i.p.) increased locomotor activity with an efficacy comparable to those of cocaine or methamphetamine (ED_{50} of 4.7±0.1 mg/kg i.p.). Together, these results indicate dopaminergic stimulation by pentedrone.

Similar to MDMA, pentedrone is one of the most hepatotoxic synthetic cathinones *in vitro* (EC_{50} value of 0.66 mM). Pentedrone further induced severe convulsions in at 70 mg/kg and was lethal at 100 mg/kg. The toxicity of pentedrone in humans (DUID, intoxications or fatal incidents) is unclear because no cases have been reported in which pentedrone was the only drug found, i.e., the incidents reported all refer to the presence of pentedrone in combination with other drugs in the specimens analysed.

No studies to the dependence potential have been performed in animals or humans. In rodents trained to discriminate cocaine (10 mg/kg, i.p.) or methamphetamine (1 mg/kg, i.p.) from saline, pentedrone (0.5 - 5 mg/kg i.p.) produced discriminative stimulus effects comparable to those of cocaine and methamphetamine (ED_{50} of 2.3±0.2 and 2.6±0.1, respectively), suggesting that pentedrone has a similar abuse potential as cocaine and methamphetamine. Pentedrone (3 and 10 mg/kg i.p.) significantly increased conditioned place preference in mice and at 0.3 mg/kg i.v. pentedrone significantly increased self-administration in rats. However, studies to the abuse potential in humans have not been performed.

No therapeutic or medical use has been described for pentedrone and pentedrone is neither marketed as medicinal product, nor used for industrial purposes.

Pentedrone has been detected in commercial products send to or sold in Italy, Poland, Portugal, the US, Spain, Canada and the UK. Pentedrone is not controlled world-wide so that in various countries pentedrone products (as powders, mixtures, crystals) are legally marketed in head shops and via the Internet. In other countries, like Austria, Estonia, the EU, Finland, France, Hungary, Italy, Poland and the US, pentedrone was detected in seizures by customs or police. Pentedrone is a controlled substance in countries like Austria, Australia, Brazil, Canada, China, Czech Republic, the UK and the US.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

879722-57-3 (base); 879669-95-1 (hydrochloride salt)

C. Other Chemical Names

PMMC, alpha-methylamino-valerophenone, α-methylamino-valerophenone, 1-pentanone-2-(methylamino)-1-phenyl**,** α-ethyl-methcathinone, 2-methylamino-1-phenyl-1-pentanone, 2-(methylamino)-1-phenylpentane-1-one.

D. Trade Names

Romeo plus, Dark Angel Dust, GNOME Eight, Neo PX, Freak TIGER, Victoria, Butterfly EDGE Deep, Sekirara, Fire, Dry super, Okamoto, Red Ball, Love free custom 3rd, Pentedrone Big Crystals, Bloom, Rush, Bliss, Kick, Coco Jumbo, Raving Dragon Voodoo Dust.

E. Street Names

'penta', 'pentakristály', 'kristály'.[1]

F. Physical Appearance

The hydrochloride salt may be monoclinic crystals[2], microcrystalline or a white powder.

G. WHO Review History

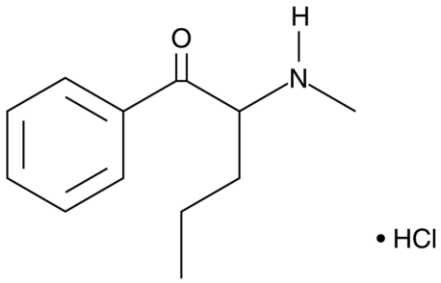
Pentedrone has not been previously reviewed or critically reviewed by the Expert Committee on Drug Dependence of the WHO. A direct critical review is proposed based on information brought to WHO's attention that pentedrone is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.[75] Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

A. Chemical Name

IUPAC Name: (±)-2-(methylamino)-1-phenylpentan-1-one
CA Index Name: Not applicable.

B. Chemical Structure



Molecular Formula: $C_{12}H_{17}NO$ (free base); $C_{12}H_{18}NOCl$ (hydrochloride salt)
Molecular Weight: 191 (free base); 228 (hydrochloride salt)

C. Stereoisomers

Pentedrone has one chiral carbon (central carbon C2 in figure 1 with the methylamino and *n*-propyl substituent) giving two stereoisomers (S)- and (R)-pentedrone.

D. *Methods and Ease of Illicit Manufacturing*

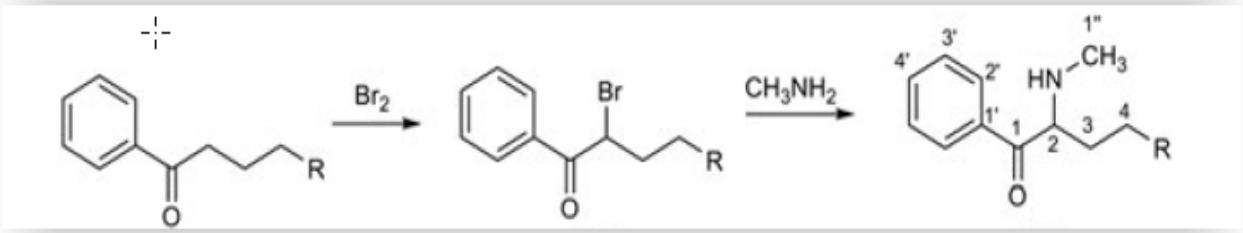


Figure 1. Synthetic pathway of pentedrone (R = CH_3).[3]

After bromination of valerophenone to α-bromovalerophenone, the bromoketone is condensated with methylamine to form the α-methylaminovalerophenone, i.e., pentedrone.[4]

E. Chemical Properties

Melting point:	176.8 °C (hydrochloride salt); free base: not reported
Boiling point:	289.3 °C at 760 mmHg (free base)
Solubility:	~ 5-10 mg/ml in PBS (pH 7.2), ~ 15-25 mg/ml in ethanol, 20 mg/ml in DMSO or DMF.

Pentedrone is a weak base with a predicted pK_a-value of 7.21. On the microgram scale, pentedrone HCl is instable: after storage of one microgram during 24 h in air at room temperature (15-18 ^{0}C), 61.4 ± 9.4% was recovered.[5]

F. Identification and Analysis

UV-Visible spectrum: λ_{max} at 249 nm. The chemical identification, analysis, and spectral characterization (NMR, mass spectrometry, infrared spectroscopy, GC-MS and ESI-HRMS (ElectroSpray Ionization High Resolution Mass Spectrometry) have been described by Maheux and Copeland (2012)[3] and by Westphal et al. (2012).[6]

3. Ease of Convertibility Into Controlled Substances

Although pentedrone is a phenethylamine having a methylated amino group and a propyl substituent on the phenethyl chain, it is unlikely that pentedrone can be easily converted into an existing controlled substance. This would include oxidative dealkylation of the pentyl side chain (e.g., de-ethylation), which is difficult if not impossible without destruction of the whole molecule.

4. General Pharmacology

A. Routes of administration and dosage

The non-commercial German website "NeuePsychoaktiveSubstanzen.de"[7] reports oral, intranasal ('snorting'), inhalation and intravenous routes of administration. Dose ranges used for recreational purposes are: 80 - 150 mg by oral route, 40 - 100 mg by nasal route, 10 - 20 mg by inhalation, and 30 - 60 mg by intravenous route.

B. Pharmacokinetics

No pharmacokinetic studies have been described in scientific literature.

On the non-commercial German website "NeuePsychoaktiveSubstanzen.de"[7] users are informed about new psychoactive substances (not peer reviewed):

- The effect of pentedrone builds up relatively slowly and disappears also slowly. Inhalation: Effects within 30 seconds with a peak effect at 5-10 minutes; duration: 60-180 minutes.
- Oral route: Effects within 20-60 minutes with a peak effect at 90-180 minutes; duration: 6-8 hours
- Intranasal route: Effects within 1-15 minutes with a peak effect at 30-120 minutes; duration: 4-6 hours
- Intravenous route: Effects within 30 seconds with a peak effect at 15-60 minutes; duration: 2-6 hours.

Metabolism of pentedrone includes keto-reduction and N-demethylation. Metabolites of pentedrone found in urine samples after presumed pentedrone administration were 2-

amino-1-phenylpentan-1-ol, 2-methylamino-1-phenylpentan-1-ol, and 2-amino-1-phenylpentan-1-one.[8]

C. Pharmacodynamics

Users of pentedrone (and methylone, 4-MEC) report more MDMA-like stimulating effects, such as euphoria, openness and increased sociability and sexual drive.[9] In contrast, MDPV being a more dopaminergic and noradrenergic drug, induces MDMA-like (and cocaine-like) subjective effects, including increased energy, but less euphoria and only mild empathogenic effects.[10]

In vitro studies

As a transporter blocker, pentedrone preferentially inhibits the uptake of dopamine (DA) and noradrenaline (NA) with minimal effects on the uptake of serotonin (SER, 5-HT) [11] (see below). In addition, pentedrone does not evoke the release of monoamines. In this respect pentedrone resembles cocaine and pentylone, but there are important differences (see below).

The effects of pentedrone on the induction of the transporter-mediated release of NA, DA, and 5-HT and its binding affinities for monoamine transporters, α1 and α2 adrenergic receptors, dopamine D_1-D_3 receptors, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, the histamine H_1 receptor, and the trace amine-associated receptor 1 ($TAAR_1$) have been assessed by Simmler et al.[11] in human embryonic kidney 293 cells (HEK 293 cells). The results are depicted in Table 1.

Table 1. Inhibition of monoamine transporters by pentedrone (IC_{50} [μM]; 95% CI in parenthesis). For 'DAT/SERT ratio' i.e. DAT/SERT inhibition ratio the ratio is given and the 95% CI is put in parenthesis.[11,12]

Substance	NAT*	DAT	SERT	DAT/SERT ratio
Pentylone	0.99 (0.72-1.4)	1.34 (1.0-1.7)	8.37 (5.4-13)	6.2 (3.2-13)
Pentedrone	0.61 (0.52-0.72)	2.50 (2.0-3.2)	135 (5-3700)	>10
Buphedrone	0.65 (0.51-0.81)	4.24 (3.3-5.5)	70 (2-2700)	>10
Methamphetamine	0.064 (0.04-0.09)	1.05 (0.74-1.5)	23 (14-40)	>10

*NAT, DAT and SERT refer to transporters of noradrenaline (NA), dopamine (DA) and serotonin (SER; 5-HT), respectively; DAT/SERT ratio is defined as $1/DAT_{IC50} : 1/SERT_{IC50}$.

The results in Table 1 show that pentedrone preferentially inhibits the catecholamine transporters NAT and DAT vs. SERT. Pentedrone does not show high potency at the DAT and has a high DAT/SERT ratio (defined as $1/DAT_{IC50} : 1/SERT_{IC50}$). The DAT/SERT ratio for pentedrone of >10 was similar to methamphetamine, possibly indicating a pronounced abuse potential.[13] Illustrative is that MDPV with a DAT/SERT ratio of >100 was found to have high reinforcing properties and compulsive use.[14] Also note that, in like pentedrone, buphedrone also inhibits the uptake of NA, DA and SER.[11]

Table 2. Affinities of substances for the monoamine transporters NAT, DAT and SERT, serotonergic 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, and α1 and α2 adrenergic receptors expressed as Ki (μM).[11]

Substance	NAT*	DAT	SERT	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	α_{1A}	α_{2A}
Pentylone	9.0±2.4	0.24±0.02	2.0±0.5	>18	>13	>13	>6	>25
Pentedrone	4.5±1.3	0.34±0.03	17.3±6.1	>18	>13	>13	>6	35.4±16
Buphedrone	8.5±4.2	1.3±0.3	28.6±18	>18	>13	>13	>6	23.9±4.2
Methamphetamine	3.0±2.2	1.8±0.7	24.6±10	8.1±0.8	>13	>13	>6	6.1±1.6

*NAT, DAT and SERT refer to transporters of noradrenaline (NA), dopamine (DA) and serotonin (SE; 5HT), respectively.

Simmler et al. (2014) also studied the affinities of several cathinones for monoamine transporters, and serotonergic and alfa-adrenergic receptors in HEK 293 cells (Table 2).[11]

Except for methamphetamine which had an affinity for the two trace amine-associated receptors ($TAAR_{1rat}$ and $TAAR_{1mouse}$) of 0.35±0.1 μM and 0.55±0.2 μM, respectively, the affinity of the four substances for the three dopamine receptor subtypes (DA_1, DA_2, DA_3), histamine H_1 receptor (H_1), and $TAAR_{1rat}$ and $TAAR_{1mouse}$ was low, i.e., respectively >12.5, >10, >16, >13, >10 and > 10 μM.

Using reverse transcription polymerase chain reaction and Western blot it was shown that pentedrone (0.01-10 nM) dose-dependently increased the mRNA expression of DA_1 receptor (10 nM: +70%), DA_2 receptor (10 nM: +105%) and DA transporter (0.1 nM: +77%) and induced phosphorylation of cAMP response element-binding protein in PC-12 cells (10 nM: +66%).[15]

***In vivo* studies**

At 10 mg/kg i.p. pentedrone significantly increased climbing in the mouse apomorphine-induced climbing behaviour test (i.e. dopaminergic activation) and decreased VMAT2 (vesicular monoamine transporter 2), but did not affect DAT in mouse striatum.[16] Pentedrone (3-10 mg/kg i.p.) dose-dependently increased locomotor activity in mice, had rewarding properties as shown by increased conditioned-place-preference test scores relative to saline, and produced self-administration (0.3 mg pentedrone/kg/infusion) in rats.[15] Results obtained by others[17,18] in mice confirm the stimulation of locomotor activity (i.e., dopaminergic activation) by pentedrone with an efficacy comparable to that of cocaine and methamphetamine (ED_{50} of 4.7±0.1 mg/kg i.p.). Effects were apparent by 10 min after administration and lasted 90 to 140 minutes. Locomotor activity (10 mg/kg i.p.) at peak effect (0-30 min) increased to 196 ± 11% of vehicle control.[17,18]

5. Toxicology

Introduction

Pentedrone was found to be a monoamine transport blocker (no release of monoamines)[11] (see Section 4C Pharmacodynamics) and such uptake inhibitors likely do not enter the intracellular space of the synapse via the transporter, which may be associated with less intracellular pharmacological effects and toxicity compared with substrate-type releasers.[19]

***In vitro* studies**

In primary rat hepatocytes, pentedrone induced LDH-leakage at 0.2 - 1.6 mM[20,21] and 1-10 mM[15] which was greater than seen for methamphetamine indicating that pentedrone may be more cytotoxic than methamphetamine.

Hepatotoxic effects of pentedrone were evaluated in primary cultures of rat hepatocytes by measuring cell viability through the (1) MTT assay, (2) glutathione (GSH) and glutathione disulfide (GSSG), (3) intracellular ATP, (4) production of reactive species (ROS/RNS), and (5) activation of caspases.

(1) Cell death was induced in a concentration-dependent manner by cathinones in the following potency order: MDPV ~ pentedrone > MDMA ~ 4-MEC > methylone. The EC_{50}-value of the hepatotoxic effect of pentedrone (MTT assay) in HepaRG cells was 3.4 mM and in PRH cells 0.66 mM.[20,21]
(2) All cathinones showed a comparable decrease of GSH levels after 48 h of exposure to pentedrone. In PHR cells, pentedrone (1.6 mM for 24 h) decreased intracellular GSH-levels (23.7±2.2 vs. 43.9±4.2 nmol/mg of protein in control cells, $P < 0.0001$), but this was not accompanied by corresponding increases in GSSG level.
(3) Under the same conditions pentedrone (1.6 mM) reduced intracellular ATP level by 40%, although it is remarkable that pentedrone at lower concentrations (0.2 - 0.4mM) increased ATP production.[20,21]
(4) Pentedrone from as low as 0.4 mM for 24 h concentration-dependently increased ROS/RNS production in PHR cells. 1.6 mM pentedrone increased ROS and RNS production 1.5-fold.[20,21]
(5) 1.6 mM pentedrone activated caspase-3 by 254.0 ± 23.5 % ($P <0.0001$ vs. control cells); similar tendency was observed for caspases 8 and 9.[21]

In summary, similar to of MDMA, pentedrone is one of the most hepatotoxic synthetic cathinones *in vitro* (EC_{50} values of 0.66 mM).[21] Note that pentedrone may penetrate in liver and that a liver-to-blood concentration ratio of 11 has been reported by Sykutera et al (2015).[22]

No data about mutagenicity, genotoxicity and carcinogenicity have been reported.

***In vivo* studies in animals**

Both pentylone and pentedrone are inhibitors of the DA transporter (DAT). Pentylone produces convulsions and is lethal at 100 mg/kg in mice.[18] Similarly, pentedrone induced severe convulsions in the Hwang et al. study (2015) at 70 mg/kg and was lethal at 100 mg/kg; data not shown). However, others reported that in contrast to pentylone (3 to 100 mg/kg i.p.), pentedrone (1 to 25 mg/kg i.p.), produced no convulsive effects, but data were not shown).[17,18]

Human studies

Driving under the influence of drug (DUID)

In two out of 24 α-PVP related DUID cases in Poland, pentedrone was found in combination with α-PVP.[23] In seven drivers α-PVP was the only substance detected and in 17 drivers combination of substances. Fourteen other drugs were involved in addition to α-PVP (α-PVP concentration ranged from 7.0 to 94 ng/ml; median 24 ng/ml) in eleven drivers without symptoms, and pentedrone was detected in one of them at a concentration of 52 ng/ml.

Eleven substances in addition to α-PVP (α-PVP concentration ranged from 17 to 99 ng/ml; median 40.5 ng/ml) were detected in the blood of six drivers with observable symptoms and in one of them pentedrone was detected in blood at a concentration of < 1 ng/ml).[23]

In a 3-year review of casework in Poland, the concentration of pentedrone in 7 DUID cases ranged from <1 ng/ml to 216 ng/ml (mean 36 ng/ml, median 10 ng/ml). In 5 of these 7 pentedrone-positive DUID cases, other cathinones, cannabinoids, amphetamines, and benzodiazepines were detected in blood in addition to pentedrone.[24]

Intoxications

In a sample of 15 subjects taken to the Emergency Department in Budapest with suspected illicit drug and/or alcohol intoxication (93% male; average age: 24.8 yrs.; 10 were regular i.v. drug users) polydrug use was highly prevalent, and pentedrone was one of the 17 drugs used in 5 cases with an averaged pentedrone serum level of 93 ng/ml (range 26 to 343 ng/ml) and pentedrone urine level of 49 to 2,493 ng/ml. A variety of clinical signs were reported, but their relation with any specific substance is unclear.[25,26]

Using UPLC-MS/MS, 19 urine samples of authentic cases of intoxication (total number unknown) analysed in Sweden by the Karolinska University Laboratory, were positive for pentedrone.[27]

In Poland, in addition to 24 DUID cases, α-PVP-associated cases were related to traffic accidents (N=4), acts of violence (N=6), non-fatal intoxications (N=4) and deaths (N=12).[23] One of the 12 fatal intoxications related to α-PVP use (case 12) was a Polish man who had been previously treated for a psychiatric disorder but died during police intervention. The following substances were detected in his blood: pentedrone (600 ng/ml), ethcathinone (64 ng/ml), 3-MMC (290 ng/ml), α-PVP (1.9 ng/ml), and zuclopenthixol (8 ng/ml), whereas substances found in urine were: morphine (21 ng/ml), pentedrone (73 ng/ml), ethcathinone (4 ng/ml), α-PVP (<1 ng/ml), and zuclopenthixol (9 ng/ml).[23] Other (fatal) intoxications were not described.

In Italy from April 2011 to April 2013, pentedrone was detected in only 1 out of 202 clinical urine specimens collected from patients admitted to the national emergency departments (concentration not reported).[28]

In Sweden from January 2010 to August 2011, pentedrone was detected in only 1 out of 189 consecutive cases of drug intoxications (33 samples were negative; 17%) presenting at emergency departments across Sweden and analysed within the Swedish STRIDA project.[29] The concentration of pentedrone or clinical signs of this case were not reported.

Fatal cases following pentedrone consumption

1. A well-documented fatal case of combined α-PVP and pentedrone poisoning was reported in Poland. A 28-year-old man was taken to hospital in asystole and died despite resuscitation efforts over 30 min. The presence of 64 of the most frequently detected drugs in toxicology casework, including amphetamines, benzodiazepines, opiates, cocaine, sedatives, hypnotics, antidepressants and cathinones was excluded. The forensic autopsy showed pulmonary oedema and moderately advanced atherosclerotic lesions of the arteries. Microscopic observation revealed chronic changes in the heart.

The concentration of pentedrone in the biological samples appeared to be very high (cf. Table 3), although literature concentrations are not available for comparison. In the present case, the blood concentration of α-PVP of 901 ng/ml was higher than the blood values of previously reported cases where α-PVP was the sole cause of death i.e. 486 ng/ml[30] and 411 ng/ml.[31] The microscopic observations of the heart specimen in this case are consistent with those previously reported α-PVP.[31,30]

Table 3. Concentrations of pentedrone, α-PVP and OH-α-PVP (a metabolite of α-PVP) in post mortem samples assayed by LC-MS.[22]

Specimen	Concentration (ng/ml blood; ng/g tissue)		
	Pentedrone	α-PVP	OH-α-PVP
Whole blood	8,794	901	185
Liver	100,044	2,610	2,264
Kidney	22,102	462	294
Brain	13,248	120	91
Stomach content	500,534	4,190	47

Considering the high blood concentration of pentedrone, it is likely that both α-PVP and pentedrone acted on the heart to cause cardiac rhythm disturbance. The pathologist in this case reported that the cause of death was attributed to multiple drug toxicity associated with α-PVP and pentedrone use.[22]

2. Liveri et al. (2016) reported on a fatal intoxication related to MDPV and pentedrone in combination with antipsychotic and antidepressant substances. A 42-year-old man (with psychiatric history) died by myocardial infarction after consumption of multiple drugs. Post mortem toxicological analysis of blood and urine showed MDPV (46 and 1300 ng/ml), pentedrone (160 and 12,000 ng/ml) and etizolam (300 and 100 ng/ml) in blood and urine, respectively. Other drugs quantitated in blood were olanzapine 4200 ng/ml, mirtazapine 570 ng/ml, and ephedrine 68 ng/ml.[32] The pentedrone concentration found in blood was lower than the concentration in the fatal case reported by Sykutera et al. (2015).

3. Adamowicz et al. (2016) reported that pentedrone was found in four fatal cases along with other cathinones,[24] but in none of these cases pentedrone was present at the highest concentration. For instance, in one of the fatal cases (a 38-year-old man) both mephedrone (692 ng/ml) and pentedrone (13 ng/ml) were found in the blood. In another fatal case, a 23-year-old man was found dead in a car parked along the road and post mortem toxicological analysis showed a blood level of MDPBP, pentedrone and MPA of 7010, 317, and 9.5 ng/ml, respectively.[24]

4. A case of drowning (as the cause of death) occurred in October 2012 in France.[33] MDPV was present in blood at a concentration of 106 ng/ml and in urine at a concentration of 760 ng/ml. Other drugs detected were: PVP (blood 40 ng/ml; urine 295 ng/ml); pentedrone (blood 33 ng/ml; urine 110 ng/ml); hydroxyzine (blood 194 ng/ml); nordiazepam (blood 47 ng/ml); oxazepam (blood 8 ng/ml); cannabinoic acid (blood 15.7 ng/ml); and ethanol (blood 0.3 g/L). No further details were provided.[33]

5. One fatal case (male adult aged 31 years) related to α-PVP and pentedrone use was reported in the US; the man was shot dead by the police after showing aggressive and

paranoid behaviour, as well as suicidal threats. Blood level of α-PVP was 290 ng/ml and pentedrone 480 ng/ml.[34]

6. Adverse Reactions in Humans

See also section 5. Toxicology, human studies.
One case report refers to a 25-year-old man with opioid and benzodiazepine addiction who was in opioid agonist therapy (buprenorphine). He developed an acute psychosis after he had abused pentedrone for the first time the day before (2 g, snorted). The man further reported continuous abuse of high doses of benzodiazepines in the previous few months, and occasional cannabis use dating back to adolescence. He had never experienced psychotic symptoms before.[35]

7. Dependence Potential

A. Animal Studies

No studies to the dependence potential have been performed in animals.

B. Human Studies

No studies to the dependence potential have been performed in humans.

8. Abuse Potential

A. Animal Studies

In Sprague-Dawley rats trained to discriminate cocaine (10 mg/kg, i.p.) or methamphetamine (1 mg/kg, i.p.) from saline, pentedrone (0.5 - 5 mg/kg i.p.) produced discriminative stimulus effects comparable to those of cocaine and methamphetamine (ED_{50} of 2.3±0.2 and 2.6±0.1, respectively),[17,18] suggesting that pentedrone has a similar abuse potential as cocaine and methamphetamine.[17,18]
Pentedrone (3 and 10 mg/kg i.p.) significantly increased conditioned place preference paradigm in mice and at 0.3 mg/kg/i.v. pentedrone significantly increased self-administration (number of infusions per session of 2 h) in rats.[15,16] RT-PCR and western blotting confirmed the involvement of dopaminergic system in rewarding effects of pentedrone, i.e., pentedrone decreased tyrosine hydroxylase mRNA level and increased DAT, DA_1 and DA_2 mRNA levels and phosphorylation of CREB in PC-12 cells.[16] The rewarding effects of pentedrone observed suggest that pentedrone has an abuse potential that may be due to dopaminergic activation.[16]

B. Human Studies

No studies to the abuse potential have been performed in humans.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

No therapeutic or medical use has been described for pentedrone.
In 1928, a series of substituted aminopropiophenones (Fig. 2) and their respective alcohols has been prepared in an attempt to develop substances that would increase blood sugar.[4]

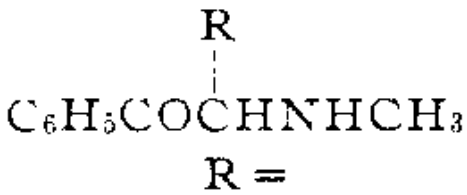


Figure 2. Basic structure of aminopropiophenones. In pentedrone R = *n*-C_3H_7

Only α-phenyl-β-methylamino-ethanol induced a dose-dependent increase in blood pressure.[4]

10. Listing on the WHO Model List of Essential Medicines

Pentedrone is not listed.

11. Marketing Authorizations (as a Medicinal Product)

Pentedrone is not marketed as medicinal product.

12. Industrial Use

Pentedrone is not used for industrial purposes.

13. Non-Medical Use, Abuse and Dependence

Detection in commercial products

Canada	Pentedrone has been detected in shipments destined for Canada.[3]
Italy	Analysis of waste water from four Italian cities (Milan, Bologna, Turin, and Perugia) showed the presence of only three NPS (tentatively attributed to buphedrone, pentedrone, and 4-MEC).[36]
Poland	The NPSs most frequently identified in 'legal-high' preparations were in 2012 UR-144, pentedrone, and ethcathinone, in 2013 UR-144 (41% of all NPS), pentedrone (21%), and iso-pentedrone (12%, however it can also be impurity present in pentedrone), and in 2014 UR-144 (34%), 3-MMC (23%), and pentedrone (16%).[37,38] Pentedrone is one of the best available NPS in Poland (in 2014 online).[39]
Portugal	Pentedrone was detected in samples ("Bloom") purchased in three different ''smart shops'' in the area of Lisbon.[40]

Spain Pentedrone was, in contrast to mephedrone and methylone, seldomly detected, as less than 10 out of 6199 samples tested by Drug Test Service in Spain in 2010–2012 were positive for pentedrone.[41]

UK Pentedrone was first seen in toxicological casework in 2012.[42] In nine cities across the UK where pooled urine was collected from street urinals that had been in place for one night in April 2014, pentedrone was only detected in Birmingham.[43]

US In 2010-2013 pentedrone was detected as one of the substances in 'bath salts'.[44] In six samples of "bath salt" products purchased from California stores and the Internet pentedrone was detected with variable content: Ivory Wave Ultra via Internet (17 mg); Stardust in San Diego (138 mg); Ultimate Sextacy Aphrodisiaca via Internet (11 mg); Vanilla Sky via Internet (4 mg); White Lightning in San Diego (224 mg).[45]

Detection in urine samples

US

A total of 34,561 urine specimens collected in 2011–2013 from various clients in the USA (originating from potential users in the USA) were submitted for designer stimulant testing to Redwood Toxicology Laboratory (Santa Rosa, CA, USA). Results showed that α-PVP was the most prevalent (N=852, 2.5%), followed by MDPV (N=586, 1.7%) and pentedrone (N=425, 1.2%).[8] Three pentedrone positive samples were detected among 62 authentic urine specimens from stimulant users screened for NPS (range 16.2 – 3,864 ng/ml).[46] In US stimulant users, pentedrone (16.2 - 3,864 ng/ml) was detected in 3 out of 62 urine specimens.[46] Blood pentedrone levels in two other cases (drug possession and offense intent) were in the range of 13–360 ng/ml.[23]

Poland

Following 3-MMC (50) and α-PVP (23), pentedrone (16) was one the most frequently detected NPS in 112 subjects in Poland in a period of three years (2012–2014). In the 2012, 2013 and 2014 the number of pentedrone-positive cases increased from 1 to 5 and 10, respectively.[24] The 16 pentedrone-related cases were classified into: intoxication (1), road accident (1), DUID (7), drug possession (2), death (other mechanism) (3) and other (2). The mean pentedrone blood level in these 16 pentedrone-positive cases was 98.4 ng/ml, median concentration was 27 ng/ml, and the range was 8.6 to 360 ng/ml. Levels per case of class were not further specified.[24]

Hungary

In 2011, only a few drug users reported primary injection of pentedrone, but it became the predominant substance injected by clients reporting 'other drug' injection in 2012.[1,47] Indeed, after banning a variety of illicit drugs in January 2012, pentedrone became the most frequently abused stimulant designer drug in Hungary.[48] In the last five years, drugs injected in Hungary shifted to synthetic cathinones[1] and pentedrone became the most common (48%) injected drug.[49]

Between July 2012 and June 2013, 2,744 and 774 drug users suspected of criminal activity were sampled (urine and/or blood) in Budapest and South-East Hungary, respectively. In Budapest and South-East Hungary 71% and 61% of cases, were positive for at least one substance, respectively.[50] In both regions, pentedrone was the most frequently detected substance among 38 different stimulant designer drugs i.e. in Budapest 34.7% (N=680 of

which 72% in combination with other substances) and in South-East Hungary 30.4% (N=144 of which 58% in combination with other substances). Pentedrone was most often combined with amphetamine (51%), benzodiazepines (44%), THC (32%) and mephedrone (22%).[50]

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Considering fatal traffic incidents due to consumption of cathinones,[51] driving under the influence of pentedrone seems hazardous, but the limited information available from DUID studies (see section 5, Toxicology) does not allow to estimate the impact of pentedrone use in traffic safety. Intravenous injection of pentedrone is popular in Hungary (see section 13, Non-medical use) and known to be associated with needle sharing related communicable diseases, like HIV.

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit Production, Consumption and International Trade

Pentedrone is not controlled world-wide so that pentedrone products (as powders, mixtures, crystals) are legally marketed in head shops and via the Internet in various countries.

16. Illicit Manufacture and Traffic and Related Information

Seizures

Austria	Pentedrone was seized by the customs at the airport in Austria. A white powder (4 kg pentedrone) was declared as a super absorbent polymer to be sent back to Shanghai, China.[6]
Estonia	Estonian customs authorities reported one seizure of MDPV (1.68 g) in incoming mail from the UK which was mixed with α-PVP and pentedrone.[33]
EU	In 2013, 197 kg pentedrone was seized (14% of all cathinones).[52] In 2014, 136 kg was seized in the EU.[53]
Finland	In 2011–2013, two samples with pentedrone were seized by police and customs. It was further shown that the content of individual ingredients varied from a few mg to several hundred mg per pack, and the percentage of the main component ranged from 5% to 100%.[54]
France	Two of the samples seized containing a mixture of α-PVP and pentedrone.[33]
Hungary	In 2012, pentedrone was most frequently found in cathinone-related seizures, whereas it was mephedrone in 2010 and 4-MEC (4-methylethcathinone) and MDPV (3,4-methylenedioxypyrovalerone) in 2011.[48]
Italy	Pentedrone was identified in 8 out of 17 seized crystals and powders.[55]
Poland	Between mid-2008 and mid-2011, Polish law enforcement and health services detected pentedrone in 12 out of 449 products seized in head shops; in 9 out of the 12 samples pentedrone was mixed with other substances.[56] Content of pentedrone in the seized products (as unique component) was 0.11 to 0.89 gram per gram.[56]

US	According to the DEA, only 13% of the Molly seized in New York State the last four years actually contained any MDMA, and even then it often was mixed with other drugs, like methylone, MDPV and pentedrone.[57] In Arkansas, US, from January 2010 through December 2012, pentedrone was commonly detected in tablets, capsules, and powders in over 3000 products seized.[47]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

Pentedrone is not scheduled under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and Past National Controls

Austria:	Illegal.[58]
Australia	Listed as a controlled drug in Schedule 1
Brazil	Resolution No. 79 of MAY 23, 2016. List of prohibited substances in Brazil. List 2 - Psychotropic substances.[59]
Canada	Schedule I (Canada's Controlled Drugs and Substances Act).
China	Controlled substance since October 2015.[60]
Czech Rep.	Pentedrone is a controlled substance.[61]
Cyprus	Cathinone derivatives are illegal drugs according to Cyprus Generic Legislation, introduced in 2011 to ban new psychotropic substances.[32]
France	Listed as controlled substance since July 2012.[62]
Germany	Anlage II (controlled substances may be sold but not prescribed) German Betäubungsmittelgesetz (BtMG; Narcotic Act).[63]
Hungary	Legal until 2014. In April 2012 pentedrone was placed on a list of temporary scheduled substances (schedule C of Government Decree 66/2012; generic definition) which only restrict trafficking while risk assessment is being conducted.[64] However, when the NPS emerges it automatically becomes "C listed".[65]
Kyrgyz Rep.	Controlled since December 4, 2015 through the Decree No 831 "On narcotic drugs, psychotropic substances and precursors subject to control in the Kyrgyz Republic".[66]
Moldova	By decree, pentedrone is a controlled substance in the Republic of Modova.[67]
Sweden	NPS, including pentedrone, are brought under control of drug laws, either as a "Narcotic drug" or "Certain goods dangerous to health"
UK	Class B (Misuse of Drugs Act 1971).
US	Schedule I (Controlled Substances Act). On January 28, 2014, the DEA listed pentedrone, along with 9 other synthetic cathinones, on the Schedule I with a temporary ban, effective February 27, 2014[68,69]; on 4th of March 2016 the temporarily schedule was extended as Schedule I compound.[70] Pentedrone is scheduled in Texas,[71,72] Vermont,[73] Iowa.[74]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

No remarks.

References

1. Peterfi A, Tarjan A, Horvath GC, Csesztregi T, Nyirady A. Changes in patterns of injecting drug use in Hungary: a shift to synthetic cathinones. Drug Test Anal. 2014;6(7-8):825-31.
2. Trzybinski D, Niedzialkowski P, Ossowski T, Trynda A, Sikorski A. Single-crystal X-ray diffraction analysis of designer drugs: hydrochlorides of metaphedrone and pentedrone. Forensic Sci Int. 2013;232(1-3):e28-e32.
3. Maheux CR, Copeland CR. Chemical analysis of two new designer drugs: buphedrone and pentedrone. Drug Test Anal. 2012;4(1):17-23.
4. Hyde JF, Browning E, Adams R. Synthetic homologs of d,l-ephedrine. J Am Chem Soc. 1928;50(8):2287-92.
5. Tsujikawa K, Yamamuro T, Kuwayama K, Kanamori T, Iwata YT, Inoue H. Instability of the hydrochloride salts of cathinone derivatives in air. Forensic Sci Int. 2015;248:48-54.
6. Westphal F, Junge T, Girreser U, Greibl W, Doering C. Mass, NMR and IR spectroscopic characterization of pentedrone and pentylone and identification of their isocathinone by-products. Forensic Sci Int. 2012;217(1-3):157-67.
7. NeuePsychoaktiveSubstanzen.de. 2016. 5F-AKB-48 / 5F-APINACA - Synthetisches Cannabinoid. Available from: http://neuepsychoaktivesubstanzen.de/5f-akb-48/
8. 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(5):233-41.
9. Van Hout MC. An Internet study of user's experiences of the synthetic cathinone 4-methylethcathinone (4-MEC). J Psychoactive Drugs. 2014;46(4):273-86.
10. De Luca P, Schifano F, Davey Z, Corazza O, Di Furia L, Group PW. 2009. MDPV Report. Available from: http://www.psychonautproject.eu/
11. Simmler LD, Rickli A, Hoener MC, Liechti ME. Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. Neuropharmacology. 2014;79:152-60.
12. Simmler LD, Simmler LD, Liechti ME, Liechti ME. Interactions of cathinone NPS with human transporters and receptors in transfected cells. Curr Top Behav Neurosci. 2016:1-24.
13. Bauer CT, Banks ML, Blough BE, Negus SS. Use of intracranial self-stimulation to evaluate abuse-related and abuse-limiting effects of monoamine releasers in rats. Br J Pharmacol. 2013;168(4):850-62.
14. Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Grabenauer M, Thomas BF, et al. Potent rewarding and reinforcing effects of the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV). Addict Biol. 2014;19(2):165-74.
15. Hwang JY, Kim JS, Oh JH, Hong SI, Ma SX, Jung YH, et al. The new stimulant designer compound pentedrone exhibits rewarding properties and affects dopaminergic activity. Addict Biol. 2015 [Epub ahead of print].
16. Kim JS, Hwang JY, Hong SI, Jung YH, Ma SX, Seo JY, et al. Pentedrone induces conditioned place preference and self-administration through dopaminergic system (Abstract P02-21). J Neurochem. 2014;130:62.
17. Forster MJ, Rutledge M, Gatch MB. Discriminative and locomotor effects of three synthetic cathinones. Drug Alcohol Depend. 2015;146:e281-e282.
18. Gatch MB, Rutledge MA, Forster MJ. Discriminative and locomotor effects of five synthetic cathinones in rats and mice. Psychopharmacology (Berl). 2015;232(7):1197-205.

19. Eshleman AJ, Wolfrum KM, Hatfield MG, Johnson RA, Murphy KV, Janowsky A. Substituted methcathinones differ in transporter and receptor interactions. Biochem Pharmacol. 2013;85(12):1803-15.
20. Araujo AM, Valente MJ, Carvalho M, Dias da Silva D, Gaspar H, Carvalho F, et al. Raising awareness of new psychoactive substances: chemical analysis and in vitro toxicity screening of 'legal high' packages containing synthetic cathinones. Arch Toxicol. 2015;89(5):757-71.
21. Valente MJ, Valente MJ, Araujo AM, Araujo AM, Bastos MdL, Bastos ML, et al. Characterization of hepatotoxicity mechanisms triggered by designer cathinone drugs (beta-keto amphetamines). Toxicol Sci. 2016 [Epub ahead of print].
22. Sykutera M, Cychowska M, Bloch-Boguslawska E. A Fatal Case of Pentedrone and alpha-Pyrrolidinovalerophenone Poisoning. J Anal Toxicol. 2015;39(4):324-9.
23. Adamowicz P, Gieron J, Gil D, Lechowicz W, Szulska A, Tokarczyk B, et al. Blood concentrations of a-pyrrolidinovalerophenone (a-PVP) determined in 66 forensic samples. Forensic Toxicol. 2016;34:227-34.
24. Adamowicz P, Gieron J, Gil D, Lechowicz W, Skulska A, Tokarczyk B. The prevalence of new psychoactive substances in biological material - a three-year review of casework in Poland. Drug Test Anal. 2016;8(1):63-70.
25. Kovacs K, Zacher G, Racka T A, Harmath A, Kereszty T, Varga T. Designer drug related intoxications in Hungary. Clinical experiences (Abstract). Rechtsmedizin. 2012;22(4):341-2.
26. Institoris L, Arok Z, Zacher G, Tóth AR, Kereszty E, Varga T. Serum, urine and oral fluid concentration of stimulant-type designer drugs in intoxicated drug users (Abstract V30). Rechtsmedizin. 2012;22:287.
27. Beck O. Detectability of new psychoactive substances, 'legal highs', in CEDIA, EMIT, and KIMS immunochemical screening assays for drugs of abuse. Drug Testing Anal. 2014;6(5):492-499.
28. Roda E, Lonati D, Buscaglia E, Papa P, Rocchi L, Locatelli CA, et al. Evaluation of two different screening ELISA assays for synthetic cathinones (mephedrone/methcathinone and MDPV) with LC-MS method in intoxicated patients. J Clin Toxicol. 2016;6(3):302.
29. Helander A, Backberg M, Hulten P, Al-Saffar Y, Beck O. Detection of new psychoactive substance use among emergency room patients: results from the Swedish STRIDA project. Forensic Sci Int. 2014;243:23-9.
30. Saito T, Namera.A., Osawa M, Aoki H, Inokuchi S. SPME-GC-MS analysis of a-pyrrolidinovalerophenone in blood in a fatal poisoning case. Forensic Toxicol. 2013;31(2):328-32.
31. 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 alpha-pyrrolidinovalerophenone. Int J Cardiol. 2014;172(1):263-5.
32. Liveri K, Constantinou MA, Afxentiou M, Kanari P. A fatal intoxication related to MDPV and pentedrone combined with antipsychotic and antidepressant substances in Cyprus. Forensic Sci Int. 2016;265:160-5.
33. EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2014. EMCDDA-Europol Joint Report on a new psychoactive substance: MDPV (3,4-methylenedioxypyrovalerone). EMCDDA-Europol, Lisbon. Available from: http://www.emcdda.europa.eu/publications/joint-report/MDPV
34. Richards-Waugh LL, Bailey KM, Clay DJ, Gebhardt MA, Newsome-Sparks CL, Mahmoud HE, et al. 2013. Deaths involving the recreational use of a-PVP (a-

pyrrolidinopentiophenone). AAFS Proceedings, Abstract K16, Washington, D.C. Available from: http://www.aafs.org/sites/default/files/pdf/ProceedingsWashingtonDC2013.pdf
35. Segrec N, Kastelic A, Pregelj P. Pentedrone-Induced acute psychosis in a patient with opioid addiction: A case report. Heroin Addict Relat Clin Probl. 2016;18(3):53-6.
36. Gonzalez-Marino I, Gracia-Lor E, Bagnati R, Martins CPB, Zuccato E, Castiglioni S. Screening new psychoactive substances in urban wastewater using high resolution mass spectrometry. Anal Bioanal Chem. 2016;408(16):4297-309.
37. CSI (Chief Sanitary Inspector). 2013. Report of the Chief Sanitary Inspector of the drug substitutes - three years working against 'legal highs' in Poland, Chief Sanitary Inspector, Warsaw, Poland. Available from: http://www.gis.gov.pl/ckfinder/userfiles/files/%C5%9Arodki%20Zast%C4%99pcze/raport2013.pdf
38. CSI (Chief Sanitary Inspector). 2014. Report of the Chief Sanitary Inspector of the drug substitutes - together against 'legal highs' 2013-2014, Chief Sanitary Inspector, Warsaw, Poland. Available from: http://www.gis.gov.pl/ckfinder/userfiles/files/BI/GIS_raport_2013-2014.pdf
39. Vavrincikova L, Fidesova H, Janikova B, Grund JP. 2016. New psychoactive substances among people who use drugs heavily. Towards effective and comprehensive health responses in Europe. Available from: http://www.npsineurope.eu/images/pdf/publication/NPS_5_country_rar_report.pdf
40. Zancajo VMR, Brito J, Carrasco MP, Bronze MR, Moreira R, Lopes A. Analytical profiles of "legal highs" containing cathinones available in the area of Lisbon, Portugal. Forensic Sci Int. 2014;244:102-10.
41. Caudevilla-Galligo F, Ventura M, Indave Ruiz BI, Fornis I. Presence and composition of cathinone derivatives in drug samples taken from a drug test service in Spain (2010-2012). Hum Psychopharmacol. 2013;28(4):341-4.
42. Elliott S, Evans J. A 3-year review of new psychoactive substances in casework. Forensic Sci Int. 2014;243:55-60.
43. Archer JRH, Hudson S, Jackson O, Yamamoto T, Lovett C, Lee HM, et al. Analysis of anonymized pooled urine in nine UK cities: variation in classical recreational drug, novel psychoactive substance and anabolic steroid use. QJM. 2015;108(12):929-33.
44. NFLIS (National Forensic Laboratory Information System). 2014. Special report: synthetic cannabinoids and synthetic cathinones reported in nflis, 2010-2013. Available from: https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS_SR_CathCan_508.pdf
45. 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 (Phila). 2014;52(7):651-8.
46. 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.
47. Seely KA, Patton AL, Moran CL, Womack ML, Prather PL, Fantegrossi WE, et al. Forensic investigation of K2, Spice, and "bath salt" commercial preparations: a three-year study of new designer drug products containing synthetic cannabinoid, stimulant, and hallucinogenic compounds. Forensic Sci Int. 2013;233(1-3):416-22.

48. HNFP (Hungarian National Focal Point). 2014. 2013 National report to the EMCDDA by the Reitox National Focal Point Hungary. Available from: http://drogfokuszpont.hu/wp-content/uploads/HU_National_Report_2013.pdf
49. Racz J, Gyarmathy VA, Csak R. New cases of HIV among people who inject drugs in Hungary: False alarm or early warning? Int J Drug Policy. 2016;27:13-6.
50. Institoris L, Arok Z, Seprenyi K, Varga T, Sara-Klausz G, Keller E, et al. Frequency and structure of stimulant designer drug consumption among suspected drug users in Budapest and South-East Hungary in 2012-2013. Forensic Sci Int. 2015;248:181-6.
51. Rojek S, Kula K, Maciow-Glab M, Klys M. New psychoactive substance alpha-PVP in a traffic accident case. Forensic Toxicol. 2016;34:403-10.
52. EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2015. New psychoactive substances in Europe. An update from the EU Early Warning System (March 2015), Publications Office of the European Union, Luxembourg. Available from: www.emcdda.europa.eu/publications/2015/new-psychoactive-substances
53. EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2016. European drug report. Trends and development 2015. Publications Office of the European Union, Luxembourg. Available from: http://www.emcdda.europa.eu/edr2016
54. Rasanen I, Kyber M, Szilvay I, Rintatalo J, Ojanpera I. Straightforward single-calibrant quantification of seized designer drugs by liquid chromatography-chemiluminescence nitrogen detection. Forensic Sci Int. 2014;237:119-25.
55. Rossi SS, Odoardi S, Gregori A, Peluso G, Ripani L, Ortar G, et al. An analytical approach to the forensic identification of different classes of new psychoactive substances (NPSs) in seized materials. Rapid Commun Mass Spectrom. 2014;28:1904-16.
56. Zuba D, Byrska B. Prevalence and co-existence of active components of 'legal highs'. Drug Test Anal. 2013;5(6):420-9.
57. Mooney L. 2015. Drugs of abuse: what you & clinicians need to know. Available from: http://www.activeresponsetraining.net/wp-content/uploads/2015/04/What-You-Should-Know.pdf
58. Wordex Archiv. 2016. Substanzinformationen zu alpha-methylamino-valerophenone. Pentedron/PMMC. Available from: http://w0rdex.eu/substanzen/substanzen.php?id=49
59. MoH (Ministry of Health). 2016. Resolution No. 79 of MAY 23, 2016. List of prohibited substances in Brazil. List 2 - Psychotropic substances. Available from: http://www.lex.com.br/legis_27142279_RESOLUCAO_RDC_N_79_DE_23_DE_MAIO_DE_2016.aspx. 2016.
60. CFDA (China Food and Drug Administration). 2015. China. 27 September 2015.
61. CZMoH (CZ Ministry of Health). 2013. List of no. 4 psychotropic substances. (Appendix 4 to the Government Regulation no. 463/2013 Coll.). Available from: http://www.mzcr.cz/Admin/_upload/files/3/Nov%C3%A9%20PL.pdf
62. Legifrance. 2012. Arrêté du 27 juillet 2012 modifiant les arrêtés du 22 février 1990 fixant la liste des substances classées comme stupéfiants et la liste des substances psychotropes. Available from: https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000026246525&dateTexte=&categorieLien=id
63. Hohmann N, Mikus G, Czock D. Effects and risks associated with novel psychoactive substances: mislabeling and sale as bath salts, spice, and research chemicals. Dtsch Arztebl Int. 2014;111(9):139-47.

64. HNFP (Hungarian National Focus Point). 2013. 2012 National report to the EMCDDA by the Reitox National Focal Point. Available from: http://drogfokuszpont.hu/wp-content/uploads/HU_National_Report_2012.pdf
65. King LA, Sedefov R. Early-Warning System on New Psychoactive Substances. Operating Guidelines. EMCDDA, Luxembourg. 2007.
66. UNODC. 2016. Kyrgyz Republic: the synthetic cathinone pentedrone identified and seized based on new NPS legislation in the Kyrgyz Republic. Available from: https://www.unodc.org/LSS/Announcement/Details/c541076a-14c7-4afe-b910-7f1a931d9e7e
67. GRM (Guvernul Republicii Moldova). 2004. Available from: http://www.gov.md/sites/default/files/document/attachments/intr17_48.pdf
68. DEA. Drug Enforcement Agency (DEA). Temporary Placement of 10 Synthetic Cathinones into Schedule I. 28 January 2014. Fed Regist. 2014;79:12938-43.
69. DEA (Drug Enforcement Administration). 2014. List of scheduling actions, controlled substances, regulated chemicals. Available from: http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0307_2.htm
70. Sacco LN, Finklea K. 2016. Synthetic Drugs: Overview and Issues for Congress. Available from: https://www.fas.org/sgp/crs/misc/R42066.pdf
71. Criminal Justice. 2013. Texas Controlled Substances Act. Available from: http://www.legis.state.tx.us/tlodocs/83R/analysis/html/SB00264S.htm
72. FindLaw. 2016. Texas Health and Safety Code § 481.103. Penalty Group 2. Available from: http://codes.findlaw.com/tx/health-and-safety-code/health-safety-sect-481-103.html
73. Vermont Board of Health. 2016. Regulated Drug Rule. Chapter 8 Alcohol and Drug Abuse Subchapter 9. Available from: http://healthvermont.gov/regs/documents/regulated_drugs_rule.pdf
74. Iowa. 2016. Iowa Senate Bill 2116. Available from: https://legiscan.com/IA/text/SF2116/id/1327939
75. WHO (World Health Organization). 2010. Guidance on the WHO review of psychoactive substances for international control. http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of Pentedrone

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 42 Member States (4 AFR, 2 EMR, 24 EUR, 6 PAH, 1 SEAR and 5 WPR) answered the questionnaire for pentedrone. Of these, 25 respondents (21 EUR, 2 PAH and 2 WPR) had information on this substance.

LEGITIMATE USE

There were 24 countries that reported no approved medical products containing pentedrone for human or veterinarian indications.

Pentedrone is not currently being used in any medical or scientific research (excluding use as an analytical reference standard) in 19 countries, or for any industrial purpose in 20 countries.

Pentedrone was not reported to be used for any cultural, religious or ceremonial purposes in 21 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 17 countries that reported pentedrone as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are oral (11 countries), injection (5 countries), inhalation (2 countries), sniffing (11 countries) and smoking (1 country). The main route of administration for pentedrone was reported as oral (5 countries), sniffing (2 countries) and smoking (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (16 countries), followed by tablets (5 countries) and liquid or solution for oral administration/use (1 country). One country also reported plant material impregnated with the pentedrone being used as a formulation.

There were 13 countries which reported that the source of pentedrone for non-medical/non-scientific use was smuggling.

Party settings were specified as subpopulations known to misuse pentedrone by one country. Recreational drug users and psychonauts were also identified by another country as a subpopulation.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (1 country), substantial (5 countries) or serious (4 countries). For

the countries that indicated a substantial or serious level of negative health-impact, they specified that it was due to the association of pentedrone with adverse events (severe intoxications, transmission of communicable disease by injection drug use) and fatalities. It was also commented that pentedrone is a potent cathinone with amphetamine-like side effects. One country mentioned that pentedrone is sold as a designer drug and has been found since 2010 as an ingredient in a number of "bath salt" mixes as legal highs, which can be dangerous in some combinations.

Three countries reported emergency room/department visits related to the non-medical use of pentedrone. A combined number of 1 case in 2012, 7 case in 2013, 14 cases in 2014, 2 cases in 2015 and 1 case in 2016 were reported (two countries). Another 10 cases where also stated, however, no further data was provided regarding the severity of the visits or the time frame.

The adverse effects which presented for pentedrone at the emergency room/department included impaired consciousness, tachycardia, hypotension, nausea, vertigo, hallucinations, high body temperature and sweating.

In regards to the mortality rate, data was provided by 3 countries. The rate where only pentedrone was involved, included 1 case in 2015. The rate which included involvement of other substances was reported to be 2 cases in 2013 and 1 case in 2015. Finally the rate, where it was unknown if other substances were involved was 1 case in 2011. One country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 23 countries reported that pentedrone was under national control. The legislation the control is based upon included Medicines Act (3 countries), Controlled Substances Act (17 countries), Criminal Law Act (2 countries) and other specific legislation (2 countries stated that it was specific legislation for new psychoactive substances). In two countries the control is a temporary provision. There were no challenges to implementing controls for pentedrone reported.

The scope of the controls includes production (19 countries), manufacturing (20 countries), exporting (19 countries), importing (22 countries), distribution (22 countries), use (14 countries) and possession (20 countries).

Reported illicit activities involving pentedrone include production of consumer products (1 country), trafficking (13 countries), smuggling (1 country), internet sales from abroad (6 countries), internet sales from unknown locations (5 countries) and finally sales to people who use this substance (4 countries).

There were 18 countries which completed the section on the number of seizures. The combined number of seizures was 801 (2014), 697 (2015) and 104 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If pentedrone was placed under international control, 24 countries responded that they would have the capacity to enforce the control at the national level. There were 24 countries which responded that they would have the forensic laboratory capacity to analyse the substance.