



Critical review report:
 α -Pyrrolidinoisohexanophenone
(α -PiHP)

Expert Committee on Drug Dependence

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Executive summary

α -Pyrrolidinoisohexanophenone (α -PiHP) (IUPAC name: 4-methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one) is a synthetic cathinone. It is a positional isomer of pyrovalerone (Schedule IV, United Nations Convention on Psychotropic Substances, 1971 (1)) and 1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one (α -PHP) (Schedule II, United Nations Convention on Psychotropic Substances, 1971 (1)). A number of α -pyrrolidino-based cathinones have originated from pharmaceutical research; the emergence of α -PiHP was first reported in 2016. α -PiHP is most likely to appear on the streets in the form of a racemate.

No specific information was available about the routes used to synthesize the α -PiHP products circulating on the drug market, but there are straightforward methods for its preparation that do not require access to internationally controlled precursors. α -PiHP cannot be converted into any other substance currently listed in the United Nations Conventions of 1961, 1971 and 1988 (1). As α -PiHP is a positional isomer of α -PHP, it might be difficult to analyse in routine casework.

α -PiHP has not previously been pre- or critically reviewed by WHO.

No clinical studies on α -PiHP were found, and information from Internet discussion forums appears to be limited. The available information indicates that α -PiHP can be administered by oral, intravenous or rectal routes, by nasal insufflation or by inhalation (vaping). Inhalation after heating of foil has also been described. Information from Internet forums shows that α -PiHP has psychostimulant effects, the duration depending on the route of administration. Assessment of such reports is difficult, not least because people who use the substances described might not have confirmed the actual substance or the amount used.

Few systematic studies are available; however, in-vitro studies suggest that α -PiHP can inhibit the uptake of dopamine and norepinephrine, with significantly higher potency than cocaine, methamphetamine and methcathinone. It is not known whether α -PiHP can also function as a substrate-type releaser, but this is unlikely in view of reports on structurally related α -pyrrolidinovalerophenone-type compounds. In terms of potency, the drug's ability to inhibit uptake of serotonin appears to be negligible, which indicates that α -PiHP is catecholamine-selective.

No studies of the preclinical acute or chronic toxicology of α -PiHP were found.

Detection of α -PiHP in biological fluids collected from cases of adverse effects (including deaths) confirms that the drug is circulating on the market and is used recreationally. The overall number of cases in which a causal relation could be unambiguously established between α -PiHP ingestion and adverse effects (including death) appears to be relatively low.

The United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory Tox-Portal lists seven cases in Sweden in which α -PiHP was detected in either blood or urine samples. More detailed information (e.g., clinical admission or post-mortem case) was not available. Between 2017 and 2019, one country in the European Union Early Warning System Network reported four deaths to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in which exposure to α -PiHP was analytically confirmed from a biological sample. In addition, between 2017 and 2021, four countries reported, in aggregated reporting, detection of α -PiHP in biological samples that were linked to serious adverse events, including 20 samples associated with deaths and 4 associated with acute poisoning. The EMCDDA pointed out, however, that some serious adverse events reported in aggregated datasets may overlap.

The US Centers for Disease Control and Prevention's State Unintentional Drug Overdose Reporting System contains 18 cases in which α -PiHP is listed as the cause of death, although no further information was available.

In Finland, α -PiHP was detected in seven post-mortem cases between May 2021 and June 2022. In those cases in which information was available, the involvement of other substances was noted.

In a series of trend reports generated by the US Center for Forensic Science Research and Education, α -PiHP or α -PHP (isomers not differentiated) was detected during toxicological analysis in 43 cases between the first quarter of 2018 and the second quarter of 2022.

Two fatal and one non-fatal intoxications associated with α -PiHP were reported in the scientific literature. The fatalities were attributed to α -PiHP alone. Other substances were detected in one of the fatal cases.

No information on potential dependence on α -PiHP was identified.

The results of studies of locomotor activity suggest that α -PiHP is a psychomotor stimulant. The maximal stimulant effects were comparable to those found with cocaine and methamphetamine, and drug discrimination studies confirmed that α -PiHP substituted for the discriminative stimulus effect produced by cocaine and (*S*)-methamphetamine.

According to the EMCDDA, α -PiHP has been available on the drug market in Europe since at least 2016. As of 15 June 2022, a total of 18 European Union Member States and Norway had reported physical detection of α -PiHP to the EMCDDA. At the time of writing, the total number of seizures was 1565, with a total quantity of 750.5 kg (all physical forms). The total quantity of powder seized was 748.4 kg. Since it was formally notified, the EMCDDA have received reports of 1565 seizures of α -PiHP, usually as a powder (approximately 88% of all cases reported), although herbal material was occasionally reported (12% of cases). Overall, approximately 750 kg of α -PiHP have been seized, of which 748 kg were in powder form and 2 kg in herbal material. Most powder was seized in 2018 (250 kg in approximately 275 seizures) and in 2022 (300 kg in a single seizure that originated from India).

Globally, the numbers of countries that reported detection of α -PiHP to the UNODC Early Warning Advisory on new psychoactive substances database since its first detection in 2016 were: 3 in 2016, 11 in 2017, 10 in 2018, 19 in 2019, 17 in 2020, 8 in 2021 and 2 so far in 2022.

The US National Forensic Laboratory Information System (NFLIS) began to list detections of α -PiHP in their drug reports in 2019. According to the US Office of National Drug Control Policy, 316 α -PiHP reports were identified in the NFLIS drug system in 2021 (queried on 28 April 2022). The total reported weight of 222 of these encounters was 2.179 kg.

No epidemiological evidence was found on use of α -PiHP. α -PiHP is available and is advertised for sale by some Internet retailers. Current information suggests that α -PiHP is likely to have abuse liability and that it has psychostimulant properties comparable to those of some other synthetic cathinones under international control, such as α -PHP and α -pyrrolidinovalerophenone (α -PVP).

Information from drug testing services in the USA suggests the presence of α -PiHP in products acquired or sold as other substances, including a number of cathinones (including α -PVP), 3,4-methylenedioxy methamphetamine and 1-(1-benzofuran-6-yl)propan-2-amine. This suggests that people who use certain recreational drugs might be exposed unintentionally to α -PiHP, either alone or in combination with other substances, which might add risks of harm (e.g., potential exacerbation of a psychostimulant toxidrome).

1. Substance identification

A. International nonproprietary name

No information was found.

B. Chemical Abstracts Service registry number

2181620-71-1 (base)
2363169-94-0 (*R*)-enantiomer
2415172-12-0 (*S*)-enantiomer
2705245-60-7 (HCl)

C. Other chemical names

α -Pyrrolidinoisohexanophenone
 α -Pyrrolidinoisohexaphenone
 α -Pyrrolidinoisohexiophenone
4-Methyl- α -PVP
 γ -Methyl- α -PVP
4-Methyl- α -pyrrolidinopentanophenone
4-Methyl- α -pyrrolidinopentiophenone
4-Methyl- α -pyrrolidinovalerophenone
4-Methyl-desmethylpyrovalerone
4-Methyl- β k-prolintane

D. Trade names

No information was found.

E. Street names

The chemical names listed above are also encountered as street names. Other code names include α -PiHP, α -PHiP, pihp, ahip and phip. In a notification received by the EMCDDA, one European Union Member State reported identification of α -PiHP with 1-(2*H*-1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)hexan-1-one in a branded product named "Insomnia". It should be noted that the composition of such branded products is likely to change over time.

F. Physical appearance

In its pure form, α -PiHP hydrochloride is expected to be odourless and white, like many other ring-substituted synthetic cathinones. It has been reported as an off-white solid or powder (2, 3), a white powder (4), a crystalline solid (5) and white powder in "rock" form (6).

G. WHO review history

α -PiHP has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

2. Chemistry

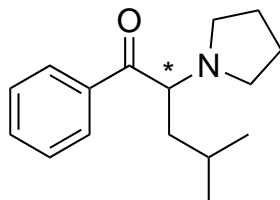
A. Chemical name

IUPAC name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one

Chemical Abstracts Service index name: 4-Methyl-1-phenyl-2-(1-pyrrolidinyl)-1-pentanone

B. Chemical structure

Free base:



Asterisk (*), a chiral centre

Molecular formula: C₁₆H₂₃NO

Molecular weight: 245.36 g/mol

C. Stereoisomers

The presence of a chiral centre at the α -carbon of the side chain gives rise to the enantiomeric pair (*S*)- α -PiHP and (*R*)- α -PiHP. α -PiHP is most likely to be available as the racemic mixture, although the appearance of individual stereoisomers cannot be excluded.

D. Methods and ease of illicit manufacture

No specific information was found on the routes used to synthesize α -PiHP products circulating on the market; however, the chemical production of synthetic cathinones is well established and straightforward. No currently controlled precursors are required. Although there are several methods, one of the most common is based on so-called α -bromination of a ketone intermediate followed by amination. These types of reactions are easy to perform and lend themselves to both small- and large-scale manufacture. An example of an α -PiHP synthesis has been reported (3). Although α -PiHP was not specifically mentioned, it was also included in a patent application on a range of synthetic cathinones, including pyrovalerone-based (i.e., α -pyrrolidino-type) compounds. The chemical method used was essentially similar (7).

E. Chemical properties

Melting-point

No information was found on certified reference material; however, the melting-point of seized material identified as α -PiHP has been reported as 76 °C (8).

Boiling-point

No information was found.

Solubility

α -PiHP hydrochloride was reported to be soluble in dimethylformamide (3 mg/mL), dimethyl sulfoxide (5 mg/mL), ethanol (3 mg/mL), methanol (1 mg/mL) and phosphate-

buffered saline (pH 7.2; 10 mg/mL) (9). A sample of α -PiHP hydrochloride was reported to be soluble in dichloromethane, methanol and water (2).

F. Identification and analysis

Identification of α -PHP, especially when it is available in larger quantities than are usually available for forensic toxicology, is straightforward. Analytical difficulties may arise, for example in the presence of closely related isomers such as α -PHP, listed in Schedule II of the United Nation Convention on Psychotropic Substances of 1971 (1) or pyrovalerone (1-(4-methylphenyl)-2-(pyrrolidin-1-yl)pentan-1-one) listed in Schedule IV of the United Nations Convention on Psychotropic Substances of 1971 (1)). Adequate separation techniques are required to reduce potential misidentification, especially in samples (e.g., biological) containing only trace quantities. α -PiHP is, however, available as a certified reference material, and analytical data have been reported using various separation techniques and spectroscopic, crystallographic and mass spectrometric methods (8, 10–17). Analysis of biological samples requires sensitive methods, e.g., gas or liquid chromatography coupled to (tandem) mass spectrometry (high and low resolution). Some chromatographic, mass spectral and spectroscopic data are available in the public domain (2, 4, 18, 19). The results of presumptive colour tests as part of drug-checking services have also been reported publicly (20). In a non-fatal case of intoxication in which 4'-fluoroisobutyrylfentanyl and α -PiHP were identified, a false-positive result for amphetamine was noted, which was attributed to the presence of α -PiHP (21).

3. Ease of conversion into controlled substances

No specific information was found on a conversion of α -PiHP to substances under international control, but this is unlikely to be feasible.

4. General pharmacology

A. Routes of administration and dosage

No clinical studies on α -PiHP were identified, and information from Internet discussion forums appears to be limited. Current information indicates, however, that α -PiHP can be administered by oral, intravenous and rectal routes, nasal insufflation and inhalation (vaping). Inhalation from the heating of foil has also been described (22–25).

Some information on doses received after different routes of administration is in the public domain (Table 1). Reports by people believed to have taken α -PiHP suggest a tendency to re-dose, so that the doses taken may exceed those reported in Table 1 (22–24).

Table 1. Reported doses of α -PiHP by different routes of administration

Dose	Oral	Insufflated	Vaporized
Threshold	3–5 mg	1–3 mg	1–2 mg
Light	5–15 mg	3–10 mg	2–10 mg
Common	15–30 mg	10–25 mg	10–20 mg
Strong	30–50 mg	25–40 mg	20–30 mg

Source: reference 25

Assessment of such reports is difficult, not least because people who use these substances might be unable to confirm the actual substance or the amount used. Given the difficulties of collecting accurate self-reported data, these reports should be interpreted with caution.

B. Pharmacokinetics

No clinical studies were identified. Some estimates of the duration of effects are in the public domain (Table 2). Reports from some people believed to have consumed α -PiHP suggest that the duration varies among individuals, including shorter durations than those listed in Table 2 (24). Reports from Internet forums in languages other than English indicate that the effects of α -PiHP were of shorter duration than those of α -PVP (11).

Table 2. Reported duration of effects of α -PiHP

	Oral	Insufflated	Vaporized
Onset	30–60 min	1–2 min	1 min
Duration	2–5 h	2–4 h	1–3 h
After-effects	6–12 h	6–12 h	6–12 h

Source: reference 25

No information was found on the metabolism of α -PiHP; however, it is expected to be similar to that of closely related cathinones such as the isomeric α -PHP, in which metabolic transformations include reduction of the keto group, various oxidations and *N*-dealkylation (26–29).

C. Pharmacodynamics

The results of in-vitro assays involving binding to monoamine transporters and inhibition of uptake are summarized in Table 3. These show higher selectivity for the dopamine (DAT) and norepinephrine (NET) transporters than for the serotonin transporter (SERT) (30). The binding affinities determined for α -PiHP in HEK293 cells expressing human recombinant DAT and NET were 35.7 and 340 nM, respectively, whereas the binding affinity for SERT was > 7500 nM. Cocaine, methamphetamine and methcathinone were tested for comparison. At DAT, the binding affinity of α -PiHP was ~16 times higher than that of cocaine and ~115 and ~132 times higher than those of methamphetamine and methcathinone. Only cocaine showed some affinity below 1000 nM. α -PiHP also showed appreciable binding affinity to NET (K_i = 340; cocaine: K_i = 1600; methamphetamine: K_i = 2470; and methcathinone: K_i = 5800 nM).

Table 3. Binding and effects of α -PiHP on uptake in HEK-hDAT, HEK-hSERT and HEK-hNET cells

HEK-hDAT	α-PiHP	Cocaine	Methamphetamine	Methcathinone
[¹²⁵ I]RTI-55 binding; IC ₅₀ (nM)	36.5	–	–	–
[¹²⁵ I]RTI-55 binding; K _i (nM)	35.7	560	4100	4700
[³ H]DA uptake; IC ₅₀ (nM)	16.5	202	107	247
HEK-hSERT	α-PiHP	Cocaine	Methamphetamine	Methcathinone
[¹²⁵ I]RTI-55 binding; IC ₅₀ (nM)	> 7 700	–	–	–
[¹²⁵ I]RTI-55 binding; K _i (nM)	> 7 500	900	174 000	268 000
[³ H]5-HT uptake; IC ₅₀ (nM)	> 10 000	303	4 800	33 600
HEK-hNET	α-PiHP	Cocaine	Methamphetamine	Methcathinone
[¹²⁵ I]RTI-55 binding; IC ₅₀ (nM)	341	–	–	–
[¹²⁵ I]RTI-55 binding; K _i (nM)	340	1600	2470	5800
[³ H]NE uptake; IC ₅₀ (nM)	41.4	222	11.0	26.2

Modified from reference 30

DA, dopamine; 5-HT, serotonin; NE, norepinephrine

With radiolabelled neurotransmitters, α -PiHP was also found to function as a monoamine transporter blocker, with pronounced selectivity for DAT (IC₅₀ = 16.5 nM) and NET (IC₅₀ = 41.4 nM) as compared with SERT (IC₅₀ >10 000 nM). In comparison with cocaine (IC₅₀ = 202 nM), methamphetamine (IC₅₀ = 107 nM) and methcathinone (IC₅₀ = 247 nM), α -PiHP was the most potent DAT inhibitor under the conditions tested. At NET, α -PiHP was about five times more potent than cocaine but slightly less potent than methamphetamine and methcathinone (Table 3). From a mechanistic perspective, cocaine is a well-established transporter inhibitor, whereas methamphetamine and methcathinone are substrate-type releasers. In rat brain synaptosomes, the positional isomer α -PHP has been established as a monoamine transporter inhibitor, similar to other cathinones, with elongated α -carbon chain length (31). This is likely to extend to α -PiHP, but further studies should be conducted.

In reports from Internet forums in languages other than English, the effects of α -PiHP were reported to be predominantly mood improvement (euphoria) and gentle stimulation. The effects of α -PiHP were considered to be similar to those reported for α -PVP. Adverse effects of this cathinone were reported to include tachycardia, vasoconstriction and paranoia (11).

5. Toxicology

No acute or chronic preclinical toxicology studies with α -PiHP were found.

6. Adverse reactions in humans

Cases of α -PiHP intoxication in humans

The UNODC Early Warning Advisory Portal lists seven cases in Sweden in which α -PiHP was detected in either blood or urine samples. No details on the type of event (e.g., clinical admission or post-mortem) were available. The cases were reported between August and October 2019 and involved five men and two women aged 25–44 years (four cases) and 45–64 years (three cases) (32).

Between 2017 and 2019, one country in the European Union Early Warning System Network reported four deaths to the EMCDDA by event-based reporting, in which exposure to α -PiHP was

analytically confirmed in a biological sample. In addition, between 2017 and 2021, four countries reported by aggregated reporting the detection of α -PiHP in biological samples that were linked to serious adverse events, including 20 samples associated with deaths and 4 samples associated with acute poisoning. As more than one biological sample may have been taken during the same event, the actual number of events cannot be ascertained. Serious adverse events reported in aggregated datasets may overlap with the event-based events presented in the previous paragraph (33).

The WHO ECDD Secretariat received information from the US Centers for Disease Control and Prevention's State Unintentional Drug Overdose Reporting System via the US Office of National Drug Control Policy. The data were from death certificates, post-mortem toxicological testing and death scene and witness findings in medical examiner and coroner reports on unintentional drug overdose deaths and those of undetermined intent in 48 participating jurisdictions, providing comprehensive details about deaths due to drug overdose that are not available from other sources. According to the Reporting System, α -PiHP was listed as the cause of death in 18 cases between January 2020 and June 2021. During the same period, α -PiHP was detected in 13 fatal cases, but no information was available to determine whether the drug contributed to the deaths.

Information was received from the National Institute for Health and Welfare in Helsinki (Finland) that α -PiHP was detected in seven post-mortem cases between May 2021 and June 2022 (Table 4). The six men and one woman were aged 26–50 years (median, 34 years). For comparison during the same period, α -PHP was detected in 16 post-mortem cases and α -PVP in eight cases. Of the approximately 6500 post-mortem cases received per year, about 500 involved controlled substances or abuse of prescription drugs (Dr Pirkko Kriikku, National Institute for Health and Welfare, personal communication).

Table 4. Detection of α -PiHP post mortem by the National Institute for Health and Welfare in Helsinki (Finland)

Matrix	Concentration (mg/L)	Role of α -PiHP in the cause of death	Manner of death
Femoral blood	0.13	Fatal poisoning by methadone, alcohol, α -PiHP and propranolol	Undetermined
Femoral blood	< 0.02	Motorcycle accident	Accident
Urine	0.04	Use of specified drugs (including α -PiHP) as contributing cause of death	
Urine	0.04	Fatal poisoning by buprenorphine, methamphetamine, amphetamine, α -PiHP and gabapentin	Accident
Femoral blood	0.08	Use of buprenorphine, amphetamine, α -PiHP and cannabis	Disease*
Urine	0.5		
Urine	0.02	Fatal poisoning by α -PiHP, methadone, THC, amitriptyline, levomepromazine and olanzapine	Accident
Femoral blood	0.04	Information not yet available	Information not yet available
Urine	0.03		
Urine	0.03	Information not yet available	Information not yet available

Courtesy of Dr Pirkko Kriikku

* Possible mislabelling of poisoning as disease

A series of trend reports (34) is published by the Center for Forensic Science Research and Education (Pennsylvania, USA) that summarizes drug detections predominantly in biological

samples during toxicological case work. Table 5 summarizes detections published quarterly. No detailed information was available about the nature of the toxicological cases, and differentiation between α -PiHP and its isomer α -PHP was not reported, precluding the exact number of α -PiHP detections from being determined.

Table 5. Summary of positivity rates (trend reports) for new psychoactive stimulants, hallucinogens and some new psychoactive dissociatives submitted for analysis to the Center for Forensic Science Research and Education.

Year	Quarter	α -PiHP / α -PHP ^a		Total ^b
		No.	%	No.
2018	Q1	2	0	616
2018	Q2	8	1	1460
2018	Q3	1	0	739
2018	Q4	1	0	473
2019	Q1	0	0	148
2019	Q2	2	2	107
2019	Q3	0	0	264
2019	Q4	1	0	321
2020 ^c	Q1	4	1	384
2020	Q2	4	1	775
2020	Q3	5	1	626
2020	Q4	1	0	714
2021	Q1	0	0	454
2021	Q2	3	1	584
2021	Q3	1	0	851
2021	Q4	3	0	621
2022	Q1	4	1	710
2022	Q2	3	1	342

Courtesy of Dr Alex J. Krotulski (CFSRE, Fredric Rieders Family Foundation, Willow Grove, Pennsylvania, USA).

^a The specific isomer was not differentiated; samples were of biological origin.

^b The total number of substances included other substances, such as fentanyl, methamphetamine, cocaine and 3,4-methylenedioxymethamphetamine.

^c In Q1 2020, one additional detection of α -PiHP/ α -PHP was reported in a seized sample (35).

Scientific literature: non-fatal cases

In Poland, an unconscious 29-year-old man was found with symmetrical, highly constricted pupils unresponsive to light. The patient showed abnormal kidney function and was treated with naloxone (0.2 mg every hour for 15 h; total dose, 3 mg), omeprazole (40 mg, per os), acetaminophen (1 g, 100 mL, intravenous injection) and mannitol (15%, 100 mL, intravenous injection). Fluid replacement and oxygen therapy were administered. The patient was discharged after 4 days in hospital. The authors attributed an increased creatine phosphokinase level to rhabdomyolysis resulting from muscle tremors induced by α -PiHP intoxication. Analysis of peripheral blood revealed the synthetic opioid 4'-fluoro-isobutyrylfentanyl (87.7 ng/mL) and α -PiHP (5.0 ng/mL). In urine, concentrations of 2291.0 ng/mL and 722.2 ng/mL were detected. The authors suggested that the patient might have smoked a mixture of these two drugs (21).

Scientific literature: fatal cases

In the fatal case reported above (21), the authors also described the case of a young woman who was found dead. 4'-Fluoro-isobutyrylfentanyl was detected in various biological samples: 119.0 ng/mL in blood, 289.0 ng/mL in urine, 101.0 ng/mL in vitreous humour, 112.0 ng/g in brain tissue and 1540.0 ng/g in liver tissue. α -PiHP concentrations were included in the analysis and found to be as follows: 6.1 ng/mL in blood, 31.7 ng/mL in urine, 2.5 ng/mL in vitreous humour, 7.8 ng/g in brain tissue and 246.0 ng/mL in gastric contents. In addition, 4-chloromethcathinone, *O*-desmethyltramadol, *cis*-tramadol and *N*-desmethyltramadol were detected. No further information was provided (21). In a previous publication (36), however, more details were presented about the deceased woman. She was 22 years old, and the death occurred in September 2018. She was believed to have taken recreational drugs in the days preceding her death and analgesics after an accident and lower limb injuries. A white powder (57.8 mg) was found at the scene, and subsequent analysis revealed 4'-fluoro-isobutyrylfentanyl (40.25 mg) and α -PiHP (1.84 mg). The autopsy revealed cerebral tissue oedema, pulmonary emphysema and acute mucositis (36).

Another case in Poland involved an 18-year-old man who was found dead in an apartment (11). He had last been seen alive the previous evening, lying in bed. At night, he was heard to be wheezing. He had a history of regular substance use, including NPS. He was reported to have become agitated after use, hallucinating and talking to himself. When he calmed down, he lay down and slept for 24 h. He had also drunk alcohol (beer). Autopsy revealed no evident lesions considered to be related to his death, although small changes to the heart and blood vessels were found, comprising a little generalized cardiac hypertrophy and slight atherosclerosis of the coronary arteries and aorta. Visible coalworker's pneumoconiosis was found in the lungs, and focal cardiac adiposis was found on microscopic examination. In addition, macro- and microscopic evidence of acute circulatory and respiratory failure were disclosed, with pulmonary and cerebral oedema and congestion of internal organs. The autopsy did not determine the primary cause of death, and it was concluded that the man had died due to acute circulatory and respiratory failure. Toxicological analysis showed α -PiHP in various tissue samples (Table 6) but also other substances, such as 4-chloromethcathinone (urine: 1477 ng/mL; bile: 41 ng/mL), *N*-ethylhexedrone (urine: 1352 ng/mL; bile 34 ng/mL; lung – bloody fluid: 3 ng/mL; brain – tissue homogenate: 5 ng/g), benzoylecgonine (urine: 30 ng/mL; hair: 0.67 ng/mg) and 3,4-methylenedioxymethamphetamine (hair: 0.34 ng/mg). No other substances (including alcohol) were detected. The authors considered that the other substances had not contributed to death and attributed the fatality to α -PiHP alone.

Table 6. α -PiHP concentrations in tissues of a fatal case in Poland

Sample material	α -PiHP concentration
Blood	69 ng/mL
Urine	2072 ng/mL
Bile	341 ng/mL
Liver (tissue homogenate)	7 ng/g
Liver (bloody fluid)	33 ng/mL
Kidney (tissue homogenate)	78 ng/g
Kidney (bloody fluid)	194 ng/mL

Sample material	α -PiHP concentration
Stomach (tissue homogenate)	478 ng/g
Intestine (tissue homogenate)	115 ng/g
Intestine (bloody fluid)	185 ng/mL
Lung (tissue homogenate)	213 ng/g
Lung (bloody fluid)	448 ng/mL
Brain (tissue homogenate)	230 ng/g

Source: reference 11

Another fatal case was reported, in which the cause of death was trauma from a fall. The contribution of the drugs present could not be determined. A bag with white powder related to the case was confirmed to contain the synthetic cannabinoid methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate. Femoral blood was also positive for flualprazolam and α -PiHP. No more information on this cathinone, including concentrations, was reported (37).

In a report of a series of post-mortem cases involving the synthetic opioid *N*-pyrrolidino etonitazene, detection of either α -PiHP or α -PHP (isomer not differentiated) was also noted, with etizolam, α -hydroxyetizolam, flubromazepam, desalkylflurazepam and 2-methyl AP-237. No other information was reported. The date of collection of a femoral blood sample, however, was reported to have been 25 May 2021 (38), and it is possible that this case was also captured in the Center for Forensic Science Research and Education trend reports described above.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

8. Abuse potential

A. Studies in experimental animals

Information received by the WHO ECDD Secretariat (unpublished, under embargo) indicates that α -PiHP induced time- and dose-dependent stimulation of locomotor activity in male Swiss-Webster mice. The maximal stimulant effect was comparable to those of cocaine and methamphetamine during the 30-min period in which maximal stimulant effects occurred (0–30 min after injection) (39).

Drug discrimination studies:

Additional data obtained from drug discrimination studies and received by the WHO ECDD Secretariat (unpublished, under embargo) confirmed that α -PiHP fully substituted for the

discriminative stimulus effect produced by cocaine (1 mg/kg) and (*S*)-methamphetamine (1 mg/kg) (40, 41).

B. Studies in humans

No information was found.

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

No information was found.

10. Listing on the WHO Model List of Essential Medicines

α -PiHP is not listed on the 22nd WHO Essential Medicines List or on the 8th WHO Essential Medicines List for Children.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No information was found on recorded industrial use.

13. Non-medical use, abuse and dependence

No epidemiological evidence on use of α -PiHP was found. α -PiHP is available in its own right and is advertised for sale by some Internet retailers. Currently available information (sections 4 and 8) suggests that α -PiHP is likely to show abuse liability and that it displays psychostimulant properties comparable to those of some other synthetic cathinones under international control, such as α -PHP (42) and α -PVP (43).

See also Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

No epidemiological data on harm associated with α -PiHP was found. The information on post-mortem cases (section 6) suggests poly-substance use in which α -PiHP was detected. No information was found on the involvement of α -PiHP in monitoring of driving under the influence of drugs.

Information from drug testing services in the USA suggests that α -PiHP was detected in products acquired or sold as other substances, including various cathinones (including α -PVP), 3,4-methylenedioxymethamphetamine and 1-(1-benzofuran-6-yl)propan-2-amine (20). According to the EMCDDA (6), two green tablets seized in one Member State in 2017 were found to contain α -PiHP.

This suggests that people who use recreational drugs might be exposed to α -PiHP unintentionally, either alone or in combination with other substances that might pose additional risks (e.g., potential exacerbation of a psychostimulant toxidrome).

See also Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

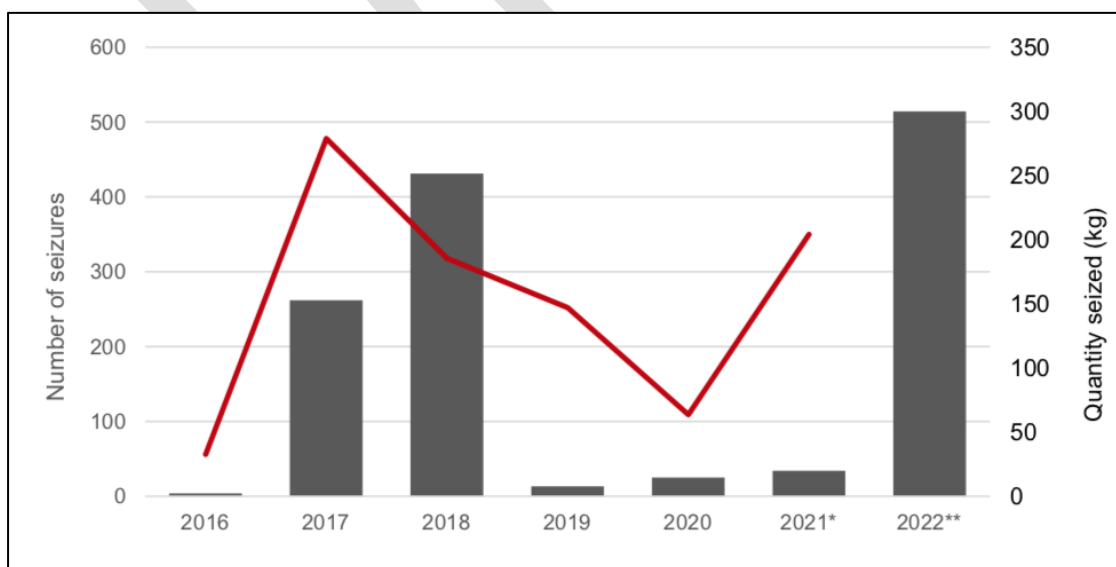
α -PiHP is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use. Some Internet retailers advertise it for sale as a “research chemical”.

16. Illicit manufacture and traffic and related information

According to the EMCDDA (33), α -PiHP has been available on the drug market in Europe since at least 2016. As of 15 June 2022, a total of 18 European Union Member States and Norway had reported physical detection of α -PiHP to the EMCDDA. At the time of writing, the total number of seizures was 1565, with a total quantity of 750.5 kg (all physical forms). The total quantity of powder seized was 748.4 kg. Since it was formally notified, the EMCDDA has received reports of 1565 seizures of α -PiHP. α -PiHP was found mainly as a powder (approximately 88% of all seizures reported), with herbal material occasionally reported (12% of cases).

Overall, approximately 750 kg of α -PiHP have been seized, of which 748 kg were in powder form and 2 kg in herbal material. Most powder was seized in 2018 (250 kg in approximately 275 seizures) and in 2022 (300 kg in a single seizure that originated from India). It should be noted that data for 2022 are incomplete and reflect only events-based data reported to the EMCDDA from the European Database on New Drugs between January and May 2022 (Fig. 1).

Fig. 1. Trends in the number of seizures of α -PiHP in all physical forms and the quantity of powder seized reported to the European Union Early Warning System on new psychoactive substances, European Union and Norway, 2016–2022



Note: Data on seizures for 2021 are preliminary and may be subject to change. Data on seizures for 2022 are incomplete and reflect only events-based data reported to the EMCDDA via the European Database on New Drugs between January and May 2022 (33).

Globally, the number of countries that reported α -PiHP detections to the UNODC Early Warning Advisory on new psychoactive substances since its first detection in 2016 were 3 in 2016, 11 in 2017, 10 in 2018, 19 in 2019, 17 in 2020, 8 in 2021 and 2 in 2022. Multiple entries were recorded from the same country for the same year (44).

The US National Forensic Laboratory Information System (NFLIS), which collects cases of drug detection submitted by state and local laboratories in the USA, has registered detections of α -PiHP (Table 7). According to the US Office of National Drug Control Policy (in a communication to the WHO ECDD Secretariat), NFLIS first identified α -PiHP in the USA in 2017. NFLIS midyear and annual reports began to list α -PiHP in 2019, in which it is listed (with other cathinones) in the substance group classified as “phenethylamines”.

Table 7. Numbers of reports received and published by NFLIS on detections of α -PiHP in law enforcement operations

Year ^a	α -PiHP	Total ^b	Reference no.
2017 (AR)	Not listed	382 297	45
2018(MY)	Not listed	198 587	46
2018 (AR)	Not listed	424 493	47
2019 (MY)	289	227 566	48
2019 (AR)	481	452 075	49
2020 (MY)	245	193 917	50
2020 (AR)	322	413 310	51
2021 (MY)	158	225 801	52

^a MY, mid-year report (January–June); AR, annual report (January–December)

^b Total number of reports in the substance group classified as “phenethylamines”

According to the US Office of National Drug Control Policy, 316 reports on α -PiHP were identified in the NFLIS Drug information system in 2021 (queried 28 April 2022). The total reported weight of 222 of these was 2.179 kg. It was noted that reports were still pending for 2021 and 2022. The Office of National Drug Control Policy also noted that, at the time of query, the total number of α -PiHP NFLIS reports was 1054.

The NFLIS “snapshot reports” are summarized in Table 8.

Table 8. NFLIS reports on the five most frequent drugs in the category “selected synthetic cathinones”

Period	α -PiHP (%)	Total	Reference no.
January–March 2020	86 (4.64)	1854	53
April–June 2020	83 (2.94)	2820	54
October–December 2020	32 (0.97)	3309	55

January–March 2021	Not listed	2809	56
July–September 2021	48 (1.51)	3186	57
October–December 2021	61 (2.72)	2244	58
January–March 2022	186 (4.83)	3852	59

Emerging Trends Reports published by the US Drug Enforcement Administration also reported identification of α -PiHP among other substances. The data for the report were compiled from archived information on seizures and analysis of drug evidence by the Administration's laboratory system (Table 9).

Table 9. Annual emerging threat reports on α -PiHP published by the US Drug Enforcement Administration

Year	α -PiHP (No.)	Total no. of cathinones	Reference no.
2018	11	327	60
2019	27	184	61
2020	6	200	62

See also Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

α -PiHP is not currently controlled under the 1961, 1971 or 1988 United Nations conventions.

18. Current and past national controls

α -PiHP is controlled in some United Nations Member States.

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

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

None.

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