World Health Organization

Critical Review Report:

alpha-PHP (α-Pyrrolidinohexanophenone) or PV-7

Expert Committee on Drug Dependence

Forty-second Meeting

Geneva, 21-25 October 2019

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Acknowledgements

This document was produced for the WHO Expert Committee on Drug Dependence (ECDD) under the overall direction of the WHO Secretariat led by Dr Gilles Forte (Division of Access to Medicines, Vaccines, and Pharmaceuticals). The document was written by Professor Rainer Spanagel under the technical direction of Dr Dilkushi Poovendran (Division of Access to Medicines, Vaccines, and Pharmaceuticals). The report was edited by Professor Kim Wolff. The member state questionnaire was produced under the technical direction of Ms Judith Sprunken (Division of Access to Medicines, Vaccines, and Pharmaceuticals).

The WHO Secretariat would also like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA), INCB, UNODC, and Member States for providing relevant information for the review of substances.

Executive Summary

Alpha-PHP, (α-Pyrrolidinohexanophenone), or PV-7 is a compound of the substituted cathinone and substituted pyrrolidine chemical classes. Its structure is comprised of hexanal bound to a phenyl ring at the 1 position and the nitrogen of a pyrrolidine ring at the 2 position. Alpha-PHP is thus a synthetic stimulant drug of the cathinone class and was already developed and patented in the 1960s. It has no therapeutic or medical use. In different regions alpha-PHP is being used and abused as a novel designer drug. In the United States, alpha-PHP is a Schedule I Controlled Substance, in the UK a Class B scheduled substance and is also a controlled substance in Italy, Sweden and China.

Pharmacokinetic analyses suggest a two-compartment model and a serum elimination half-life of 37 h. More than 20 metabolites have been reported – some of them also with a very long half-life. The long-lasting psychotic symptoms induced by alpha-PHP appear to be correlated with its pharmacokinetic characteristics, such as its long half-live.

Alpha-PHP is an uptake inhibitor at the DAT, SERT and NET, based on its ability to inhibit uptake and inability to induce release. The rank order of potency for inhibition of uptake is DAT > NET >> SERT.

In general, the intensity of the effects of this substance is comparable to strong stimulants such as methamphetamine (Crystal Meth), MDPV and alpha-PVP. Adverse effects associated with alpha-PHP use or abuse included vomiting, agitation, paranoia, hypertension, unconsciousness, tachycardia, seizures, cardiac arrest, rhabdomyolysis, or death. Paranoia and mild anxiety is felt even in small doses, not only in overdose.

The pharmacological data for alpha-PHP alone or combined with documented case reports, demonstrate that the potential for fatal and non-fatal overdoses exists; thus, these substances pose an imminent hazard to the public health and safety.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

13415-86-6
alpha-PHP HCl: 13415-59-3

PubChem CID 102107923
ChemSpider 52084419
UNII 297J9K8A4G

C. Other Chemical Names

(RS)-1-Phenyl-2-(pyrrolidin-1-yl)hexan-1-one
alpha-Pyrrolidinohexiophenone

α-PHP is a compound of the substituted cathinone and substituted pyrrolidine chemical classes. Its structure is comprised of hexanal bound to a phenyl ring at the 1 position and the nitrogen of a pyrrolidine ring at the 2 position.

α-PHP is the longer chain homolog of α-PVP, possessing an additional carbon on the alkyl side chain.

D. Trade Names

None

E. Street Names

None

F. Physical Appearance

Crystals and powder with bitter taste.

Alpha-PHP is usually in the form of transparent to whitish, sometimes yellowish crystals or in the form of a brownish, beige powder[1].

In seized material from the Silesia region of South Poland crumbled pale pink powder and lumped beige powder was described[1].

Since there are also clear to white crystals, it can be assumed that the brownish color of the powder is due either to synthetic impurities or to the fact that the brownish powder is the freebase and the crystals are the HCl salt. Against the latter thesis speaks that also the brownish powder according to some consumers who tested it acts nasally, and in similar dosages as the transparent crystals. If it were a freebase, it would be difficult to consume nasal.

G. WHO Review History

Alpha-PHP has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that alpha-PHP is manufactured by several chemical companies and other sources, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

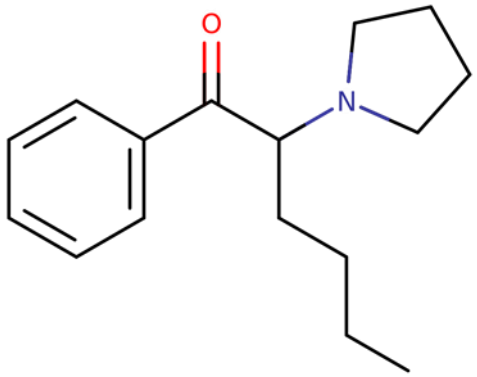
2. Chemistry

A. Chemical Name

IUPAC Name: (RS)-1-Phenyl-2-(pyrrolidin-1-yl)hexan-1-one
CA Index Name: 1-Phenyl-2-(1-pyrrolidinyl)-1-hexanone

B. Chemical Structure

Free base: Chemical
Molecular Formula: $C_{16}H_{23}NO$
Molecular Weight: 245.36 g/mol



C. Stereoisomers

-

D. *Methods and Ease of Illicit Manufacturing*

The synthesis of alpha-PHP was first described in a US patent that was granted in 1967 (Publication of US3314970A). The patent expired in 1984.

Alpha-PHP is an analog of the cathinone α-pyrrolidinopropiophenone wherein the side chain is elongated by the addition of three methylene groups.

E. Chemical Properties

Melting point 108.90 °C

Boiling point 339.06 °C

Solubility: water solubility at 25 °C (mg/L): 39.83. Please note: Internet-based information from consumers report that 50 mg can be easily dissolved in 100 mL of water.

F. Identification and Analysis

Liquid chromatography-tandem mass spectrometry (LC-MS) has been used to detect *alpha*-PHP.

Detection has been described in serum, whole blood and urine.

Multiple analytical analysis has been reported by Majchrzak et al.[1]. They have used high-performance liquid chromatography–mass spectrometry (HPLC–MS) and high-performance liquid chromatography–diode array detection (HPLC–DAD), ion trap mass spectrometry with electrospray ionization (ESI) in the MS2 and MS3 modes, gas chromatography–mass spectrometry (GC–MS), hermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, ultraviolet-visible (UV-VIS) spectroscopy and proton and carbon nuclear magnetic resonance spectroscopy (1H NMR and 13C NMR) to detect alpha-PHP.

3. Ease of Convertibility Into Controlled Substances

Alpha-PHP is not readily converted into other internationally controlled substances.

Legal status of alpha-PHP:

UK: Class B
US: Schedule I
Illegal in China, Sweden, Poland, and Italy

4. General Pharmacology

Alpha-PHP is a first synthesized upper in the 1960s that belongs to the cathinones and is very closely related to alpha-PVP and pyrovalerone.

In addition to being a member of the cathinones, a-PHP also belongs to the pyrovalerones.

A. Routes of administration and dosage

Oral, intranasal, vaporization, intravenous, rectal, sublingual, subcutaneous (see https://en.wikipedia.org/wiki/Alpha-Pyrrolidinohexiophenone).

It is common to consume alpha-PHP nasally, orally or sublingually. Most consumers consider nasal consumption to be less well-suited than sublingual consumption, as the sublingual effect is even faster and requires the same dosages as nasal. Sublingual consumption, however, harms the oral mucosa and teeth whereas the nasal consumption is very painful and seems to damage the nasal mucosa extremely. Thus, some consumers report that daily nasal consumption, even at lower doses, can lead to nasal and nasal septum damage in just a few days.

Information on dosage is based on reports from consumers provided by different internet-based fora. Since this substance is extremely potent, consumers suggest to take a maximum of 5-10mg oral, nasal, sublingual & rectal maximal 4-7mg and a maximum of 2-4mg for inhalation or intravenous application. Dose ranges and efficacy are provided by the forum http://neuepsychoaktivesubstanzen.de/a-php/ :

Oral application:
First effects from: 3-5mg
Light effect: 5-15mg
Normal: 10-25mg
Strong effect: 25-40mg
Very strong effect: 40mg +

Nasal / sublingual / rectal:
First effects from: 2-4mg
Light effect: 4-10mg
Normal: 10-20mg
Strong effect: 20-35mg
Very strong effect: 35mg +

Intravenous / inhaled:
First effects from: 1-2mg
Light effect: 3-6mgmissing
Normal: 6-15mg
Strong effect: 15-25mg
Very strong effect: 25mg +

Accordingly to the route of administration following effect duration is reported (http://neuepsychoaktivesubstanzen.de/a-php/):

Oral application:
Effect starts after: 15-45 minutes
Main effect: 4-6 hours
Of which peak ("Flash"): 1-2 hours
Afterglow: 4-10 hours

Nasal / sublingual:
Effect starts after: 5-15 minutes
Main effect: 2-4 hours
Of which peak ("Flash"): 1-2 hours
Afterglow: 4-10 hours

Intravenous / inhaled:
Effect starts after: a few seconds to a few minutes
Main effect: 30-90 minutes
Of which peak ("Flash"): 1-2 minutes
Afterglow: 2-5 hours

B. Pharmacokinetics

Paul et al.[2] reported on the detection of α-PHP and its phase I and II metabolites in a human urine sample of a drug abuser. Determination and structural elucidation of these metabolites were achieved by liquid chromatography electrospray ionisation quadrupole time-of-flight mass spectrometry (LC-ESI-QTOF-MS). In this report the exact and approximate structures of 19 phase I metabolites and nine phase II glucuronides were described. Major metabolic pathways revealed the reduction of the ß-keto moieties to their corresponding alcohols, didesalkylation of the pyrrolidine ring, hydroxylation and oxidation of the aliphatic side chain leading to n-hydroxy, aldehyde and carboxylate metabolites, and oxidation of the pyrrolidine ring to its lactam followed by ring cleavage and additional hydroxylation, reduction and oxidation steps and combinations thereof. The most abundant phase II metabolites were glucuronidated ß-keto-reduced alcohols. Besides the great number of metabolites detected in this sample, α-PHP was still one of the most abundant ions together with its ß-keto-reduced alcoholic dihydro metabolite. Monitoring of these metabolites in clinical and forensic toxicology may unambiguously prove the abuse of alpha-PHP.

In a recent case report[3] from Japan toxicological analysis was performed in a heavy alpha-PHP abuser using liquid chromatography-tandem mass spectrometry with a solid phase extraction method (QuEChERS). In this male patient alpha-PHP was detected in serum at a concentration of 175 ng/mL. His serum concentrations of alpha-PHP were serially determined and their natural logarithms were plotted against time after admission to the emergency room. Although serum concentrations at early time points (<24h) were lacking, the obtained curve was consistent with a two-compartment model and indicated a serum

elimination half-life of 37 h. The long-lasting psychotic symptoms induced by alpha-PHP appear to be correlated with its toxicokinetic characteristics, such as its long half-live.

Vignali et al.[4] report the analysis of alpha-PHP in blood, urine, gastric contents, main tissues and hair of a deceased person. Qualitative and quantitative analyses were performed by LC-MS-MS. All the biological samples were collected during autopsy and extracted/purified onto a solid phase extraction cartridge before instrumental analysis. The method was validated for blood and urine and proved to be highly sensitive (limit of quantification: 0.5 ng/mL). Hair analysis proved that the man was a heavy alpha-PHP user. Bile and urine concentrations (1.2 and 5.6 ng/mL, respectively) were fairly lower than blood collected into the thoracic cavity (15.3 ng/mL). The highest concentrations were measured for lung (71.1 ng/mL) and spleen (83.8 ng/mL). Concentrations of 3.5, 7.9, 4.7 and 23.6 ng/mL were measured in liver, kidney, brain and heart, respectively.

A time course study in mice[5] shows that alpha-PHP resulted in time- and dose-dependent stimulation of locomotor activity following 10 and 25 mg/kg. Stimulant effects of 10 mg/kg occurred within 10 minutes following injection and lasted 100 minutes. Based on the 30-minute time period in which maximal stimulant effects occurred (10 to 30 minutes following injection), an ED_{50} of 2.29 mg/kg was calculated. The maximal stimulant effect of alpha-PHP was 97% of the maximal stimulant effect of (+)-methamphetamine and 87% that of cocaine.

C. Pharmacodynamics

Information on binding and functional activity at monoaminergic transporters has been provided by the Drug Enforcement Administration (DEA)[6]. Using radioligand binding and functional assays, alpha-PHP was tested at the dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters. Results from these assays show that alpha-PHP is an uptake inhibitor at the DAT, SERT and NET, based on its ability to inhibit uptake and inability to induce release. The rank order of potency for inhibition of uptake is DAT > NET >> SERT.

In radioligand binding assays[6], alpha-PHP has high affinity for the DAT, low affinity for the NET, and very low affinity for the SERT. In functional uptake assays with transporter cell lines, alpha-PHP is an uptake blocker with moderate potency at the DAT and NET and very low potency at the SERT. In functional release assays with transporter cell lines, alpha-PHP does not induce release of preloaded [^{3}H]neurotransmitter via the DAT, SERT or NET.

In particular, alpha-PHP has high affinity (7.8 nM) and moderate potency (16.1 nM) at the DAT and is probably not a substrate for the DAT, since it had minimal releasing efficacy. alpha-PHP has very low affinity (33,000 nM) and very low potency (40,000 nM) at the SERT and is probably not a substrate for the SERT, since it has minimal releasing efficacy. Alpha-PHP has low affinity (352 nM) and moderate potency (40 nM) at the NET and is probably not a substrate for the NET, since it has minimal releasing efficacy[6].

In a further study alpha-PHP was compared to other substituted cathinone's and structure-activity relationships of those compounds with transporter binding, uptake, and release was reported[7]. Their analysis on inhibition of [^{125}I] RTI-55 binding to, and [^{3}H] neurotransmitter uptake by hDAT, hSERT, or hNET in clonal cells retrieved following results (Table 1):

	Inhibition of [^{125}I]RTI-55 Binding K_i ± S.E.M. (*n*)			**Inhibition of [^{3}H]Neurotransmitter Uptake IC_{50} ± S.E.M. (*n*)**		
Drug	**hDAT**	**hSERT**	**hNET**	**hDAT [^{3}H]DA**	**hSERT [^{3}H]5-HT**	**hNET [^{3}H]NE**
	μM	*μM*	*μM*	*μM*	*μM*	*μM*
α-PHP	0.0160 ± 0.0044 (8)	33 ± 12 (5)	0.339 ± 0.037 (9)	0.0216 ± 0.0035 (6)	40 ± 11 (3)	0.0363 ± 0.0077 (7)

Table 1. Shows affinity and potency of alpha-PHP at hDAT, hSERT, and hNET. Data are normalized to specific binding or specific uptake in the absence of the drug. n, number of independent experiments conducted in duplicate[6] .

5. Toxicology

There are currently no published safety data available concerning the toxicity, reproductive impact and carcinogenic / mutagenic potential of alpha-PHP.

6. Adverse Reactions in Humans

Available evidence on the overall public health risks associated with the use of alpha-PHP can cause acute health problems leading to emergency department admissions, violent behaviours causing harm to self or others, or death. Acute adverse effects of synthetic cathinone substances including alpha-PHP are those typical of sympathomimetic agents (e.g., cocaine, methamphetamine, amphetamine) and include among other effects tachycardia, headache, palpitations, agitation, anxiety, mydriasis, tremor, fever or sweating, and hypertension. Other effects, with possible public health risk implications, include psychological effects such as psychosis, paranoia, hallucinations, and agitation. In particular, adverse effects associated with alpha-PHP abuse included vomiting, agitation, paranoia, hypertension, unconsciousness, tachycardia, seizures, cardiac arrest, rhabdomyolysis, or death (see section on Acute intoxications and Deaths).

The pharmacological data for alpha-PHP alone or combined with documented case reports[2,3,8-13], demonstrate that the potential for fatal and non-fatal overdoses exists; thus, these substances pose an imminent hazard to the public health and safety.

As found with other synthetic cathinone substances, products containing synthetic cathinone's often do not bear labeling information regarding the ingredients or the health risks and potential hazards associated with these products. The limited knowledge about product content and its purity, as well as lack of information about its effects, pose additional risks for significant adverse health effects to the users.

In the following, a summary of effects and side-effects provided by several internet-based consumer websites is listed (please note that the effects and side effects listed are all very subjective and may be perceived differently by each person; i.e., they may not always occur and there may be other, unmentioned effects).

- Stimulation (stimulating, awakening) - alpha-PHP is one of the very strong stimulating pyrovalerones
- Strongly appetite –reducing effect (stronger than many other stimulants)
- Increased concentration and performance – However, due to the highly confusing, euphoric, stimulating or anxiety-enhancing and other side effects, alpha-PHP is not suitable as a cognitive enhancer or performance enhancer, even if a certain increase in concentration and performance is felt
- Aphrodisiac - increase sexual desire and delay orgasm
- Euphoric - The euphoria occurs above all after the onset of action, then decreases slowly after a short time and leaves the consumer with the feeling of wanting more; i.e., craving
- Improvement of the music sense

In general, the intensity of the effects of this substance is comparable to strong stimulants such as methamphetamine (Crystal Meth), MDPV and α-PVP.

Side effects include:

- Strong abuse potential - similar to methamphetamine / MDPV / and pentedron
- Dehydration
- Increased blood pressure, tachycardia - Increased heart rate is a very common side effect of alpha-PHP, which according to some consumers is stronger than other pyrovalerones.
- Suppression of physiological functions (e.g., urinary urgency, hunger and thirst)
- Hangover including depressed mood, irritability, headache, and insomnia
- Nausea
- Compulsive behaviour Can lead to automatic refilling without the consumer worrying about risks!
- Pronounced paranoia, anxiety states & psychotic phases ("drug psychosis") possible, especially in overdose - alpha-PHP is considered a very strong anxiety and paranoia-producing substance with quite strong psychotic component.
- Hallucinations - Possible with overdose, overuse or onset of a psychotic phase. In very high doses (usually combined with several days of sleep deprivation consumer

hallucinates shadows and cannot at first not be distinguished from a true shadow which leads to violent paranoia (a prominent example is provided in http://nymag.com/intelligencer/2016/09/the-obscure-legal-drug-that-fuels-john-mcafee.html about the anti-virus software pioneer John McAfee who underwent a dramatic personality shift.

Acute intoxications and deaths

INCB and UNODC report that 9 incidents with alpha-PHP have been communicated through the International Narcotics Control Board (ION Incident Communication System - IONICS. Two incidents took place in 2015, 2 in 2016, 3 in 2017 and 1 in 2018. All the incidents were reported from countries in West and Central Europe. United Kingdom reported 5 incidents, Estonia 2 incidents, Netherlands 1 incident and Spain 1 incident. Netherlands was identified in 4 incidents, China in 3 incidents, Spain in 1 incident. The origin was unknown in 1 incident. While it is not clear from IONICS if the substance is prevalent, it appears to be relatively persistent in the market as incidents involving it continued to be reported from 2015 to 2018.

The UNODC Early Warning Advisory Tox. Portal lists 12 cases with alpha-PHP:

1. France 2019: 45-64 male, clinical admission, only alpha-PHP, route of administration: iv, matrix: blood by LC/MS/MS; Relative/Probable Contribution: causal (high)

2. France 2018: 25-44 male, clinical admission, alpha-PHP and 4-Methyl-α-pyrrolidinohexiophenone, route of administration: unkown, matrix: blood and urine by LC/MS/MS; Relative/Probable Contribution: contributory (medium)
3. France 2018: 25-44 female, clinical admission, alpha-PHP and 4-Methyl-α-pyrrolidinohexiophenone, route of administration: unkown, matrix: blood and urine by LC/MS/MS; Relative/Probable Contribution: contributory (medium)

4. France 2017: 25-44 male, post-mortem, U-47700 and alpha-PHP, route of administration: iv, matrix: blood by LC/MS/MS 3040µg/L and 41,7µg/L, respectively; Relative/Probable Contribution: causal (high) for U-47700 and present but non-contributory (low) for alpha-PHP
5. France 2017: 15-24 male, post-mortem, U-47700 and alpha-PHP, route of administration: iv, matrix: blood by LC/MS/MS 3040µg/L and 41,7µg/L, respectively; Relative/Probable Contribution: causal (high) for U-47700 and present but non-contributory (low) for alpha-PHP
6. France 2016: 25-44 male, clinical admission, only alpha-PHP, route of administration: inhalation, matrix: blood by LC/MS/MS 313µg/L; Relative/Probable Contribution: causal (high)
7. Finland 2018: 25-44 female, post-mortem, only alpha-PHP, route of administration: unknown, matrix: urine by LC/MS/MS positive; Relative/Probable Contribution: -
8. Finland 2018: 25-44 male, post-mortem, only alpha-PHP, route of administration: unknown, matrix: urine by LC/MS/MS 20µg/L; Relative/Probable Contribution: -

9. Finland 2018: 45-64 male, post-mortem, only alpha-PHP, route of administration: unknown, matrix: urine by LC/MS/MS 320µg/L; Relative/Probable Contribution: -
10. Finland 2018: 25-44 male, post-mortem, only alpha-PHP, route of administration: unknown, matrix: urine by LC/MS/MS positive; Relative/Probable Contribution: -
11. Finland 2018: 25-44 male, post-mortem, only alpha-PHP, route of administration: unknown, matrix: urine by LC/MS/MS 580µg/L; Relative/Probable Contribution: -
12. Russia 2016: 25-44 male, clinical admission, alpha-PHP and phenobarbital, route of administration: iv and per os, respectively, matrix: blood by GC/MS; Relative/Probable Contribution: causal (high)

Case reports have been reported from different countries. From Germany a report of a positive urine for alpha-PHP in a drug abuser[2], in Slovenia a suicide attempt from a 38-year-old male was reported who had ingested a mix of cathinones including alpha-PHP[8], in Sweden 45 cases of intoxication with alpha-PHP are described in the STRIDA project[9], in Japan chronic abuse and acute intoxication with psychotic symptoms, such as hallucinations and delusion was described in a 39 years old male patient[3] and 13 positive urine samples were detected in cathinone's users[10]; in Italy alpha-PHP was found in post-mortem tissue in two chronic user[4, 11].

In Poland, a 21-year-old woman in the 36th week of pregnancy presented with psychomotor agitation. Fetal demise was demonstrated and a caesarean delivery performed. 3,4-MDPHP and alpha-PHP were detected and quantified in both the fetus' and the mothers blood, as well as in the mothers urine samples. The determined concentrations of 3,4-MDPHP and α-PHP were, 76 ng/mL and 12 ng/mL in the fetal blood sample, 16 ng/mL and traces in the mothers blood, and 697 mg/mL and 136 ng/mL in the mothers urine, respectively. The presented case demonstrates that alpha-PHP transfers from maternal blood to fetal blood. Blood concentrations of these compounds were higher in the fetus than in the mother. Based on the known effects of these substances and the patient's presentation and clinical course, it would seem that these substances contributed to the fetal death[12].

Since 2014, alpha-PHP has been identified in the United States' illicit drug market and seizures, intoxications and deaths have been reported in 395 cases in more than 20 States. Since May 2019 alpha-PHP is a Schedule I Controlled Substance[13].

7. Dependence Potential

A. Animal Studies

No information available

B. Human Studies

No information available

8. Abuse Potential

A. Animal Studies

Alpha-PHP was tested for its ability to substitute for the discriminative stimulus effects of cocaine (10 mg/kg) in rats. Alpha-PHP substituted fully (ED_{50}= 2.86 mg/kg) for the discriminative stimulus effects produced by 10 mg/kg of cocaine. Response rate failed to show significant change from vehicle control following 0.5 to 5 mg/kg alpha-PHP[14].

Alpha-PHP was tested for its ability to substitute for the discriminative stimulus effects of (+)-methamphetamine (1 mg/kg) in rats. For this purpose 6 male Sprague-Dawley rats were trained to discriminate (+)-methamphetamine (1mg/kg) from saline using a two-lever choice methodology. Alpha-PHP substituted fully (ED_{50}= 1.23 mg/kg) for the discriminative stimulus effects produced by 1 mg/kg of (+)-methamphetamine. Response rate failed to show significant change from vehicle control within the dose range of 0.25 to 5 mg/kg alpha-PHP[15].

Intravenous self-administration experiments were carried out in female rats. Female Wistar rats were prepared with intravenous catheters and trained to self-administer α-PVP (N=8; 0.05 mg/kg per infusion) using a fixed-ratio 1 (FR1) response contingency. Following acquisition of self-administration, animals were subjected to dose substitution with alpha-PHP[16]. A monotonic descending limb was observed for alpha-PHP. Increased infusions of α-PHP were obtained, compared with α-PVP, at the 0.025 and 0.05 mg/kg/inf doses. This is consistent with higher potency as reinforcer compared to pentylone, pentedrone and methylone. The addition of the 0.0125 mg/kg dose in the follow-up study further confirmed this potency shift, but more importantly it confirmed that efficacy of alpha-PHP is as high as, or higher than, the other cathinones since peak responding was observed when a 0.0125 mg/kg/infusion dose was available.

In summary, the drug discrimination experiments and substitution experiments in an intravenous self-administration procedure suggests a strong abuse liability of alpha-PHP.

B. Human Studies

No data available; however, several case reports from the emergency room as well as the similarity to other cathinones (with known abuse potential) suggest that alpha-PHP has a pronounced abuse potential as it produces strong craving reactions and repeated relapses.

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

Alpha-PHP has not been used therapeutically.

10. Listing on the WHO Model List of Essential Medicines

Alpha-PHP is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)

Alpha-PHP has never been marketed as a medicinal product.

12. Industrial Use

Alpha-PHP has no industrial use.

13. Non-Medical Use, Abuse and Dependence

See under 6. Adverse reactions.

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

See under 6. Adverse reactions

15. Licit Production, Consumption and International Trade

Not applicable.

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

16. Illicit Manufacture and Traffic and Related Information

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

17. Current International Controls and Their Impact

Alpha-PHP is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Controlled in UK (Class B), US (Schedule I), illegal in China, Sweden, Poland, and Italy.

Please refer 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 data.

References

1. Majchrzak M, Rojkiewicz M, Celiński R, Kuś P, Sajewicz M (2016) Identification and characterization of new designer drug 4-fluoro-PV9 and α-PHP in the seized materials. Forensic Toxicol. 34:115-124
2. Paul M, Bleicher S, Guber S, Ippisch J, Polettini A, Schultis W (2015) Identification of phase I and II metabolites of the new designer drug α-pyrrolidinohexiophenone (α-PHP) in human urine by liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS). J Mass Spectrom. 50(11):1305-17. doi: 10.1002/jms.3642. Erratum in: J Mass Spectrom. 51(4):322.
3. Fujita Y, Mita T, Usui K, Kamijo Y, Kikuchi S, Onodera M, Fujino Y, Inoue Y (2018) Toxicokinetics of the Synthetic Cathinone α-Pyrrolidinohexanophenone. J Anal Toxicol. 42(1):e1-e5. doi: 10.1093/jat/bkx080.
4. Vignali C, Moretti M, Groppi A, Osculati AMM, Tajana L, Morini L (2019) Distribution of the Synthetic Cathinone α-Pyrrolidinohexiophenone in Biological Specimens. J Anal Toxicol. 43(1):e1-e6. doi: 10.1093/jat/bky047.
5. Sumien N, Flores E, Forster MJ (2015) Time-course (8-h) mouse locomotor activity test vs (+)-methamphetamine, and cocaine time course. N01DA-13-8908 (HHSN271201300001)
6. Janowsky A (2015) DEA-VA Interagency Agreement Title: "In Vitro Receptor and Transporter Assays for Abuse Liability Testing for the DEA by the VA"
7. Eshleman AJ, Wolfrum KM, Reed JF, Kim SO, Swanson T, Johnson RA, Janowsky A (2017) Structure-Activity Relationships of Substituted Cathinones, with Transporter Binding, Uptake, and Release. J Pharmacol Exp Ther. 360(1):33-47.
8. Klavž J, Gorenjak M, Marinšek M (2016) Suicide attempt with a mix of synthetic cannabinoids and synthetic cathinones: Case report of non-fatal intoxication with AB-CHMINACA, AB-FUBINACA, alpha-PHP, alpha-PVP and 4-CMC. Forensic Sci Int. 265:121-4. doi: 10.1016/j.forsciint.2016.01.018.
9. Beck O, Bäckberg M, Signell P, Helander A (2018) Intoxications in the STRIDA project involving a panorama of psychostimulant pyrovalerone derivatives, MDPV copycats. Clin Toxicol (Phila) ;56(4):256-263. doi: 10.1080/15563650.2017.1370097.
10. Matsuta S, Shima N, Kakehashi H, Kamata H, Nakano S, Sasaki K, Kamata T, Nishioka H, Miki A, Zaitsu K, Tsuchihashi H, Katagi M (2018) Metabolism of α-PHP and α-PHPP in humans and the effects of alkyl chain lengths on the metabolism of α-pyrrolidinophenone-type designer drugs. Forensic Toxicol. 36(2):486-497. doi: 10.1007/s11419-018-0428-7.
11. Freni F, Bianco S, Vignali C, Groppi A, Moretti M, Osculati AMM, Morini L (2019) A multi-analyte LC-MS/MS method for screening and quantification of 16 synthetic cathinones in hair: Application to postmortem cases. Forensic Sci Int 298:115-120. doi: 10.1016/j.forsciint.2019.02.036.
12. Adamowicz P, Hydzik P (2019) Fetal death associated with the use of 3,4-MDPHP and α-PHP. Clin Toxicol (Phila) 57(2):112-116. doi: 10.1080/15563650.2018.1502443.
13. "Schedules of Controlled Substances: Temporary Placement of N-Ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-Chloro-α-PVP in Schedule I". Drug Enforcement Administration. [Federal Register Volume 84, Number 84 (Wednesday, May 1, 2019)]
14. Forster MJ, Gatch MB, West A (2016) Test of substitution for the discriminative stimulus effects of cocaine. N01DA-13-8908 (HHSN271201300001)

15. Forster MJ, Gatch MB, Dolan SB (2016) Test of substitution for the discriminative stimulus effects of (+)-methamphetamine. N01DA-13-8908 (HHSN271201300001)
16. Javadi-Paydar M, Nguyen JD, Vandewater SA, Dickerson TJ, Taffe MA. (2018) Locomotor and reinforcing effects of pentedrone, pentylone and methylone in rats. Neuropharmacology 134(Pt A):57-64. doi: 10.1016/j.neuropharm.2017.09.002.

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances