



Critical Review Report: 3-Methoxyphencyclidine 3-MeO-PCP

Expert Committee on Drug Dependence

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Executive summary

This critical review has been proposed based on information brought to the attention of the World Health Organization (WHO) that 3-methoxyphencyclidine (3-MeO-PCP) is manufactured by several chemical companies and other producers. Case reports demonstrate that the ingestion of this new psychoactive compound can lead to severe intoxication and death. There are also clear warnings on user forums, for example, “3-MeO-PCP may be more likely to cause mania, delusions and psychosis than other dissociatives”.

3-MeO-PCP is a controlled substance in at least 12 countries including Austria, Brazil, Denmark, Germany, Sweden, Switzerland, Turkey and the United Kingdom.

3-MeO-PCP was first synthesized in 1979 and has been available on the grey market since 2010, with wide distribution beginning in 2011. Owing to its short history of human usage (approximately 10 years), only limited information about the pharmacological properties, metabolism and toxicity of 3-MeO-PCP is available.

Chemistry: Based on its structure, 3-MeO-PCP is an arylcyclohexylamine and 3-methoxy derivative of phencyclidine (PCP, a substance controlled under Schedule II of the 1971 UN Convention on Psychotropic Substances). Three positional isomers (2-, 3- and 4-MeO-PCP) have been identified. These structural isomers can be differentiated by analytical forensic methods. 3-MeO-PCP can be synthesized via at least one standard procedure within a few days, from standard starting materials, reagents and solvents that can be obtained from various chemical companies.

Pharmacology: 3-MeO-PCP is usually taken orally and nasally, although it may also be smoked and injected. 3-MeO-PCP is already active in the single milligram range and, therefore, accurate dosing can be a problem. Threshold oral doses start at 1 mg and range up to 30+ mg (considered as heavy doses). The onset of effects occurs 30–90 minutes after oral ingestion. The duration is 4–8 hours with a peak effect after 2–3 hours. The duration of after-effects ranges from 4 to 48 hours – the after-effects are also known as a “hangover” or an “afterglow”. 3-MeO-PCP has a much more rapid onset and a shorter duration of effects when vaporized or smoked.

3-MeO-PCP undergoes extensive metabolism (at least 30 phase I and II metabolites can be generated) and its half-life was estimated to be 10–11 hours.

In vitro as well as in vivo studies show that 3-MeO-PCP is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. 3-MeO-PCP binds to NMDA receptors more effectively than phencyclidine or ketamine. Like phencyclidine, 3-MeO-PCP also binds to the serotonin transporter. It also binds effectively to the σ 1 receptor.

Adverse reactions in humans: Information is available from published case reports (on severe and fatal intoxications), from the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) Tox-Portal and various Internet sources. These reports show that 3-MeO-PCP can cause acute behavioural, emotional, motivational, cognitive and somatosensory, and motoric changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to psychotic behaviour, amnesia and emergency department admissions or even death. User forums warn that users are strongly discouraged from taking this substance in high dosages, for several days in a row or in combination with other substances that increase the risk of psychosis.

In summary, a search of all available information showed that worldwide at least 19 cases of severe intoxication that required hospitalization and intensive care have been reported. Furthermore, 20 deaths were reported and in at least 7 of those cases 3-MeO-PCP was determined to be the cause of death. Blood concentrations of 3-MeO-PCP in non-fatal cases ranged from 49 to 350 µg/L and in fatal cases from 50 to 3200 µg/L. This suggests that there is no clear distinction between non-fatal and fatal blood concentrations. In most cases of 3-MeO-PCP intoxication, the user had also taken other synthetic drugs or classic drugs.

Dependence and abuse potential: No controlled studies in animals or humans have been conducted to assess the dependence or abuse potential of 3-MeO-PCP. According to user reports on online forums, 3-MeO-PCP has greater euphoric properties than other PCP analogues.

Potential therapeutic applications: No information available.

Magnitude of public health problems: An estimation of public health problems associated with 3-MeO-PCP is provided by the STRIDA project from Sweden. Over a 21-month period from July 2013 to March 2015, 1243 cases of suspected intoxication with new psychoactive substances (NPS) originating from emergency room or intensive care unit admissions were tested for PCP-analogues. In this primarily high-risk population (e.g. psychonauts from the drug scene) 56 (4.5%) patients tested positive for 3-MeO-PCP. Importantly, other NPS and/or classical drugs of abuse could only be detected in seven of those cases (12%) indicating that most intoxications were directly related to 3-MeO-PCP single-substance intoxications. The most prominent clinical signs seen in the single-substance 3-MeO-PCP intoxications were hypertension, tachycardia and altered mental status including confusion, disorientation, dissociation and/or hallucinations. Patients typically required medical care for 1–2 days, and 37% of all cases were graded as severe intoxications.

Drug seizures that contained 3-MeO-PCP have been reported to the European Monitoring Centre for Drugs and Drug Addiction by national focal points from Lithuania, Romania, Italy, Spain, Latvia, Austria, Slovenia and France.

1. Substance identification

A. International Nonproprietary Name (INN)

NA

B. Chemical Abstract Service (CAS) Registry Number

CAS Number: 72242-03-6

C. Other chemical names

- 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine
- 3-methoxyphencyclidine
- 3-methoxy PCP

D. Trade names

—

E. Street names

3-MeO-PCP (no other names were used in user forums)

F. Physical appearance

Powder, tablets

G. WHO review history

3-MeO-PCP has not been previously pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry

A. Chemical Name

IUPAC Name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine

CA Index Name: —

B. Chemical Structure

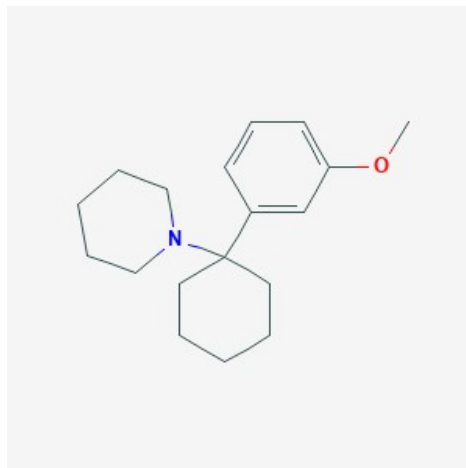
Free base:

Molecular formula: C₁₈H₂₇NO

Molecular weight: 273.412 g/mol

Fig. 1

Structure of 3-MeO-PCP



Source: PubChem

C. Stereoisomers

No stereoisomers of 3-MeO-PCP have been described. However, it has structural (positional) isomers as shown in Figure 2.

Based on its structure, 3-MeO-PCP is an arylcyclohexylamine and 3-methoxy derivative of phencyclidine (PCP, a substance controlled under Schedule II of the 1971 UN Convention on Psychotropic Substances). The synthesis of 3-MeO-PCP was first described by Geneste et al. (3). Wallach et al. (2) slightly modified this original synthesis procedure and used the primary amine 3-MeO-PCA as the starting material.

The procedure described by Wallach et al. (2) can easily be adapted by forensic laboratories, but also by chemists who supply the grey market. Using this procedure, 3-MeO-PCP can be synthesized within a few days from standard starting materials, reagents and high-performance liquid chromatography (HPLC) grade solvents that can be obtained from various chemical companies.

D. Chemical properties

Melting point 204 °C

Boiling point 381 °C

Solubility Although 3-MeO-PCP is soluble in water, no specific information was available on the absolute amount that gets into solution.

E. Identification and analysis

De Paoli et al. (4) described a method using HPLC with tandem mass spectrometry (MS-MS) for the quantification of 3-MeO-PCP in human blood and urine.

Wallach et al. (2) applied a range of analytical methods that enabled discrimination between the positional isomers 3-MeO-PCP and 4-MeO-PCP derived from chemical synthesis.

Michely et al. (5) used liquid chromatography-high-resolution (LC-HR) MS-MS to detect a broad range of 3-MeO-PCP metabolites in urine samples from rats.

To detect 3-MeO-PCP and its metabolites in human urine and blood Ameline et al. (6) used standard ultra-performance LC-MS (UPLC–MS) and UPLC–MS-MS. They verified their analysis in vitro after incubation of 3-MeO-PCP with human liver microsomes – which allows for the production of metabolites. They were able to identify *O*-demethyl-3-MeO-PCP, piperidine-hydroxy-3-MeO-PCP, *O*-demethyl-piperidine-di-hydroxy-3-MeO-PCP, piperidine-di-hydroxy-3-MeO-PCP and cyclohexyl-hydroxypiperidine-di-hydroxy-3-MeO-PCP with a retention time of less than 6 minutes. 3-MeO-PCP and four of the five metabolites mentioned above could be detected in urine and blood samples from two fatal cases (7).

Recently, Nisbet et al. (8) introduced a GC-MS quantification method for the analysis of more than 20 new psychoactive substances (NPS) in whole blood and urine. The detection limit was 0.5 µg/L for 3-MeO-PCP in blood and urine samples. This method particularly useful to laboratories that lack access to LC–MS-MS and for the detection of multiple NPS with different chemistries in acute fatalities (8).

An old classical technique for drug identification is the microcrystalline test. In this test a unique crystalline precipitates when a compound is combined with a specific reagent. Given its high sensitivity and selectivity, microcrystalline testing is a rapid and inexpensive technique for analysing new designer drugs. Quinn et al. (9) described a new microcrystalline test that could clearly differentiate and identify PCP and four of its structural analogues including 3-MeO-PCP.

3. Ease of convertibility into controlled substances

3-MeO-PCP is not readily converted into other internationally controlled substances.

4. General pharmacology

A. *Routes of administration and dosage*

3-MeO-PCP is usually taken orally and nasally; it may also be smoked and injected. 3-MeO-PCP is already active in the single milligram range and accurate dosing can therefore be difficult. Threshold oral doses start at 1 mg and range up to 30+ mg (considered as heavy doses). The onset of effects occurs 30–90 minutes after oral ingestion. The duration is 4–8 hours with a peak effect after 2 to 3 hours. The duration of the after-effects ranges from 4 to 48 hours (10). The after-effects are also known as a “hangover” or an “afterglow”. 3-MeO-PCP has a much more rapid onset and shorter duration of effects when vaporized or smoked (10). On an online forum for people who use psychoactive substances (10) there is a clear warning that “*It is strongly discouraged to take this substance in high dosages, for*

multiple days in a row, or in combination with other substances that increase the risk of psychosis”.

Another online forum (11) provides more detailed information on oral and nasal dosing. Threshold oral doses mentioned range from 1.5 to 3 mg, light doses from 3 to 5 mg, commonly used doses from 5 to 10 mg, strong doses from 10 to 15 mg and a heavy dose is 15+ mg. Threshold nasal doses range from 1 to 2 mg, light doses from 2 to 5 mg, commonly used doses from 5 to 8 mg, strong doses from 8 to 12 mg and a heavy dose is 12+ mg. From these narrow dosing ranges it is evident that the single milligram range can make a pronounced difference to the perceived effects and that accurate dosing is problematic.

B. Pharmacokinetics

Michely et al. (5) studied the phase I and II metabolism of 3-MeO-PCP in rats and in human liver microsomes. They also examined the CYP isoenzymes involved. 3-MeO-PCP was administered at a dose of 10 mg/kg body weight for the identification of the metabolites and one 1 mg/kg dose that corresponds roughly to commonly used doses. 3-MeO-PCP was extensively metabolized. Thirty different phase I metabolites could be detected via hydroxylation, carboxylation, *O*-demethylation and glucuronidation. Phase II metabolism included seven glucuronides. The findings of this rat screening experiment were transferred to a screen in human liver microsomes. *O*-demethylation and hydroxylation were also observed and hence five metabolites were detected in both preparations. For 3-MeO-PCP, CYP 2B6 was found to be responsible for aliphatic hydroxylation and CYP 2C19 and CYP 2D6 for *O*-demethylation (5).

Allard et al. (12) applied a molecular networking approach to a large set of MS-MS data. With this in silico approach they were able to identify 12 of the metabolites of 3-MeO-PCP that had been described in the initial biotransformation study by Michely et al. (5) These included seven phase I and five phase II metabolites.

In summary, 3-MeO-PCP undergoes extensive metabolism and its half-life was estimated to be 11 hours. However, the elimination half-life of 3-MeO-PCP was calculated from samples taken from only one case of non-fatal intoxication by repeated sampling over 2 days (13). Nevertheless, this half-life estimation is supported by the findings of Bäckberg et al. (14) who calculated a half-life of about 10 hours from two blood samples obtained from one case of intoxication.

C. Pharmacodynamics

Effects in vitro

3-MeO-PCP is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. In vitro tests have shown that 3-MeO-PCP binds to NMDA receptors more effectively than phencyclidine or ketamine. In vitro receptor binding studies by Roth et al. (15) show that 3-MeO-PCP has a sub-micromolar affinity (K_i 20 nM) for the NMDA receptor, which is greater than that of phencyclidine (250 nM) or ketamine (659 nM). Wallach and Brandt (1) reported a similar K_i of 38 nM for the NMDA receptor.

Mitsuoka et al. (16) developed an immunocytochemical assay based on hippocampal neurons to study NMDA receptor inhibition of phencyclidine analogues and to estimate the inhibitor concentration that reduces activity by half maximal inhibitory concentration (IC_{50}) values. The inhibitory activity at the NMDA receptor of 3-MeO-PCP ($IC_{50} = 1.51 \mu M$) was comparable to that of PCP ($IC_{50} = 2.02 \mu M$).

Roth et al. (15) described K_i determinations, receptor binding profiles and functional assays conducted in a panel of central nervous system receptors and transporters. They found that, like phencyclidine, 3-MeO-PCP also binds to the serotonin transporter (SERT) (K_i 216 nM), whereas a much higher K_i value of 1571 nM for SERT was reported by Wallach and Brandt (1) but 3-MeO-PCP has no or low affinity for the dopamine or norepinephrine transporter (DAT and NET). In contrast both 3-MeO-PCP and PCP inhibit dopamine uptake into synaptosomes, which suggests a functional interaction with the DAT (1). In addition, 3-MeO-PCP also binds effectively to the σ_1 receptor whereas phencyclidine does not.

Importantly, although little discussed in the literature, 3-MeO-PCP shows affinity for sigma one receptors (σ_1 $K_i = 42$ nM) (15). Wallach & Brandt (1), however, report – under the same in vitro experimental conditions – a higher K_i value of 436 nM on the σ_1 binding site. Although the functional interaction of 3-MeO-PCP with the sigma binding site is not understood, it is noteworthy that the σ_1 receptor is a membrane protein expressed throughout the human body, which acts like an inter-organelle signalling regulator and fine tunes electrical activity and calcium homeostasis. These regulatory effects may favour cell survival in pathological contexts such as stroke or neurodegenerative diseases. Hence ligands targeting the σ_1 receptor are undergoing clinical trials for treatment of Alzheimer's disease, ischaemic stroke and neuropathic pain (17). Whether or not the σ_1 receptor activity of 3-MeO-PCP may have potential therapeutic implications is not known – so far there is no experimental or anecdotal evidence to support such a conclusion.

Effects in vivo

NMDA receptor antagonists such as PCP or ketamine interfere with the maximal electroshock seizure (MES) test. 3-MeO-PCP also inhibits the tonic hindlimb extension in the MES test in mice and rats (1) and the ED_{50} values are similar to those of PCP and ketamine (18) suggesting that 3-MeO-PCP also acts as an NMDA receptor antagonist in vivo.

5. Toxicology

No published safety data concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of 3-MeO-PCP are available.

6. Adverse reactions in humans

Information from published case reports (on severe and fatal intoxications), the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) Tox-Portal and various Internet sources is summarized below. User experiences from 2011 to 2020 were retrieved from three different websites (19-21). In

summary, 3-MeO-PCP can cause acute behavioural, emotional, motivational, cognitive and somatosensory and motoric changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to psychotic behaviour, amnesia and emergency department admissions or even death.

Stevenson & Tuddenham (22) reported a case of severe intoxication with 3-MeO-PCP. In their case report from Glasgow they describe a man in his twenties who had snorted large quantities of 3-MeO-PCP and methylenedioxypyrovalerone (MDPV). He had also inhaled butane gas. He got into a psychotic state and heard a voice saying “kill your father”. He immediately attacked his father who only survived the attack because neighbours heard his screams and called an ambulance. After his arrest the man experienced visual hallucinations for almost 6 weeks. Despite a previous diagnosis of drug-induced psychosis he was convicted of attempted murder and sentenced to 4 years in prison (22). MDPV can also induce paranoid psychosis (23) and, therefore, it cannot be concluded that 3Meo-PCP was the sole reason for the psychotic state that led to this violent behaviour.

Johansson et al. (13) reported a case of intoxication in a 19-year-old male drug addict who required hospitalization. He presented with tachypnoea, tachycardia, hypertension, catatonia and mydriasis. His condition later worsened as he developed a fever and lactic acidosis concomitant with psychomotor agitation and hallucinations. On day 3 all physical parameters were normal and he was discharged from hospital. Four blood samples were taken during his stay in hospital, which allowed the elimination time of 3-MeO-PCP to be estimated. The concentration of 3-MeO-PCP was 0.14 µg/g at admission. The half-life of 3-MeO-PCP was calculated assuming first-order elimination. Taking all the samples into account, the half-life was estimated to be 11 hours (13).

The first two cases of intoxication with 3-MeO-PCP in Italy were reported by Bertol et al. in 2017 (24). Two young men 19 and 21 years old were hospitalized in Florence in a comatose state, showing respiratory acidosis, right anisocoria, mydriatic pupils and hypothermia. They recovered within a few hours and reported consumption of a large amount of alcohol and ingestion of unknown pills. Blood alcohol concentrations were 2.0 g/L and 1.7 g/L, respectively. The presence of 3-MeO-PCP was confirmed and quantified by LC–MS–MS. The concentrations were 350 and 6109 ng/mL (in blood and urine, respectively) in one patient and 180 and 3003 ng/mL (in blood and urine, respectively) in the other (24).

The first detection of 3-MeO-PCP in Spain, which occurred in poly-drug poisoning of two patients during the summer of 2018 in Ibiza, was reported by Gomila et al. (25). Urinary concentrations of 3-MeO-PCP were 9645 and 560 ng/L, respectively (25).

Thornton et al. (26) described a case from the United States of America of a 27-year-old male with a medical history of attention deficit hyperactivity disorder, bipolar disorder and hypertension. He was admitted to hospital 8 hours after insufflation of an Internet-obtained product. His physical parameters were quite normal except that he had hypertension. But he could only respond to questions in

a very delayed manner and had complete amnesia about the preceding 8–12 hours. Blood samples were taken repeatedly at 0, 2 and 3 hours after arrival at the hospital. Quantitative analysis with LC–MS–MS yielded 3-MeO-PCP concentrations of 167 ng/mL, 131 ng/mL and 90 ng/mL for the three time points, respectively (which would imply a more rapid half-life of 3-MeO-PCP than reported in cited references 13 and 14). Methoxetamine was also detected in all three samples (26).

A further case report from the United States described 3-MeO-PCP intoxication in a 27-year-old man who was found unconscious in his car by the police (27). On arrival at the hospital, the patient was awake. He did express delusions including that he “was an alien with green blood”. He had a medical record of schizophrenia and auditory hallucinations secondary to noncompliance with risperidone therapy. His urine was positive for 3-MeO-PCP (27).

Two severe cases of intoxication with 3-MeO-PCP that required hospitalization were reported from Prague by Zidkova et al. (28). Two men had consumed a powdered drug together with alcohol at a party. After 15 minutes they began experiencing disorientation, hallucinations and spastic leg postures. Following admission, one patient remained hypertensive and tachycardic. He also displayed prominent signs of psychosis. After 24 hours in the intensive care unit the patient was discharged but reported complete amnesia regarding the entire period of intoxication. The other patient, a 40-year-old man, was admitted to the intensive care unit with cramps and a deteriorating state of consciousness. He was discharged after regaining a normal clinical status after 8 hours in hospital. This patient also reported complete amnesia regarding the duration of the episode. 3-MeO-PCP serum levels 2 hours after drug ingestion were 49 ng/mL (for patient 1) and 66 ng/mL (for patient 2) (28).

A case of intoxication in France was reported by Allard et al. (12). A 17-year-old man was admitted to the emergency department with altered consciousness and agitation. He had a history of substance abuse, and a small bag of white powder labelled “3-MeO-PCP” was found in his belongings. The main complication was rhabdomyolysis. After 2 days the patient was discharged from hospital (12, 29). The concentrations of 3-MeO-PCP in blood and urine were 71.1 ng/mL and 706.9 ng/mL, respectively. Seven days later, he returned to the emergency department after sniffing 50 mg of 3-MeO-PCP (12).

Another case report from France is described by Kintz et al. (30). A 39-year-old woman with a history of drug use (heroin, cannabis, cocaine and GHB) was found dead at home after being killed by her partner. The partner was under influence of various drugs. During the autopsy, femoral blood, urine and hair were collected. 3-MeO-PCP or 4-MeO-PCP was identified in the femoral blood. The differentiation between the two structural (positional) isomers was made using GC–MS and the presence of 3-MeO-PCP was confirmed. Concentrations of 3-MeO-PCP were 63 and 94 ng/mL in femoral blood and urine, respectively. The hair sample also tested positive for 3-MeO-PCP on 3 × 2-cm segments at 731, 893 and 846 pg/mg, indicating long-term abuse of the drug (30).

In the UNODC EWA Tox-Portal, five cases of intoxication requiring clinical admission are reported from Finland and Italy. Blood concentrations of up to 49 ng/mL of 3-MeO-PCP were measured (no other drugs were detected). Five postmortem analyses were reported from Finland and the United States. 3-MeO-PCP concentrations of up to 299 ng/mL were measured. In three of these five cases other drugs such as cocaine and U-47700 were also detected. It is assumed that the intoxication and fatal cases reported in the UNODC EWA Tox-Portal do not overlap with the ones described in the literature.

A fact sheet on 3-MeO-PCP compiled for the Belgian Early Warning System is available online (31). In this fact sheet the Belgian National Focal point reported that one death associated with 3-MeO-PCP had occurred in June 2017. Another death was reported from the Portuguese Focal Point on 14 October 2016. In this case, postmortem femoral blood analysis revealed 0.525 mg/L of 3-MeO-PCP and several other drugs. From Norway (2011), there had been reports of at least three cases of overdose with 3-MeO-PCP that required hospitalization.

In summary, following a search of all available information worldwide, at least 19 cases of severe intoxication that required hospitalization and intensive care have been reported. Furthermore, 21 deaths were reported and in at least seven of those cases 3-MeO-PCP was determined to be the cause of death. Blood concentrations of 3-MeO-PCP in these 16 non-fatal cases ranged from 49 to 350 µg/L whereas blood concentrations in fatal cases ranged from 50 to 3200 µg/L. This suggests that a clear distinction between toxic and fatal concentration cannot be made. Importantly, most of the non-fatal and fatal intoxications were associated with use of other synthetic drugs or classic drugs. Fourteen fatal cases are described in more detail below.

Bakota et al. (32) reported on a fatal case from the United States. A 29-year-old male with a history of illicit drug use was found dead in his bed. A bag with a white powder labelled “fumaric acid 5 G” purchased on the Internet from China was found next to him. His parents reported that he had been hospitalized on several occasions as a result of abusing this substance and that their son had a previous medical history of attention deficit disorder and depression. Using a quantitative LC–MS–MS method, a concentration of 139 µg/L 3-MeO-PCP was measured in his blood. Diphenhydramine and amphetamine (<0.10 mg/L) were also detected and the toxicological conclusion was that the cause of death was combined 3-MeO-PCP, diphenhydramine and amphetamine toxicity (32).

Mitchell-Mata et al. (33) reported the first two deaths involving 3-MeO-PCP in Washington State (United States). Case 1 was a 21-year-old male with a history of drug use who was found naked and unresponsive. He was a university student who had recently been discharged from a drug treatment centre. Case 2 was a 58-year-old male with a history of significant health problems and of previous drug use that included opiates and methamphetamine. The GC–MS method was used for quantification of the 3-MeO-PCP concentrations in blood, which were 0.63 and 3.2 mg/L for case 1 and case 2, respectively. Methamphetamine was also detected in the blood of one of the men while the other tested positive for ethanol, bupropion,

delorazepam, paroxetine and mitragynine. The conclusion of the toxicologists was that in both cases death was the result of acute intoxication due to poly-drug consumption (33).

Johansson et al. (13) reported seven deaths involving 3-MeO-PCP from Sweden. The first death involving 3-MeO-PCP occurred in March 2014 and the seventh death occurred in June 2016. The cases involved six males and one female who were in their twenties to thirties. All had psychiatric problems and/or ongoing drug abuse. Intoxication was considered to be the cause of death in six of the cases and asphyxia in one case. The femoral blood concentrations of 3-MeO-PCP ranged from 0.05 mg/g to 0.38 mg/g. Apart from one case, all cases involved several other drug intoxications with either new synthetic compounds or classical drugs such as buprenorphine, fentanyl and amphetamine. In three out of six cases 3-MeO-PCP was considered contributory to the cause of death whereas in the remaining three cases the cause of death was most likely unrelated to 3-MeO-PCP. As an example, in one of those cases that only involved 3-MeO-PCP, a 27-year-old male was found dead at home in the bathtub. He had a history of substance use and regularly ordered hallucinogenic drugs online. Autopsy revealed some swelling of the brain, pulmonary oedema, and burns on the head, arms, torso and legs due to hot water from the shower. The cause of death in this case was certified as intoxication with 3-MeO-PCP (13).

Ameline et al. (6) described two fatal cases from France. Case 1 was a 39-year-old woman with a history of illicit drug use who was found dead (involving suspected family violence) (see also 30). Case 2 was a 41-year-old man with a history of substance use who was also found dead at home (7). Using UPLC-MS-MS, 3-MeO-PCP and its metabolites were quantified in samples of urine and blood. In case 1, 3-MeO-PCP was identified in femoral blood and urine at concentrations of 63 and 94 ng/mL, respectively. In case 2, 3-MeO-PCP was identified in femoral blood and urine at concentrations of 498 and 16 700 ng/mL, respectively (6).

The first fatal 3-MeO-PCP intoxication in The Netherlands was reported by de Jong et al. in 2019 (34). A man in his mid-thirties was found dead at a lake. He had a medical history of amphetamine and cannabis addiction. He had taken “ant poison” (named “Thrive Soluble”), which was sold on the Internet as a product “not for human use”. The urine drug test was positive for tetrahydrocannabinol and cocaine. Ethanol concentration in the blood was 1.2%. 3-MeO-PCP was quantified using a UPLC-MS-MS system – serum and blood concentrations were 123 µg/L and 152 µg/L, respectively (34).

7. Dependence potential

A. *Animal studies*

No information available

B. *Human studies*

No information available

8. Abuse potential

A. *Animal studies*

Abiero et al. (35) provided some indirect evidence that the structural isomer 4-MeO-PCP produces rewarding (measured by conditioned place preference) and reinforcing effects (measured by different self-administration schedules) through activation of the mesolimbic dopamine reward pathway and alteration of accumbal CREB, deltaFosB and BDNF levels – all three molecules are key players in mediating the reinforcing effects of drugs of abuse. Given that 4-MeO-PCP is a less active structural isomer of 3-MeO-PCP it is very likely that 3-MeO-PCP produces conditioned place preference, is self-administered in rats and activates the reward pathway.

B. *Human studies*

According to experiences from various drug user forums 3-MeO-PCP is reported to have greater euphoric properties and be “mentally clearer” than other PCP analogues.

Two case reports (12, 30) also point to long-term use of the drug. In one of these cases this was confirmed by positive hair testing (30).

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

No information available

10. Listing on the WHO Model List of Essential Medicines

3-MeO-PCP 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)

3-MeO-PCP has never been marketed as a medicinal product.

12. Industrial use

3-MeO-PCP has no industrial use.

13. Nonmedical use, abuse and dependence

See sections 6 and 7.

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

An estimation of public health problems associated with 3-MeO-PCP is provided by the STRIDA project (a collaborative project between the Swedish Poisons Information Centre and the Karolinska Institute, which monitors cases of acute intoxication related to NPS) from Sweden. Over a 21-month period from July 2013 to March 2015, 1243 samples from cases of suspected NPS intoxication originating from emergency room or intensive care unit admissions were tested for PCP-

analogues (14). During this period, 56 (4.5%) patients tested positive for 3-MeO-PCP and 11 (0.9%) for the PCP-analogue 4-MeO-PCP; 8 of these cases involved both substances. The 59 patients were aged 14–55 years (median: 26 years) and 51 (86%) were men. Importantly, other NPS and/or classical drugs of abuse were only detected in 7 of those cases (12%). This indicated that most intoxications were directly related to 3-MeO-PCP alone. The most prominent clinical signs seen in the cases where 3-MeO-PCP alone had led to intoxication were hypertension, tachycardia and altered mental status including confusion, disorientation, dissociation and/or hallucinations. Patients typically required medical care for 1–2 days, and 37% of all cases were graded as severe intoxication. In addition to standard supportive therapy, half of the patients were treated with benzodiazepines and/or propofol (14).

In a report from the United States on intoxication with Black Mamba (which is sold as a synthetic cannabinoid) three out of eight cases also tested positive for 3-MeO-PCP (concentrations of up to 114 ng/mL were measured in urine samples) (36).

Systematic Internet searches were performed by Hearne and van Hout (2016) using the terms “synthetic dissociative” and “3-MeO-PCP”, in combination with “forum”. More than 50 000 hits were obtained. Following screening of user trip reports and forums, threads from seven drug forum websites were analysed by conducting content analysis. Consistent information was found on the theme “Advice on administering 3-MeO-PCP in combination with other drugs”. Mixing with other illicit drugs such as heroin, MDMA and cocaine was not advised in most cases. Mixing 3-MeO-PCP with opiates was considered particularly risky due to the potential for respiratory depression from the opiates, the anaesthetized state and the feeling of a near-death experience (more commonly known as the “k-hole” (37) induced by 3-MeO-PCP. Forums members advised against combinations of different types of NPS with 3-MeO-PCP particularly because of the untested nature of some of these compounds and their unpredictable qualities (38).

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

Several reports of drug seizures that contained 3-MeO-PCP have been reported to the EMCDDA from national focal points in Austria, France, Italy, Latvia, Lithuania, Romania, Slovenia and Spain (31).

17. Current international controls and their impact

3-MeO-PCP is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

Legal status of 3-MeO-PCP (information obtained from references 10, 39):

3-MeO-PCP is currently controlled in at least 14 countries including Austria, Belgium, Brazil, Canada, Denmark, Germany, Italy, Japan, Poland, Singapore, Sweden, Switzerland, Turkey and the United Kingdom.

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

No data.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of 3-MEO-PCP

Data were obtained from 105 Member States (19 African Region, 13 Eastern Mediterranean Region, 40 European Region, 16 Region of the Americas, seven South-East Asia Region and 10 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three African Region, two Eastern Mediterranean Region, two European Region, three Region of the Americas, one South-East Asia Region and two Western Pacific Region), leaving 92 active countries. Of these, 31 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on 3-MEO-PCP

Region	Number of countries without information	Number of countries with information on substance
Africa Region	15	1
Eastern Mediterranean Region	7	4
European Region	21	17
Region of the Americas	10	3
South-East Asia Region	5	1
Western Pacific Region	3	5
Total 92	61	31

LEGITIMATE USE

No countries reported approved human medical products or veterinary products containing 3-MEO-PCP.

One country (Region of the Americas) reported 3-MEO-PCP being currently used in medical or scientific research (excluding use as an analytical standard), specifically in cell line studies (binding/functional assays) and animal studies.

Two countries (one Region of the Americas, one Western Pacific Region) reported 3-MEO-PCP being used in industrial or other non-medical or non-scientific use.

No countries reported approved therapeutic indications for 3-MEO-PCP.

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

Fifteen countries reported that 3-MEO-PCP is being misused or abused for its psychoactive properties/recreational use.

The most common known route of administration reported was sniffing followed by oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	7
Injection	0
Inhalation	0
Sniffing	9
Smoking	1
Don't know	15

To the above, one country added:

- “Plugged (rectally)”.

The most common known formulation of 3-MEO-PCP reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	14
Tablets	1
Liquid for oral use	1
Solution for injection	0
Don't know	13

To the above, countries added:

- blotting paper
- plant matter.

Ten countries reported the level of negative health-impact originating from 3-MEO-PCP's non-medical consumption as “serious” or “substantial” (Table 4).

Table 4. Level of negative health-impact

Serious	Substantial	Negligible	Don't know
3	7	9	10

One country (Western Pacific Region) added, “The social harm caused by 3-MEO-PCP is substantial”. Another country (European Region) remarked, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers, etc.”.

Five countries (five European Region) reported emergency room admissions related to the non-medical use of 3-MEO-PCP.

Concerning adverse effects, one country (European Region) noted, “speech disorders, transient gait disturbances, mystical delirium lasting a few hours, behaviour disturbances, delirium, auditory and visual hallucinations, hypertonic crises with eye revulsion, dissociation, mydriasis, tachycardia, ...”. Another (European Region) listed, “High blood pressure, tachycardia, neurological manifestations”. A third country (European Region) noted, “plucky, tense, disoriented, fever”.

No countries reported users of 3-MEO-PCP presenting for drug dependence treatment.

Regarding mortality, only three countries (two European Region, one Region of the Americas) reported deaths involving 3-MEO-PCP:

- one fatal case where other substances were also involved (2020)
- one fatal case where other substances were also involved (2019)
- three fatal cases where other substances were also involved (2017).

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

Fifteen countries responded that 3-MEO-PCP is currently controlled under national legislation to regulate its availability.

Table 5 shows the main reported activities involving 3-MEO-PCP.

Table 5. Reported illicit activities involving 3-MEO-PCP

Activities	Number of countries
Smuggling from other countries	5
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	1
Trafficking	5
Diversion from legal supply chain	0
Internet sales – seller or website located in country	2
Internet sales – from abroad to buyers in country	1
Internet sales – other, or location of sellers and website unknown	5
Direct sales to people who use the substance	2
Don't know	14

To the above, countries added:

- trafficking through postal service
- Internet sales (without other information)
- probably drug dealing.

Twelve countries reported seizures (Table 6).

Table 6. Reported seizures of 3-MEO-PCP

Year	Seizures
2020	31
2019	84
2018	199
Total	314

Twenty-four countries have the forensic laboratory capacity to analyse 3-MEO-PCP.

One country (European Region) commented, “Forensic laboratories have the capacity to analyse 3-MEO-PCP if reference material is available. “