



Critical review report: 2-Methyl AP-237

**Expert Committee on Drug Dependence
Forty-fifth Meeting
Geneva, 10–14 October 2022**

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Executive summary

2-Methyl AP-237 (IUPAC name: 1-{2-methyl-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazin-1-yl}butan-1-one) is a synthetic opioid typically classed as a 1-cinnamylpiperazine. It first emerged in 2019. 2-Methyl AP-237 is most likely to be traded in the form of a racemate and in the (*E*)-form.

2-Methyl AP-237 has not previously been pre- or critically reviewed by WHO.

No specific information was available of the routes used to synthesize the 2-methyl AP-237 products circulating on the drug market, but straightforward methods for its preparation exist that do not require access to internationally controlled precursors. It is not feasible to convert 2-methyl AP-237 into another substance currently listed in the UN conventions of 1961, 1971 and 1988.

Descriptions on online forums suggest that 2-methyl AP-237 is typically administered orally and by nasal insufflation (snorting), although smoking and sublingual and rectal administration have also been described.

In-vitro pharmacological studies have shown that 2-methyl AP-237 is qualitatively similar to other synthetic opioids such as morphine and fentanyl. 2-Methyl AP-237 was shown to bind to the μ -opioid receptor (MOR), although it was 22 and 18 times less potent than fentanyl and morphine, respectively. In the [³⁵S]GTP γ S binding assay, 2-methyl AP-237 showed low potency and efficacy. In mini-G_i- and β -arrestin 2 recruitment assays, 2-methyl AP-237 also showed low potency, although its efficacy was comparable to that of hydromorphone.

2-Methyl AP-237 had analgesic effects in rodents (writhing and hot-plate test and warm-water tail flick assay). In the latter test, 2-methyl AP-237 was as potent as fentanyl and more potent than morphine.

In male and female CD-1 mice (25–40 g), the reported LD₅₀ values for 2-methyl AP-237 were 55 mg/kg (intravenously), 350 mg/kg (orally) and 550 mg/kg (subcutaneously, s.c.). The acute toxicity observed in animals resembled effects seen with other opioids, including increased body tone, gasping, subsequent loss of posture and death due to respiratory blockage under complete muscular relaxation.

In rats, 2-methyl AP-237 (ED₅₀ = 0.25 mg/kg) fully substituted for the discriminative stimulus effects of morphine (ED₅₀ = 1.08 mg/kg). The ED₅₀ for a fentanyl standard was 0.0042 mg/kg. Naltrexone (1 mg/kg) blocked the morphine-like discriminative stimulus effects of 2-methyl AP-237, reducing the morphine-appropriate response to 12 ± 11%.

Taken together, these findings suggest that 2-methyl AP-237 is likely to display abuse liability similar to that of synthetic opioids under international control.

No studies on dependence potential were identified, although some people who reported 2-methyl AP-237 use also described the development of tolerance and withdrawal symptoms. In view of its MOR agonist activity, use of 2-methyl AP-237 would be expected to be associated with the development of opioid tolerance and physical dependence.

No information was found about therapeutic use. 2-Methyl AP-237 is not known to have any marketing authorization, and no information was found on any agricultural, industrial or cosmetic use. 2-Methyl AP-237 is used as reference material in scientific research.

No epidemiological evidence on the use of 2-methyl AP-237 was available in household surveys. Detection of 2-methyl AP-237 in biological fluids confirms that this substance is used recreationally (intentionally or unintentionally). Information obtained from Internet forums suggest that people who use heroin, prescription opioid analgesics and other synthetic opioids might use this substance.

Information on detections of 2-methyl AP-237 in fatal and non-fatal cases of intoxication suggests the involvement of poly-substance use, but fatal intoxications associated with 2-methyl AP-237 use alone have also been reported.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), between 2019 and 2020, two countries reported detection of 2-methyl-AP-237 in biological samples from cases of serious adverse events, including one sample associated with a death and one associated with acute poisoning.

The EMCDDA received reports of 31 seizures in which 2-methyl AP-237 was found mainly as a powder, although liquids and tablets were also reported. As of 15 July 2022, a total of approximately 121 g of 2-methyl AP-237 had been seized.

In the USA, at least 10 confirmed fatal poisonings and non-fatal poisonings associated with 2-methyl-AP-237 were reported.

The US Drug Enforcement Administration (DEA) reported that 45 reports were identified by the National Forensic Laboratory Information System in 2021. According to the US Customs and Border Protection National Targeting Center, hubs with the country of origin were identified as China, Germany, the Netherlands and Switzerland, with the majority from the Netherlands, and it was believed that 2-methyl AP-237 was transhipped through Europe.

2-Methyl AP-237 is currently not controlled under the 1961, 1971 or 1988 United Nations Conventions but is controlled in some United Nations Member States.

1. Substance identification

A. International nonproprietary name

No information was found.

B. Chemical Abstracts Service registry number

98608-61-8 (base)

98608-59-4 (HCl)

Not yet assigned (2-methyl AP-237-d₇ hydrochloride)

C. Other chemical names

2-Methyl-1-(1-oxobutyl)-4-(3-phenyl-2-propenyl)-piperazine

1-{2-Methyl-4-[(2E)-3-phenylprop-2-en-1-yl]piperazin-1-yl}-1-butanone

1-[2-Methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one

1-{2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl}-1-butanone

1-{2-Methyl-4-[3-phenylprop-2-enyl]piperazin-1-yl}butan-1-one

2-Methyl-BCP

2-Methyl buccinazine

N-Butyryl-N'-cinnamyl-2-methyl-piperazine

1-(4-Cinnamyl-2-methylpiperazin-1-yl)butan-1-one

Methyl-AP-237

1-Butyryl-2-methyl-4-cinnamylpiperazine

D. Trade names

2-Methyl AP-237

E. Street names

2-Methyl AP-237 appears to be most commonly used but other names are also encountered in Internet forums, including 2map, 2MAP, MAP, 2MAP237, 2m-AP237, 2-MAP, 2methylap237 and 2-M-AP-237.

F. Physical appearance

In its pure form, 2-methyl Ap-237 hydrochloride is expected to be odourless and white, like many other synthetic opioids. It has been described as a white crystalline powder (1, 2) and as a crystalline solid (3). Seized material identified as 2-methyl AP-237 was also described as a white solid (4).

G. WHO review history

2-Methyl Ap-237 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:

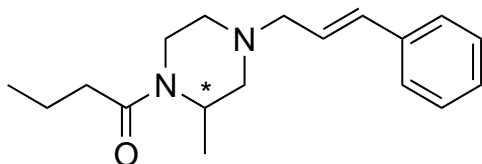
1-{2-Methyl-4-[(2E)-3-phenylprop-2-en-1-yl]piperazin-1-yl}butan-1-one

Chemical Abstracts Service index name:

1-Butanone, 1-[2-methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-

B. Chemical structure

Free base:



Note: Asterisk (*) refers to a chiral centre

Molecular formula: C₁₈H₂₆N₂O

Molecular weight: 286.41 g/mol

C. Stereoisomers

The presence of a chiral centre at the 2-position of the piperazine ring gives rise to the enantiomeric pair of (*S*)-2-methyl AP-237 and (*R*)-2-methyl AP-237. 2-Methyl AP-237 is most likely to be available as the racemic mixture, although the occurrence of individual stereoisomers cannot be excluded. The presence of the double bond in the *N'*-cinnamyl group reflects a stereoisomeric olefin that could give rise to an (*E*)- and a (*Z*)-isomer.

D. Methods and ease of illicit manufacture

No specific information on routes of synthesis used for 2-methyl AP-237 products circulating on the market was found. The chemistry of producing 2-methyl AP-237 and related substances is straightforward and lends itself easily to small and large-scale manufacture. One method published in the literature involves use of racemic 2-methylpiperazine to which cinnamyl chloride is added to give the cinnamyl-piperazine intermediate. This intermediate is then acylated with butanoyl chloride (1, 2) to give 2-methyl AP-237. Other routes are also possible, such as use of variations used for the synthesis of the demethyl analogue AP-237 buccinazine (e.g., 5, 6).

E. Chemical properties

Melting-point

211–213 °C (hydrochloride salt) (1, 2)

Boiling-point

No information was found.

Solubility

2-Methyl AP-237 hydrochloride was reported to be soluble in dimethylformamide (10 mg/mL), dimethyl sulfoxide (15 mg/mL), ethanol (30 mg/mL) and phosphate-buffered saline (pH 7.2; 10 mg/mL) (7). A collected sample of 2-methyl AP-237 hydrochloride was reported to be soluble in dichloromethane, methanol and water (8).

F. Identification and analysis

Identification of 2-methyl AP-237, especially when it is available in larger quantities than are usually available for forensic toxicological work, is straightforward. Analysis of biological samples requires adequate separation techniques and sensitive analytical methods, such as gas or liquid chromatography coupled to (tandem) high- and low-resolution mass spectrometry. 2-Methyl AP-237 is available as a certified reference material, and some analytical data have been reported in the scientific (and patent) literature, including melting-point and elemental analysis, infrared spectroscopy, chromatography and mass spectrometry (1, 2, 9–11). In synthetic blood samples spiked with a mixed standard containing *para*-fluorofuranylfentanyl, U-48800, isotonitazene, etonitazene, metonitazene, phenylfentanyl, tianeptine, 2-methyl AP-237 and *para*-methylacetylfentanyl, cross-reactivity was observed on common enzyme-linked immunosorbent assay testing kits (Immunalysis Opiates, Oxycodone/Oxymorphone, Fentanyl and Buprenorphine Direct ELISA kits) (12). Some analytical information, including chromatographic, mass spectral, spectroscopic and presumptive spot test data, is available in the public domain (4, 8, 13–16). No information was found on differentiation of the two enantiomers, and not all laboratories might be able to do so routinely. As the two olefinic protons on the *N'*-cinnamyl group are most likely to be in the (*E*)-configuration, the (*Z*)-form would constitute another isomer; however, no information was found about this isomer.

3. Ease of conversion into controlled substances

2-Methyl AP-237 cannot be converted into other substances under international control.

4. General pharmacology

A. Routes of administration and dosage

Descriptions on online forums suggest that 2-methyl AP-237 is typically administered orally (e.g., 17, 18) and by nasal insufflation (snorting) (e.g., 19, 20), although smoking (e.g., 20, 21), sublingual (22) and rectal administrations (e.g., 23) have also been described. In a case of non-fatal intoxication, 2-methyl AP-237 was administered with a nasal spray containing the drug dissolved in water (9, 24) (section 6). The “caustic” properties (e.g., “caustic burn”) of 2-methyl AP-237 are mentioned frequently, indicating unpleasant sensations associated with certain routes of administration (e.g., gastric problems after oral ingestion or burning sensations after snorting).

“Typical” dosages depend on factors such as the route of administration, the tolerance of users, use of other drugs and the desired effects. Given the difficulty of collecting such data, the doses cited below should be viewed with caution. For example, the following dosage ranges have been described for smoked 2-methyl AP-237: low (5–15 mg), common (15–30 mg), strong (30–50 mg), heavy (> 50–60 mg) and overdose threshold (~80 mg) (20). Oral doses of 7–50 mg have been reported, but several administrations and higher oral doses have also been described (e.g., 18, 25).

B. Pharmacokinetics

No clinical studies were identified. Incubation of 2-methyl AP-237 with human liver microsomes resulted in the detection of four monohydroxylated phase-I metabolites (15, 16).

Some people believed to have taken 2-methyl AP-237 considered that the effects were relatively short-lived (e.g., 18, 22, 26).

C. Pharmacodynamics

2-Methyl AP-237 was found to bind to MOR with appreciable affinity ($K_i = 12.9$ nM) and high selectivity over the δ ($K_i = 2910$ nM) and κ subtypes ($K_i = 5259$ nM) (27) (Table 1). The binding affinities of DAMGO, fentanyl and morphine were 42, 21 and 18 times higher, with K_i values < 1 nM.

Table 1. Receptor binding and functional activity of 2-methyl AP-237

MOR	2-Methyl-AP-237	DAMGO	Fentanyl	Morphine	Naltrexone
[³ H]DAMGO binding					
K_i (nM)	12.9 ± 2.7	0.304 ± 0.034	0.620 ± 0.033	0.730 ± 0.090	0.156 ± 0.012
IC ₅₀ (nM)	82 ± 19	–	–	–	–
[³⁵ S]GTPγS binding					
Stimulation EC ₅₀ (nM)	620 ± 180	25.2 ± 2.3	27.9 ± 4.2	41 ± 10	–
Maximal stimulation (%)	46.7 ± 5.3	100	92.1 ± 2.0	77.0 ± 4.3	–
DOR	2-Methyl-AP-237	DPDPE-OH	Fentanyl	Morphine	Naltrexone
[³ H]DPDPE binding K_i (nM)	2910 ± 390	3.18 ± 0.68	292 ± 40	222 ± 30	19.3 ± 4.3
IC ₅₀ (nM)	5020 ± 710	–	–	–	–
[³⁵ S]GTPγS binding					
Stimulation EC ₅₀ (nM)	> 10 000	7.1 ± 1.1	1330 ± 270	970 ± 280	–
Maximal stimulation (%)	18.40 ± 0.50	102.7 ± 2.7	69.1 ± 7.6	80.0 ± 1.3	–
KOR	2-Methyl-AP-237	U50,488H	Fentanyl	Morphine	Nor-BNI
[³ H]U-69,593 binding K_i (nM)	5259 ± 90	0.320 ± 0.054	187 ± 21	43.1 ± 9.7	0.169 ± 0.055
IC ₅₀ (nM)	8490 ± 610	–	–	–	–
[³⁵ S]GTPγS binding					
Stimulation EC ₅₀ (nM)	1750 ± 590	0.53 ± 0.19	379 ± 97	78 ± 18	–
Maximal stimulation (%)	36.5 ± 5.4	99.7 ± 1.4	86.4 ± 4.7	91.5 ± 3.4	–

Adapted from reference 27

DOR, δ opioid receptor; KOR: κ opioid receptor; MOR: μ opioid receptor.

Transfected Chinese hamster ovary (CHO) cells expressing human δ - and κ -opioid receptors and rat μ -opioid receptors were used in receptor binding experiments. The standard compounds were the agonists DPDPE (δ), U50,488H (κ), DAMGO (μ), morphine and fentanyl, and the antagonists were naltrexone (δ and μ) and nor-BNI (κ). The results include the standard error of the mean.

[³⁵S]GTPγS binding: maximal stimulation by test compound normalized to the maximal stimulation by DPDPE (δ), U50,488H (κ) or DAMGO (μ) above basal.

In an in-vitro GTPγS binding assay, 2-methyl AP-237 activated MOR with low efficacy ($E_{max} = 46.7\%$ when compared with DAMGO) and potency ($EC_{50} = 620$ nM). DAMGO, fentanyl and morphine were 25, 22 and 15 times more potent. When compared with DAMGO, fentanyl and morphine activated MOR with an efficacy of 91.1 and 77.0% (27) (Table 1). Relatively low

potency was also observed in MOR activation assays with β -arrestin 2 or mini-G_i signalling (Table 2).

Table 2. Results for β -arrestin 2 and mini-G_i-mediated signalling

Compound	B-arrestin 2 (EC ₅₀ / nM)	E _{max} (%)	Mini-G _i (EC ₅₀ / nM)	E _{max} (%)	Reference no.
2-Methyl AP-237	2229	109	2229	142	28
	749	125	–	–	9
Hydromorphone	51.0	100	44	100	28
	26.9	98.6	–	–	9
Fentanyl	14.3	163	32.7	284	28
	23.1	187	–	–	9
For 2-methyl AP-237, an EC ₅₀ value of 568 nM was reported in an AequoScreen® assay (Perkin Elmer) with recombinant CHO-K1 cells expressing human MOR.					Cited in reference 28 as a personal communication

Source: reference 28

The analgesic effects of 2-methyl AP-237 have been studied in mice, and it was found to have antinociceptive properties when tested for peripheral and central effects (Tables 3 and 4). In the writhing test (Table 3), 2-methyl AP-237 was active at all doses in some of the tested animals. The activity of 2-methyl AP-237 was considered slightly greater than that of acetylsalicylic acid and phenylbutazone but slightly lower than that of dextropropoxyphene at an s.c. dose of 20 mg/kg.

Table 3. Analgesic properties of 2-methyl AP-237 in the *para*-phenylbenzoquinone test (“abdominal constriction response” and “writhing test”)

Compound	Dose (mg/kg)	No. of animals exhibiting contortions	Mean no. of contortions
Control	–	18/18	21.8 ± 2.6
2-Methyl AP-237	100 oral	2/6	5.5 ± 1.4
	50 oral	3/6	3.3 ± 0.6
	25 oral	4/6	11.5 ± 7.0
Acetylsalicylic acid	100 oral	4/6	13.5 ± 11.1
Phenylbutazone	100 oral	3/6	2.7 ± 1.5
	50 oral	5/6	11.4 ± 11.0
Dextropropoxyphene	20 s.c.	2/6	2.5 ± 2.1

From references 1 and 2

Groups of six male CD-1 albino mice weighing 25–30 were given *para*-phenylbenzoquinone (0.2 mg/mL) intraperitoneally 30 min after oral administration of the test drug. Contortions observed in the next 20 min were counted.

In the hotplate test, 2-methyl AP-237 increased response latency before nocifensive behaviour at all tested doses (Table 4).

Table 4. Analgesic properties of 2-methyl AP-237 in the hot plate test

Compound	Dose (mg/kg)	Reaction times (s)		
		Basic (s)	After 30 min	After 60 min
2-Methyl AP-237	100 oral	9.3	>42	34
	50 s.c.	9.7	>60	>58
	25 s.c.	6.0	34.3	25.7
	10 s.c.	10.3	19.7	5.3
Dextropropoxyphene	20 s.c.	6.9 ± 7.0	13.8 ± 1.2	–
	10 s.c.	7.5 ± 0.7	14.4 ± 2.5	–

Source: references 1 and 2

Female CD-1 albino mice (20–25 g); plate temperature kept at 54.5 °C. Reaction time (s) measured when an animal showed obvious symptoms of pain in its rear paws (paws trembled and withdrawn backwards or licked). The reaction time for a normal mouse was 5–13 s. Basic reaction time measured twice for each animal at an interval of 15 min; test drug administered after a further 15 min; reaction time again measured 30 min and 60 min after treatment.

In a separate study, 2-methyl AP-237 was tested in the warm water tail-flick assay in 10 Swiss-Webster mice to evaluate its analgesic effects (29). A cumulative dosing procedure was used, followed by a time-course study of the peak effect. Mice were tested for baseline tail withdrawal latency in 50 °C water, followed immediately by s.c. injection of the vehicle (0.9% saline). After 15 min, tail-withdrawal latency was re-determined in each mouse, followed immediately by injection of the lowest dose of 2-methyl AP-237. Testing continued with increasing cumulative doses until the mouse failed to remove its tail from the water before the 10-s cut-off time (maximum antinociception) or until toxic effects (e.g., respiratory depression, convulsions) were observed. Tail-withdrawal latencies were transformed into percentages of the maximal possible effect (% MPE).

2-Methyl-AP-237, tested at doses of 0.1–3.2 mg/kg (ED_{50} = 0.078 mg/kg), dose-dependently increased tail-flick latencies to a maximum of $99 \pm 1\%$ MPE. The ED_{50} for the morphine standard was 0.38 mg/kg. The maximum peak effect of morphine (E_{max}) was 100% MPE. The ED_{50} for the fentanyl standard was 0.063 mg/kg, and the maximum peak effect of fentanyl (E_{max}) was 98% MPE. The peak analgesic effects of 2-Me-AP-237 lasted 45 min and returned to baseline within 135 min. Naltrexone (1 mg/kg) blocked the analgesic effects of 2-Me-AP-237, reducing the tail-flick latency to $30 \pm 4\%$ MPE (29). These results suggest that 2-methyl AP-237 is as potent as fentanyl and more potent than morphine in this assay.

5. Toxicology

No toxicology studies in humans were identified. In male and female CD-1 mice (25–40 g), acute toxicity was tested after intravenous, oral and s.c. administration. The reported LD_{50} values were 55 mg/kg (intravenous), 350 mg/kg (oral) and 550 mg/kg (s.c.) (1, 2).

Furlan (1, 2) reported the following observations after intravenous administration: “at 70 mg/kg and in those animals that died at 60 mg/kg, immediate tonic convulsions with stiffening of the tail, increase in body tone, gasping, subsequent loss of posture and death due to respiratory blockage under complete muscular relaxation, within a few minutes after treatment: at 50 mg/kg, immediate jumping with tonic convulsions, dyspnea and gasping, stiffening of the body and tail, and an increase in the tone of the limbs. Touching produced brief tonic-clonic convulsions of low intensity, followed by violent jumping and excessive reaction to environmental stimuli, and central analgesia with Straub tail. Exophthalmos was not observed in these animals. At lower doses, immediately after inoculation, jumping and psychomotor excitement, loss of posture, stiffening of the tail and limbs, dyspnea, abnormal walking, stereotypy and strong central analgesia”.

Furlan (1, 2) reported the following observations after oral and subcutaneous administration: “at 1000 mg/kg (oral and subcutaneous administration), immediately after inoculation animals showed psychomotor excitement with Straub tail, and contracting of the limbs which determines abnormal walking. Animals remained immobile lying on their back or on their side, with their limbs hypertonic; reacted positively to acoustic stimuli with brief tonic convulsions, and dyspnea; mortality observed between the 6th and 16th hour following treatment. There was an analogous symptomatology at the lower doses, and cyanosis was observed at the tail and ear vessels. For equal doses the effects were much more evident with oral administration. A certain central analgesia persisted up to three hours following treatment”.

6. Adverse reactions in humans

Cases of 2-methyl AP-237 Intoxication in humans

The Early Warning Advisory Tox-Portal of the United Nations Office on Drugs and Crime (UNODC) lists two post-mortem cases involving detection of 2-methyl AP-237 (30). One case was reported from Sweden in July 2019, with a concentration of 46 ng/mL in femoral blood. SL-164 (dicloqualone) was also detected but not quantified. No further information was available. The second case, notified by the USA, occurred in May 2021. 2-Methyl AP-237 and bromazolam were detected in blood (vena cava) but were not quantified, and no further information was provided. In both cases, the relative or probable contribution of the drug was listed as “contributory – medium”.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), two countries reported detection of 2-methyl-AP-237 in biological samples related to serious adverse events between 2019 and 2020, with one sample associated with a death and one associated with acute poisoning. No further details were available (31).

The WHO ECDD Secretariat received data from the US Centers for Disease Control and Prevention’s State Unintentional Drug Overdose Reporting System from the US Office of National Drug Control Policy. The data are from death certificates, post-mortem toxicology testing and death scene and witness findings from medical examiner or coroner reports on deaths due to unintentional drug overdose and those of undetermined intent in 48 participating jurisdictions, with comprehensive details not available from other data sources. 2-Methyl AP-237 was listed as the cause of death in 11 cases between January 2020 and June 2021. During the same period, 2-methyl AP-237 was detected in 10 fatal cases, but no information was available to assess whether this drug had contributed to the deaths.

The WHO ECDD Secretariat received copies of redacted autopsy reports in which 2-methyl AP-237 and other substances were detected. In one case from San Diego (CA, USA), a 28-year-old man was found dead in a motel, with loose pills and drug paraphernalia. Toxicological analyses revealed 2-

methyl AP-237 (1.0 mg/L, peripheral blood), quetiapine (0.4 mg/L), citalopram (0.28 mg/L), propranolol, desmethylcitalopram, etizolam and mitragynine. A blue tablet found at the scene was found to contain etizolam. An orange residue found in a “baggie” contained propranolol, and white powder found in a capsule contained 2-methyl AP-237. The death was ruled as an accidental acute drug intoxication (overdose) due to the combined acute toxic effects of 2-methyl AP-237, etizolam, mitragynine, citalopram and quetiapine. There was no evidence of suicidal intent. This case may be one of those reported by the DEA (32, 33).

In another case, a 26-year-old man was found unresponsive in a restroom at his workplace in Texas (USA). Used syringes and an empty vial of 2-methyl AP-237 were present at the scene. Analyses of blood samples revealed 2-methyl AP-237 (1400 ng/mL) and fluconazole (positive). Synthetic opioid toxicity (2-methyl AP-237) was ruled as the cause of death, and the manner of death was determined to be accidental.

The WHO ECDD Secretariat also received a number of reports of toxicological analyses of biological samples carried out on behalf of the DEA, which included detection of 2-methyl AP-237 and other substances. Further details (e.g., clinical vs post-mortem) were only available in some cases (Table 5); however, some of the cases may have also been reported by the DEA elsewhere (32–34).

Table 5. Substances detected in biological samples analyzed for the US Drug Enforcement Administration, 2020–2021

Date	Sample	Substances detected (ng/mL)
June 2020	Serum	Sample origin: Seattle (WA, USA). 2-Fluoro-deschloroketamine (5.0), 2-fluoromethamphetamine (10.3), 2-methyl AP-237 (13.5), 5-MAPB (109), mitragynine (185), 7-hydroxy-mitragynine (22.9), etizolam (6.8), fentanyl (11.4), norfentanyl (4.5), flualprazolam (9.5), MDMA (181), HMMA (1.7), MDA (74.3), morphine (1.5), promethazine. This fatal case may be one of those reported by the DEA (32, 33). No more information was available.
January 2021	Whole blood	Sample origin: Olathe (KS, USA). 2-Methyl-AP-237 (141), etizolam (4.5), lidocaine, alprazolam, α -hydroxy alprazolam. This may be the case reported by Samano et al. (35), but further confirmation is required. It may also be one of the cases reported by the DEA (32–34). No more information was available.
March 2021	Whole blood	Sample origin: Omaha (NE, USA). 2-Methyl-AP-237 (208.1), cocaine (0.9), benzoylecgonine (86.5), ecgonine methyl ester (23.7), 11-nor-9-carboxy-delta 9-THC (111), methadone (1.1), EDDP (0.8), alprazolam. This fatal case may be one of those reported by the DEA (32–34). No more information was available.
April 2021	Whole blood	Sample origin: Richmond (VA, USA). 2-Methyl AP-237 (141.0), bromazolam (94.7), desalkylfurazepam (65.0), oxycodone (1.6), benzoylecgonine (28.8), diphenhydramine.
June 2021	Whole blood	Sample origin: Bellingham (WA, USA). 2-Methyl AP-237 (313), mitragynine (0.8), citalopram (2.2), fluoxetine (7.5), norfluoxetine (300), naloxone. A previous toxicological analysis by an alternative provider showed the presence in central blood of citalopram/escitalopram (100 ng/mL), norfluoxetine (710 ng/mL), δ -9-THC (4.1 ng/mL) and δ -9-carboxy-THC (48 mg/mL), naloxone (positive). A 22-year-old man was found dead. He had a history of substance use disorder and was reported to have purchased increasing quantities and strengths of narcotics on the Internet. Autopsy revealed acute cardiorespiratory failure with

marked pulmonary oedema filling his lungs, airways and endotracheal tubes. Cause of death: mixed drug intoxication with 2-methyl AP-237, mitragynine, citalopram, fluoxetine, norfluoxetine, naloxone. Manner of death was ruled suicide.

August 2021	Plasma	Sample origin: Wilmington (DE, USA). 2-Methyl AP-237 (171), benzoylecgonine (4.7), lorazepam (876), lormetazepam (28.5), clonazepam (1.5), nordiazepam (0.8), naloxone, clonazepam, dextromethorphan, meprobamate.
August 2021	Urine	Same case, different matrix. 2-Methyl AP-237, cocaine (12.7), benzoylecgonine (322), ecgonine methyl ester, lorazepam, lormetazepam (1570), 7-aminoclonazepam, naloxone, dextromethorphan, dextrorphan, gabapentin, phenibut, nordoxepin.
September 2021	Whole blood	Sample origin: Kansas City (KS, USA). 2-Methyl AP-237 (379), δ -9-THC (56.8), 11-nor-9-carboxy- δ -9-THC (141), 8-amino clonazepam (4.6), <i>O</i> -desmethyl- <i>cis</i> -tramadol (10.9), mitragynine (2.7), 7-amino clonazepam, diphenhydramine, fluoxetine, norfluoxetine, trazodone, mCPP, propranolol.

^a Analyses carried out by the Clinical Toxicology and Environmental Biomonitoring Laboratory at the University of California, San Francisco (CA), USA. Information on whether the cases were clinical or post-mortem cases (or both) was not provided.

According to the DEA (33), two fatal intoxications involving 2-methyl AP-237 were reported in King County (WA, USA). The presence of 2-methyl AP-237 was confirmed in drug samples. A white powder was found near the body at one scene, and the other was associated with what appeared to be counterfeit Xanax bars. No further information was reported. In January 2021, an overdose death attributed to 2-methyl AP-237 was reported in Kansas (SA). Evidence at the scene indicated that the victim encapsulated 2-methyl AP-237 powder into clear capsules prior to death (33).

Trend reports are published by the Center for Forensic Science Research & Education (PA, USA) that provide summaries of drug detections, predominantly in biological samples during toxicological case work. Table 6 summarizes detections published quarterly. No more details on the toxicological cases could be obtained.

Table 6. Positivity rates for 2-methyl AP-237 in samples submitted for analysis to the Center for Forensic Science Research & Education

Year		2-Methyl Ap-237		Total number ^a
		No.	%	
2020	Q2	1	0	775
2020	Q3	3	0	626
2020	Q4	5	1	714
2021	Q1	0	0	454
2021	Q2	6	1	584
2021	Q3	10	1	851
2021	Q4	1	0	621
2022	Q1	2	0	710
2022	Q2	2	1	342

Courtesy of Dr Alex J. Krotulski (Center for Forensic Science Research & Education, Fredric Rieders Family Foundation, Willow Grove (PA), USA).

^a The total included other substances, such as fentanyl, methamphetamine, cocaine, MDMA, eutylone, metonitazene, α -PiHP/ α -PHP and dimethylpentylone.

Scientific literature: non-fatal cases

A 20-year-old man was admitted to intensive care after snorting a substance reported as a synthetic opioid, with worsening dyspnoea 48 h after ingestion. Investigations revealed an acute pulmonary syndrome referred to as a “crack-lung”, involving diffuse ground-glass opacities and acute dyspnoea. The investigation showed bilateral parenchymal ground-glass opacity, mainly with bilateral near-hilum distribution and mediastinal widening. The patient received symptomatic treatment for 72 h and was discharged after 10 days. Blood analysis (25 ng/mL) showed the presence only of 2-methyl AP-237 (36).

A 31-year-old man was found unresponsive at home with respiratory depression after using a nasal spray containing 2-methyl AP-237 (1 g/30 mL) 4 h earlier. Administration of naloxone (0.4 mg intravenously, then 0.8 mg) improved his respiratory and mental status. In the emergency department, he was found to be somnolent but arousable and oriented. The patient reported having ingested methadone earlier in the day and reported long-term use of benzodiazepines. The opioid intoxication symptoms resolved approximately 24 h after reported use. Analyses of whole blood showed 2-methyl AP-237 (peaking at 35 ng/mL about 7 h after nasal administration). Other substances detected included clonazepam (63 ng/mL), pyrazolam (4200 ng/mL), mitragynine, *O*-desmethyltramadol, eutylone and methadone (24). The same case was reported twice elsewhere (9, 37). The patient was reported to have a history of use of 2-methyl AP-237. The blood concentration on admission was reported to be 21 ng/mL. Other substances identified were *O*-desmethyltramadol, eutylone, naloxone, pyrazolam, methadone, 7-aminoclonazepam, etizolam, caffeine, mitragynine, 7-hydroxymitragynine and clonazepam (9).

In a case report of suspected 2-methyl-AP-237 intoxication, a 24-year-old man was found unresponsive and hypoxic at home. Naloxone was administered, and the patient regained consciousness and was transported to an emergency department. The urine drug screen was negative, and supportive treatment was recommended. No details on the analysis of biological samples confirming the detection of 2-methyl AP-237 were reported (38).

Scientific literature: fatal cases

A 29-year-old man was found unresponsive at home. A white substance, a scale and other paraphernalia were found at the scene. Femoral blood contained alprazolam (41.1 ng/mL) and etizolam (19 ng/mL), and qualitative analyses showed naloxone, caffeine and cotinine. The urine also contained alprazolam and α -hydroxyalprazolam. The white crystalline powder found on the scene was tested and identified as 2-methyl AP-237. An investigation performed by the reference laboratory provided qualitative identification of 2-methyl AP-237 in femoral blood in two separate aliquots. Autopsy revealed moderate-to-marked pulmonary oedema, constipation and cerebral oedema with uncal herniation. No natural disease was considered to have accounted for death (35). This case was reported from the Johnson County Medical Examiner’s Office in Olathe (KS, USA). Confirmation is required of whether this is the same case reported above.

A 54-year-old man was found dead under a tree. A plastic container labelled “2MAP” and a cut straw were found in the decedent’s backpack. Field-testing showed that a white powder in the plastic container and the straw were positive for fentanyl. The decedent had a history of

depression, shoulder pain and early signs of dementia. His medical history revealed he had been treated for a drug overdose in October 2018. The concentrations of 2-methyl AP-237 in blood and urine were 480 ng/mL and 4200 ng/mL, respectively. Alprazolam was also detected in blood, at 55 ng/mL (39).

A summary was published of four fatal cases with detection of 2-methyl AP-237 and other substances (9) (Table 7). The cases were received between February 2020 and April 2021. Post-mortem blood concentrations were reported to range between 820 and 5800 ng/mL.

Table 7. Fatal cases with detection of 2-methyl AP-237 and other substances

Age (years), sex	Comments
29/M	Decedent discovered unresponsive at a “sober living” facility. 2-Methyl AP-237 concentration in blood: 5800 ng/mL. Caffeine, cotinine, quinine, naloxone, trazodone, phenibut (77 000 ng/mL) were also found. Further details of this case were presented elsewhere (40). The deceased had a history of nonmedical benzodiazepine and gabapentin use, chronic gastrointestinal problems, back pain and depression. The previous evening, the decedent had appeared drowsy, and his roommate had helped him to bed. When the roommate woke in the morning, he saw a bloody purge emanating from the decedent’s nose and called the emergency services. Naloxone was administered without improvement, and death was pronounced on the scene. The “sober living” supervisor noted that residents underwent weekly drug testing and the decedent had tested negative 2 days before his death. A white powder collected at the scene was identified as 4-phenyl-2-pyrrolidinone, and pill fragments collected from the small intestine at autopsy revealed 4-phenyl-2-pyrrolidinone, menthol and nicotine. 4-Phenyl-2-pyrrolidinone is an acidic compound and was not detected in a comprehensive in-house panel of blood specimens, which does not include extraction for acidic drugs. Research showed that this compound is the cyclic product of phenibut created at high temperatures. The cause of death was certified as the combined effects of 2-methyl AP-237 and phenibut, and the manner of death was listed as accidental.
35/M	The individual was found dead in a car in a ditch. 2-Methyl AP-237 was found (ng/mL) in: blood (1100), urine (5000) and vitreous humor (270). Also detected were caffeine, carisoprodol (840), meprobamate (7300), δ -9-THC (1.1), carboxy-THC (6.1), promethazine (33), amphetamine (8.9), methamphetamine (45), etizolam (22), meclonazepam (26), 2-FDCK and 3-HO-PCP.
29/M	The man had a history of purchasing drugs on the black market, including 2-methyl AP-237. 2-Methyl AP-237 was detected (ng/mL) in blood (820) and urine (1600). Other substances detected were caffeine, cotinine, naloxone, 7-aminoclonazepam (37), THCOH (3.5), THCCOOH (57), THC (9), tadalafil (49), amphetamine (15) and mitragynine (32).
Unknown	The decedent had a bag labeled 2-methyl AP-237 in their hand. The 2-methyl AP-237 concentration in blood was 1400 ng/mL. Other substances detected were naloxone, trazodone and hydroxyzine.

Source: references 9

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No clinical studies on withdrawal from or physical dependence on 2-methyl AP-237 were identified. Self-reports by people who reported having used 2-methyl AP-237 suggest that regular consumption is associated with the development of tolerance and withdrawal in some cases (e.g., 22, 26, 41).

8. Abuse potential

A. Studies in experimental animals

Drug discrimination: In a two-lever discrimination task was given to nine male Sprague-Daley rats that had received a morphine sulfate training dose of 3.2 mg/kg in a fixed-ratio (FR10) schedule of reinforcement, 2-methyl AP-237 (test doses, 0.1–1 mg/kg) fully substituted ($ED_{50} = 0.25$ mg/kg) for the discriminative stimulus effects of morphine ($ED_{50} = 1.08$ mg/kg). The ED_{50} for a fentanyl standard was 0.0042 mg/kg. The peak morphine-appropriate response (E_{max}) was $92 \pm 5\%$. The response rate was decreased to 39% that of the vehicle control after 1 mg/kg of 2-methyl AP-237. Naltrexone (1 mg/kg) blocked the morphine-like discriminative stimulus effects of 2-methyl AP-237, reducing the morphine-appropriate response to $12 \pm 11\%$ (42).

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 WHO Model Lists of Essential Medicines

2-Methyl AP-237 is not listed on the 22nd WHO Model List of Essential Medicines or the 8th WHO list of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No information was found.

13. Non-medical use, abuse and dependence

No epidemiological evidence was found in household surveys of use of 2-methyl AP-237. Detection of 2-methyl AP-237 in biological fluids confirms that this substance is used recreationally

(intentionally or unintentionally). Information from Internet forums suggests that people who use heroin, prescription opioid analgesics and other synthetic opioids also use this substance. 2-Methyl AP-237 is available in its own right and is advertised for sale by some Internet retailers, including those operating on the “cryptomarket” (43). Current information suggests (sections 4 and 8) that 2-methyl AP-237 shows abuse liability and that this probably extends to dependence-producing properties comparable to those of other non-fentanyl synthetic opioids that are under international control.

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 were found on harm associated with 2-methyl AP-237. The detection of this substance in fatal and non-fatal intoxications (section 6) suggests poly-substance use in most cases; although fatal intoxications associated with 2-methyl AP-237 alone have been reported. No data were found on the effect of 2-methyl AP-237 on the ability to drive and operate machines. As it is well established that opioid analgesics affect the mental and physical ability required for driving and operating machinery, this is likely to extend to 2-methyl AP-237. People who inject opioids might also use synthetic opioid “research chemicals”; however, they may not be aware of the high potency of some synthetic opioids, which might increase the risk of life-threatening overdoses. The risk of poisoning may be greater with the unintentionally high doses that users may take, especially when combined with other substances, such as other opioid analgesics and other central nervous system depressants that can increase the risk of life-threatening respiratory depression. In a review of all fatal poisonings related to new synthetic opioids in Australia recorded in the National Coronial Information System between 2000 and 2021, 2-methyl AP-237 was identified in one of 31 cases (44). In a count of cases in 2019 (no details), 2-methyl AP-237 was listed among new synthetic opioids observed in case work recorded in Sweden (45). A data-mining exercise involving a retrospective analysis of raw data obtained on post-mortem cases and driving under the influence of drugs included four cases of use of 2-methyl AP-237. It was first detected in the USA in 2019 (46).

The US DEA’s Toxicology Testing Program, a surveillance programme for detecting new psychoactive substances in biological samples in the USA, reported two detections of 2-methyl AP-237 in the second quarter of 2021 (47); three detections in the third quarter of 2021 (with concentrations of 13.5 ng/mL in serum, 171 ng/mL in plasma and 141 ng/mL in blood) (48); one detection in the fourth quarter of 2021 (313 ng/mL in whole blood) (49) and two detections in the second quarter of 2022 (“313–379” ng/mL in whole blood) (50). It was not clear whether the two detections of 313 ng/mL 2-methyl AP-237, both reported in Washington State (49, 50) were the same. It was also unclear whether they were the same cases described in section 6.

In the USA, at least 10 confirmed cases of fatal poisonings and several reports of emergency room visits associated with 2-methyl-AP-237 (possibly including those reported in section 6) have been reported (51).

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

15. Licit production, consumption and international trade

2-Methyl AP-237 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

2-Methyl AP-237 was formally notified to the European Union Early Warning System Network on behalf of Sweden in April 2019 after a seizure during a house search on 29 January 2019 and a sample purchased on the Internet by the Public Health Agency of Sweden on 26 February 2019 (31). 2-Methyl AP-237 has been available on the drug market in Europe since at least 2019. Since it was formally notified, the EMCDDA has received reports of 31 seizures of 2-methyl AP-237. In seizures, 2-methyl AP-237 was mostly found as a powder (approximately 55% of all cases reported), although liquids (26% of cases) and tablets (13% of cases) were also reported. As of 15 July 2022, approximately 121 g of 2-methyl AP-237 had been seized in total; 109 g were in liquid form and 12 g were powders. All of the liquids were seized in 2019 (109 g in eight seizures), and approximately half of the powder was seized in 2019 (5.1 g in 12 seizures) (31).

The numbers of countries that reported detections of 2-methyl AP-237 to the UNODC Early Warning Advisory on new psychoactive substances database were eight in 2019, three in 2020, two in 2021 and two in 2022. In some instances, multiple entries from the same country were counted for the same year (52).

The National Forensic Laboratory Information System, which collects drug cases submitted by state and local laboratories in the USA, has registered detections of 2-methyl AP-237. The numbers of reports of 2-methyl AP-237 in the public domain were 21 in 2019 (the first time), four in 2020 and two in 2021 (as of June 2021). 2-Methyl-AP-237 was found alone or with other substances (53). The presence of 2-methyl AP-237 was confirmed in 27 samples submitted to the Forensic Laboratory Information System when queried on 27 May 2021 (34). On 21 May 2021, it stated that laboratories that report to the System had received 27 submissions on 2-methyl AP-237 since April 2019 (33). A total of 45 reports were received in 2021 (51).

The US Customs and Border Protection National Targeting Center compiled all known shipments of 2-methyl AP-237 to the USA between January 2019 and May 2021 (33). The shipments arrived in New York City (NY), Miami (FL) and Memphis (FL) from countries of origin identified as China, Germany, the Netherlands and Switzerland, with the majority from the Netherlands. The data indicate that most shipments were sent from Europe, although it was considered possible that the shipments originated from China or another country and were trans-shipped through Europe. While the report does not align precisely with those of the DEA, it identifies China as the origin of 63.8 g of 2-methyl AP-237 shipped to the USA in April 2020 (33).

In a study of trends in the listing of novel non-fentanyl synthetic opioids on one cryptomarket (43), 2-methyl AP-237 was identified as one of the most widely sold synthetic opioids between 1 June and 18 August 2020. A total of 136 listings were identified with 2592 sales transactions and 163 sales, for a total of 530.5 g sold. The average volume was 163.1 g (minimum, 0.5 g; median, 10 g; maximum, 100 g). The countries of origin were identified as Australia (52.4%), China (40.1%) and the USA (7.5%), and the destinations were Australia (52.4%), the world (40.1%) and the USA (7.5%).

A white powdered material found in a capsule ordered from an Internet retailer in China was found to contain 2-methyl AP-237 (13).

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

17. Current international controls and their impact

2-Methyl AP-237 is currently not controlled under the 1961, 1971 or 1988 United Nations conventions.

18. Current and past national controls

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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