ACMD

Advisory Council on the Misuse of Drugs

Acyl Piperazine Opioids, Including 2-Methyl-AP-237

Contents

1. Introduction

1.1. New synthetic opioids (NSO) have been identified as a substantial current international public health threat. As with traditional opioids such as heroin, these drugs activate μ opioid receptors, leading to dose-dependent adverse effects, including potentially fatal respiratory depression. They are also associated with a high potential for addiction and dependence.

1.2. In Europe, illicit opioid use primarily involves heroin derived from opium poppy cultivation in Afghanistan. As a result of the prohibition of opium poppy cultivation by the Taliban in April 2022, there has been a 95% reduction in the areas of Afghanistan cultivating opium poppies between 2022 and 2023. This has resulted in a 95% decline in both the opium harvested and heroin produced, from 6,200 tons and 350-580 tons respectively in 2022, to 333 tons and 24-38 tons respectively in 2023. [UNODC, 2023a]

1.3. There is increasing concern that the reduction in availability of heroin obtained from Afghanistan, if sustained, will result in the European and UK illicit opioid markets shifting to illicitly synthesised NSO. [EMCDDA, 2023a; Caulkins et al., 2024]

1.4. Fentanyl analogues (fentanyls) are highly potent NSO, responsible for a substantial number of deaths in North America over recent years. Fentanyls are often mixed with heroin to increase its potency, added to non-opioid drugs, or simply taken on their own. Consequently, legal steps have been deployed to control the production of fentanyl-related drugs and United Nations member states have subjected fentanyls and fentanyl precursors to international control. [Wang et al., 2022; CRS, 2023; White House, 2023]

1.5. Nevertheless, a reduction in fentanyl precursor availability may prompt illicit drug suppliers to seek alternative NSO, whose precursors are not yet captured by drug legislation [EMCDDA, 2023b], thus contributing to the highly dynamic and complex illicit drug market, increasingly populated with emerging NSO.

1.6. The Advisory Council on the Misuse of Drugs (ACMD) has recently provided advice to government on the potential risks to public health from the use of highly potent NSO, including fentanyl and fentanyl analogues [ACMD, 2020], and more lately the 2-benzyl benzimidazole (nitazene) and piperidine benzimidazolone (brorphine-like) opioids. [ACMD, 2022]

1.7. Acyl piperazine opioids, also referred to as cinnamylpiperazines or AP-series opioids, are a group of potent NSO [Barlocco et al., 1993], which have been recently detected in drug seizures internationally. [WHO, 2022]

1.8. Specific acyl piperazine opioids that have been detected in international drug markets or in overdose cases, include 2-methyl-AP-237, AP-237 (bucinnazine), AP-238, and para-methyl-AP-237 (Annex A). In addition, more complex, chemically bridged derivatives, such as azaprocin, have been reported in the scientific literature to be significantly more potent than

morphine as opioid agonists. [Cignarella et al., 1988] It is, therefore, appropriate at this time to consider the group as a whole.

1.9. The ACMD has therefore produced the following report to review the evidence of use and harms of 2-methyl-AP-237 and other acyl piperazine opioids and advise on appropriate legislative controls.

2. Legal Control

2.1. In the United Kingdom (UK), acyl piperazine opioids are not currently controlled under the Misuse of Drugs Act 1971. However, acyl piperazine opioids are psychoactive substances and subject to the Psychoactive Substances Act 2016 ("the PSA 2016"). The PSA 2016 makes it an offence to import, export, supply, and possess with intent to supply a psychoactive substance (with certain exceptions) where the person carrying out those actions knows, or is reckless as to whether, the psychoactive substance is likely to be consumed by some other person for its psychoactive effects. It also makes it an offence to possess psychoactive substances in a custodial institution. It should be noted, however, that compounds that meet the definition of a 'medicinal product' in Human Medicines Regulations of 2012 are exempted from the Act and this can include medicines licensed elsewhere in the world.

2.2. Following a critical review report on 2-methyl-AP-237 published by the World Health Organization's Expert Committee on Drug Dependence (ECDD) [WHO, 2022], the United Nations Commission on Narcotic Drugs (CND) announced the addition of 2-methyl-AP-237 to Schedule 1 of the 1961 Single Convention on Narcotic Drugs [WHO, 2023]. Consequently, many countries are in the process of considering or including 2-methyl-AP-237 to their national legislation, in accordance with the requirements placed on them as signatories of the UN Drug Conventions. The UN CND action obliges the UK, as a signatory, to consider and introduce appropriate legal control measures for this particular compound. Hence, the ACMD was commissioned by Government on 19 June 2023, to review the harms and consider control of 2-methyl-AP-237 and associated compounds, to comply with our international obligations.

2.3. Several countries have already introduced 2-methyl-AP-237 into their national drug control. For example, Sweden introduced this compound to their list of controlled drugs in June 2019 [General Counsel Pär Ödman, 2019]. Japan made 2-methyl-AP-237 a Designated Substance in November 2020 [MHLW, 2019], and Norway [Ministry of Health and Care Services of Norway, 2023] and Germany [Federal Republic of Germany, 2019] have controlled it as a narcotic drug.

2.4. In November 2023, Canada announced its intention to nationally control AP-237, its derivatives and analogues, which includes 2-methyl-AP-237, para-methyl-AP-237 and AP-238, by adding these compounds to Schedule 1 of their Controlled Drugs and Substances Act (CDSA) and to the Schedule to the Narcotic Control Regulations. This inclusion is anticipated for completion by Spring 2024. [Government of Canada, 2023]

2.5. Other countries are also addressing closely related acyl piperazines, with Italy controlling AP-238, in addition to 2-methyl-AP-237 and AP-237, in October 2021. [Ministry of Health of Italy, 2023]

2.6. Acyl piperazine opioids, such as 2-methyl-AP-237, are not currently approved for medical use in the United States of America (USA) and are not controlled under the Controlled Substances Act. [DEA, 2022]

3. Chemistry, Pharmacology and Toxicology

Chemistry

3.1. Acyl piperazines contain a piperazine core linked to a cinnamyl moiety (Annex A). The synthetic opioid MT-45, controlled under the Misuse of Drugs Act in 2015 following ACMD advice [ACMD, 2014], also contains a piperazine core but is otherwise structurally different.

3.2. Chemical modifications to the acyl piperazine structure of AP-237, that retain agonist activity at the μ opioid receptor, include piperazine ring substitution (e.g. 2-methyl-AP-237, AP-238), changes to the length of the acyl group (e.g. AP-238) and bridging of the piperazine ring (e.g. azaprocin) (Annex A).

3.3. AP-238, 2-methyl-AP-237, and para-methyl-AP-237 are structural isomers, with the same chemical formula and parent mass. However, their chemical properties and mass fragmentation patterns differ, allowing for differentiation during analytical testing. [CSFRE, 2020a; CSFRE, 2020b]

3.4. 2-Methyl-AP-237 incorporates a chiral centre at the 2-position of the piperazine ring (Annex A) which gives rise to a pair of enantiomers (mirror image compounds) designated (S)- and (R)-. 2-Methyl-AP-237 detected in recreational drug markets is likely to be a mixture of these enantiomers (racemic mixture).

3.5. Further complexity is introduced by the presence of a double bond in the cinnamyl group, which could also give rise to a pair of stereoisomers ((E)- and (Z)-). 2-methyl-AP-237 encountered in recreational drug markets is likely to be in the form of a racemate and in the (E)-form, although availability as individual stereoisomers cannot be excluded. [WHO, 2022]

3.6. Chemical syntheses of 2-methyl-AP-237, AP-237, para-methyl-AP-237, and AP-238, were originally patented in the 1980s, though compounds of this type have been known since the 1960s. [DEA, 2022] Methods for producing these drugs are relatively simple and adaptable to small- or large-scale manufacture. [WHO, 2022]

3.7. Azaprocin and para-nitroazaprocin are single ethylenic bridged acyl piperazines (Annex A). Other bridged acyl piperazine analogues are known, yet only the singly bridged acyl piperazine analogues (e.g. azaprocin) or analogues with the bridge between carbons 3 and 5, are straightforward to synthesise from readily available starting materials. [Cignarella et al., 1965]

Pharmacology

'In Vitro' Studies

3.8. AP-237, 2-methyl-AP-237, AP-238, para-methyl-AP-237 and azaprocin all bind to and activate the μ opioid receptor (i.e. they are μ receptor agonists). [Cignarella et al., 1988; Vianello et al., 2000; Vandeputte et al., 2020; Fogarty et al., 2022] AP-237, 2-methyl-AP-237 and azaprocin exhibit selectivity for the

μ receptor, over δ and κ opioid receptors. Of importance, these compounds activate the μ opioid receptor in a similar manner to the prototypical opioid agonists, morphine, and fentanyl.

3.9. The rank order of potency of acyl piperazines and fentanyl in an *in vitro* assay of μ receptor-mediated signalling was: fentanyl > AP-238 > 2-methyl-AP-237 >> AP-237 > para-methyl-AP-23. [Vandeputte et al., 2020; Fogarty et al., 2022] In addition, 2-methyl-AP-237 did not exhibit any bias (preference) for μ receptor-mediated G protein activation over β-arrestin 2 translocation. [Vandeputte et al., 2020]

'In Vivo' Studies

3.10. Studies in rodents have demonstrated analgesic effects of several acyl piperazines administered orally, subcutaneously, intramuscularly, or intraperitoneally. These include 2-methyl-AP-237, AP-237 and azaprocin [Carrano et al., 1975a; Carrano et al., 1975b; Furlan 1984; Justia Patents, 1984; Cignarella et al., 1988; Vianello et al., 2000]. The analgesic effects observed lasted for over an hour. When administered subcutaneously, 2-methyl-AP-237 was as potent as fentanyl and 5 times more potent than morphine [Gatch, 2021]. Likewise, azaprocin and para-nitroazaprocin were 5 and 15 times more potent than morphine, respectively, when administered intraperitoneally. [Cignarella et al., 1988]

3.11. In rats pre-exposed to morphine, 2-methyl-AP-237 fully substituted for the discriminative stimulus effects of morphine. In fact, 2-methyl-AP-237 was 4 times more potent than morphine in this behavioural test. [Gatch, 2021]

3.12. Self-administration experiments in rats have previously demonstrated a marked reinforcing effect for AP-237. Antagonist withdrawal precipitation tests in rats and mice pre-treated with AP-237, indicate physical dependence potential but with a potency lower than that of morphine. [Tao et al., 1986]

3.13. Various opioid receptor antagonists have been shown to reverse the behavioural effects of AP-237, 2-methyl-AP-237 and azaprocin. Previous studies have indicated that levallorphan antagonised the analgesic effect of AP-237, naltrexone antagonised the discriminative stimulus effect of 2-methyl-AP-237 and naloxone antagonised the analgesic effect of azaprocin. [Carrano et al., 1975b; Cignarella et al., 1988; Gatch et al., 2021]

3.14. The reported doses that would kill 50 % of animals (LD_{50} values) for AP-237 and 2-methyl-AP-237 in mice were similar, being 50 and 55 mg/kg (intravenously), 400 and 350 mg/kg (orally) and 625 and 550 mg/kg (subcutaneously) respectively [Furlan, 1984]. Nevertheless, how these murine lethal doses translate into humans remains uncertain.

3.15. No formal human pharmacokinetic studies on acyl piperazines have been identified, but psychoactive effects are reported to be short-lived. [WHO, 2022]

3.16. No human studies on withdrawal from or dependency on 2-methyl-AP-237 and other acyl piperazine opioids have been described. However, user reports suggest that regular use of 2-methyl-AP-237 is associated with tolerance and withdrawal symptoms. [WHO, 2022]

4. Legitimate Use

4.1. AP-237 (Bucinnazine), initially synthesised in Japan in 1968 [Irikura et al., 1968], has been licensed in China for treatment of pain in cancer patients since 1986, where it is referred to as Qiang Tong Ding. [Tao et al., 1986]

4.2. 2-methyl-AP-237 was first described in Italian drug patents filed in 1984 and 1985, alongside several other acyl piperazine opioids [Furlan, 1984]. None of these are currently licensed as medicines anywhere in the world.

4.3. Other than as reference standards; no other legitimate uses of acyl piperazines in the UK have been identified.

4.4. The Medicines and Healthcare products Regulatory Agency (MHRA) was consulted about the legitimate uses of the following compounds: AP-237, 2-methyl-AP-237, AP-238, para-methyl-AP-237. The MHRA confirmed that none of these compounds are authorised for medicinal use in the UK. Moreover, the MHRA have no record of the aforementioned substances being an Investigational Medicinal Product in a clinical trial, where the sponsor has applied to the MHRA for their clinical trial use. Because AP-237 is licensed as a medicine in China, it may meet the ‘medicinal product’ exemption if its formulation and presentation are consistent with medicinal use.

4.5. The ACMD does not have information on use of any of these compounds as unlicensed medicines or the possible use of bridge analogues in clinical trials.

5. Misuse

5.1. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) first reported the detection of 2-methyl-AP-237 in powder analysed in Slovenia during March 2019. Around the same time, this compound also emerged onto the synthetic drugs market in the USA, as evidenced by its identification in seized material in July 2019. [CSFRE, 2019a]

5.2. In the USA, the National Forensic Laboratory Information System (NFLIS) reported 21 detections of 2-methyl-AP-237 in 2019, 5 detections in 2020 and 48 detections in 2021 [DEA 2022]. In the third quarter of 2021, 2-methyl-AP-237 was the second most identified NSO (11 detections), behind fluorofentanyl (95 detections), by The Centre for Forensic Science Research and Education (CSFRE) in the USA. [CSFRE, 2021]

5.3. Capsules containing 2-methyl-AP-237 powder have been seized in the USA [DEA, 2022]. Typical oral doses usually range between 5 to 60 mg, but use of higher doses has been reported. [WHO, 2022]

5.4. 2-Methyl-AP-237 had been identified in overdose cases and involved in at least 10 deaths in the USA by the end of 2022. [WHO, 2022]

5.5. AP-237 was first notified to the EU Early Warning System in May 2019 [EMCDDA, 2019] and identified in USA-seized materials in August 2019. [CFSRE, 2019b]

5.6. AP-238 was detected in a post-mortem blood sample collected in the USA during August 2020 [CFSRE, 2020a], and also in a test purchase made in Slovenia in October 2020. [National Forensic Laboratory, 2019].

5.7. Para-methyl-AP-237 was first identified in November 2019 in material seized by the US Department of Homeland Security (DHS). [CSFRE 2020b]

5.8. There is no information available on detections of azaprocin in Europe or North America.

6. Health Harms

6.1. As a consequence of their μ opioid receptor agonist activity, the adverse effects of acyl piperazines are expected to be similar to those of heroin, fentanyls, and nitazenes. The most serious acute health risk is likely to be respiratory depression, which in overdose could lead to respiratory arrest and death. [WHO, 2022]

6.2. Non-fatal overdose cases involving 2-methyl-AP-237 have been reported. [WHO, 2022; Fogarty et al., 2022]. In one case, the clinical features included a pulmonary syndrome similar to 'crack lung'; this developed after nasal insufflation. However, the frequency of 2-methyl-AP-237 use prior to this incident was not reported. In several of the overdose cases administration of naloxone improved the patient's condition.

6.3. In the USA, 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 a further 10 fatal cases, but no information was available to confirm whether this drug had contributed to the deaths.

6.4. Deaths involving 2-methyl-AP-237 were also reported from Sweden in 2019 and Australia between 2020-2021. In many fatal and non-fatal episodes of poisoning, polysubstance use was apparent, however some fatal cases were associated with 2-methyl-AP-237 alone. [WHO, 2022]

6.5. In a study of 4 post-mortem cases in the USA, concentrations of 2-methyl-AP-237 were reported to range from 820 to 5800 ng/ml. Moreover, concentrations of AP-238 in another 2 post-mortem cases were 87 and 120 ng/ml, respectively. Of note, in all 6 cases other substances were also detected. Despite this, in a non-fatal case of 2-methyl-AP-237 intoxication, the measured concentration was 21 ng/ml. [Fogarty et al., 2022]

6.6. In samples of acyl piperazines obtained through unregulated sources, the identity, purity, and quantity of drug present would be inconsistent, thus posing significant potential adverse health risks to the end user.

6.7. The routes of administration for 2-methyl-AP-237 vary and are reported to include oral, nasal insufflation (snorting), smoking, sublingual, and rectal [WHO, 2022]. Additionally, since the compound is water soluble (hydrophilic), users may inject it intravenously, but the presence of contaminants may make this painful and damaging. In China, AP-237 (Bucinnazine) is administered orally or by subcutaneous injection to treat cancer pain.

6.8. On online discussion fora people who have used 2-methyl-AP-237 frequently describe it as being 'caustic', with mention of repeated use causing irritation and damage to the linings of the stomach and intestines following oral administration, and to the nasal septum after insufflation. This may be due to the presence of contaminants in illicitly synthesised drug samples, arising from the synthetic process or from adulterants (additives). The medical use of AP-237 in China to treat cancer pain does not appear to be associated with

tissue damage [Yu et al., 2016; Resnik et al., 2021]. This suggests that clinical use of this acyl piperazine does not cause tissue damage.

6.9. There is no information on the chronic health effects of acyl piperazine opioids, but these are likely to resemble those of established illicit opioids such as heroin, fentanyl and nitazenes, especially in relation to the development of addiction and dependence.

7. Social Harms

7.1. There is little evidence available on the social harms caused by acyl piperazine opioid use. Nevertheless, they are anticipated to elicit similar significant social harms to those of established illicit opioids such as heroin, fentanyls and nitazenes.

8. UK Prevalence

8.1. The ACMD engaged with a range of relevant stakeholders to gather evidence on acyl piperazine-related seizures, poisonings, and deaths. A list of stakeholders approached during this data request can be found in Annex B.

8.2. The ACMD received notification of one positive detection from the Defence Science and Technology Laboratory (DSTL) in 2022. DSTL identified a single occurrence and detection of AP-238 in 2022 and no other indications. The Forensic Early Warning System (FEWS) also confirmed there is a PSA statement report confirming the psychoactivity of 2-methyl-AP-237 and therefore it is controlled under the PSA 2016.

8.3. All other stakeholders contacted provided nil returns in response to the data request. However, it should be noted that the ACMD cannot confirm whether participants were testing for the aforementioned acyl piperazines during the period for which data was requested.

8.4. In the UK, screening, and chemical testing for acyl piperazines is extremely limited. Many laboratories do not possess appropriate resources to routinely check for acyl piperazines, plus these NSO are often not incorporated into post-mortem or law enforcement toxicological screening protocols, hence causing uncertainties in estimating the prevalence of their use.

9. Options For Legislation

9.1. The Working Group considered four options for legislation which are not all mutually exclusive.

9.2. **Option 1 – listing only 2-methyl-AP-237 for control under the Misuse of Drugs Act 1971**

Control of only 2-methyl-AP-237 under the Misuse of Drugs Act 1971 (MDA) would be compliant with the UN CND addition of 2-methyl-AP-237 to Schedule 1 of the 1961 Single Convention on Narcotic Drugs. [WHO, 2023]

The import, export, supply, and possession with intent to supply or in a custodial institution of other acyl piperazines that have agonist activity at the μ opioid receptor, will remain subject to the PSA 2016, with the exception of AP-237, which may be exempted if presented as a medicine. Monitoring would continue to detect any evidence of the misuse of acyl piperazine opioids. If other acyl piperazines begin to appear on the UK illicit drug market, their control under the MDA can be reconsidered.

9.3. **Option 2 – listing 2-methyl-AP-237 alongside specific, closely related acyl piperazine compounds that have appeared outside of the UK as NSO**

In addition to 2-methyl-AP-237, several other acyl piperazines have already been identified as synthetic opioid novel psychoactive substances (NPS) in other jurisdictions, this option would allow the control of 2-methyl-AP-237 and these other compounds under the Misuse of Drugs Act 1971. This option would also comply with the UN CND's addition of 2-methyl-AP-237 to Schedule 1 of the 1961 Single Convention on Narcotic Drugs [UNODC, 2023b] and extend classification and scheduling to other similar acyl piperazines. These compounds have appeared on the illicit drugs market, are known to have significant agonist activity at the μ opioid receptor and are associated with detrimental health harms.

i) 2-Methyl-AP-237 (1-[2-methyl-4-[2E]-3-phenyl-2-propen-1-yl]-1-piperazinyl-1-butanone)
ii) AP-237 (also known as bucinnazine) (1-[4-([2E]-3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone)
iii) para-methyl-AP-237 (1-[4-[2E]-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl-1-butanone)
iv) AP-238 (1-[2,6-dimethyl-4-[2E]-3-phenyl-2-propen-1-yl]-1-piperazinyl-1-propanone)

9.4. **Option 3 - To control chemically bridged acyl piperazine derivatives azaprocin and para-nitroazaprocin under the Misuse of Drugs Act 1971**

Although there is no evidence of misuse of azaprocin and para-nitroazaprocin at this time in the UK or elsewhere, they have the potential for serious health harms and are known to be potent, brain penetrant μ opioid receptor agonists. This option would extend control to acyl piperazines that are synthesised from different precursors from those listed in Option 2, and which penetrate the blood brain barrier and are potent agonists at the μ opioid receptor. Therefore, given their commensurate potency and relatively simple chemical synthesis, the compounds have the potential to become illicit drugs and would be expected to have similar detrimental health harms as other acyl piperazines opioid agonists.

9.5. **Option 4 - introducing generic controls, intended to 'future-proof' the legislation by covering known and predicted variants which appear likely to present significant risks of physical, mental, and social health harms.**

This option would introduce generic controls on acyl piperazine variants to cover 2-methyl-AP-237-related materials and new examples of substituted acyl piperazines that may be encountered, which are agonists at the μ opioid receptor and thus present a serious risk of harm.

Consultation with stakeholders, including academia and the chemical and pharmaceutical industries, would ensure that any proposed legislation does not produce unintended barriers to research or legitimate commercial activity. In the meantime, monitoring should continue to detect any evidence of the misuse of new acyl piperazine opioids.

10. Conclusions

10.1. There is a substantial risk that the recent Taliban ban on growing opium poppy for heroin production in Afghanistan will result in an increase in the appearance of new synthetic opioids, such as the acyl piperazines, in the UK illicit drug market.

10.2. Acyl piperazines are μ opioid receptor agonists that penetrate the central nervous system. They are therefore likely to cause dose-dependent adverse effects, including potentially fatal respiratory depression.

10.3. Repeated use of acyl piperazine opioids are likely to display abuse liability and have the potential for addiction and dependence, similar to that of heroin and synthetic opioids under international control.

10.4. In the UK, the involvement of acyl piperazines in non-fatal overdose cases may not yet be recognised, because detailed sample analysis is not a component of standard clinical care. Similarly, the association of acyl piperazines in fatal drug overdose cases may be missed if the presence of these drugs is not tested for routinely.

10.5. The potential emergence of these potent opioid agonists in the UK demonstrates the importance of a fully functioning UK-wide forensic early warning system.

10.6. In some instances, the opioid antagonist naloxone has been used and demonstrated subsequent clinical improvement. This is consistent with experimental evidence, indicating that it antagonises the behavioural effects of acyl piperazine opioids, as it does those of established opioids.

10.7. The ACMD has reviewed the current evidence available and considered four options for control in the report, including listing compounds by name and generic controls. Specifically listing currently identified compounds for control is the simpler approach, but risks being overtaken in the future by the development of further variants, an observation seen among other families of NPS. The acyl piperazine NSO that have been identified are as follows:

(i) AP-237 (bucinnazine), 2-methyl-AP-237, para-methyl-AP-237
(ii) AP-238
(iii) Azaprocin, para-nitroazaprocin

10.8. The ACMD advises that control of 2-methyl-AP-237 and closely related acyl piperazine compounds via the Misuse of Drugs Act 1971 is necessary. Due to the likelihood of further increases in their prevalence and the potential health and social harms associated with specific acyl piperazines, listing in Class A is recommended. In addition, listing in Schedule 1 of the Misuse of Drugs Regulations is recommended, given that 2-methyl-AP-237 and closely related acyl piperazine compounds have no medicinal use in the UK. AP-237 is licensed as a medicine in China so, following listing in Schedule 1, those legitimately prescribed AP-237 in that country would need an appropriate license to bring it into the UK.

10.9. The risk that substituted acyl piperazine compounds, other than those listed in paragraph 9.6, may be developed, and misused in the UK is unknown. In the absence of a generic control, these new compounds would not be classified under the Misuse of Drugs Act 1971, but examples with demonstrated psychoactive activity would be captured by the PSA 2016.

10.10. The ACMD consulted with an external stakeholder to check the proposed generic definition against a comprehensive chemical database, to assess the scope and likely impact of the statement. The returned hit rate result from the substructure search was minimal, suggesting that the potential impact and risk of this proposed generic causing any unintended impact on the pharmaceutical and chemical industry is likely to be low. Nevertheless, the Home Office would need to undertake a thorough consultation with the research community and industry stakeholders, should the generic definition be introduced.

11. Recommendations

Recommendation 1 (Option 2): The following named compounds which have appeared on the international illicit drug scene, should be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids.

As these materials have no medicinal use in the UK, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, to which Section 7(4) of the Misuse of Drugs Act 1971 applies. The control of the compounds should extend to include any stereoisomeric forms, any salts of such compounds and any preparation or product containing such compounds.

(i) 2-Methyl-AP-237 (1-[2-methyl-4-[2E]-3-phenyl-2-propen-1-yl]-1-piperazinyl-1-butanone)
(ii) AP-237 (1-[4-([2E]-3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) (bucinnazine)
(iii) para-methyl-AP-237 (1-[4-[2E]-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl-1-butanone)
(iv) AP-238 (1-[2,6-dimethyl-4-[2E]-3-phenyl-2-propen-1-yl]-1-piperazinyl-1-propanone)

Leads: Home Office

Measure of outcome: The inclusion of the listed compounds in Class A of the Misuse of Drugs Act 1971, Schedule 1 of the Misuse of Drugs Regulations 2001 and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001.

Recommendation 2 (Option 3): Consistent with the classification of other potent opioids, the following compounds should be added to Class A of the Misuse of Drugs Act 1971 as a short-term approach, due to their potencies as μ agonists, relative ease of synthesis and potential to become drugs of misuse.

As these materials have no medicinal use in the UK, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, to which Section 7(4) of the Misuse of Drugs Act 1971 applies.

(i) Azaprocin (1-[3-[(E)-3-phenyl-2-propen-1-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]propan-1-one)
(ii) para-nitroazaprocin (1-[3-[(E)-3-(4-nitrophenyl)-2-propen-1-yl]-3,8-diazobicyclo[3.2.1]octan-8-yl)propan-1-one)

Leads: Home Office

Measure of outcome: The inclusion of the listed compounds in Class A of the Misuse of Drugs Act 1971, Schedule 1 of the Misuse of Drugs Regulations 2001, and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001.

Recommendation 3 (Option 4): The ACMD recommends that a consultation should be undertaken with stakeholders, including academia and the chemical and pharmaceutical industries on the introduction of a generic control to cover 2-methyl-AP-237-related variants, as new examples may be encountered and could present a serious risk of harm.

Following this consultation, materials covered by the generic should be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids.

As these materials have no medicinal use in the UK, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001, to which Section 7(4) of the Misuse of Drugs Act 1971 applies.

The proposed wording for the generic for addition to the Misuse of Drugs Act is as follows:

*AP-237 (bucinnazine) (*1-[4-([2E]-3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone*) and any compound structurally derived from bucinnazine by modification in any of the following ways:*

(i) By substitution to any extent by methyl in the piperazine or phenyl rings.
(ii) By replacement of the butyryl group by another acyl group containing three, four or five carbon atoms.
(iii) By substitution in the phenyl ring by a nitro group.
(iv) By addition of an ethylenic bridge across the piperazine ring

Leads: Home Office.

Measure of outcome: The inclusion of the generic definition in the Misuse of Drugs Act 1971, following appropriate consultation in addition to Schedule 1 of the Misuse of Drugs Regulations 2001 and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015.

Recommendation 4: Information should be provided in an appropriate format to the general public, including people vulnerable to drug related harms (such as through Frank) and to harm reduction services on the potential harms that acyl piperazines, such as 2-methy-AP-237, might cause if they become available on the illicit drug markets in the UK. This should include information on the potential health effects.

Leads: UK Health Security Agency (UKHSA), Office for Health Improvement and Disparities (OHID), Public Health Wales, Public Health Scotland, the Department of Health Northern Ireland and the Association of the Directors of Public Health.

Measure of outcome: Readily accessible information is available for the general public, including people vulnerable to drug-related harms, their families and the wider public.

Recommendation 5: In the view of the highly dynamic synthetic opioids landscape in the UK and the associated risks they present, responsible agencies in the devolved administrations should monitor for the appearance of acyl piperazines and other emerging new synthetic opioids in the opioid market across the UK. Adequate resources should be provided to facilitate the analysis of seized materials or submitted drug samples thought to contain opioids, as well as the analysis of patient toxicology and postmortem samples. These data should be collected, collated, and monitored by the relevant public health agencies in the UK and reviewed in a consistent and methodical manner by the UK Government, for example the newly established Synthetic Opioid Taskforce and the Early Warning System. To encourage ongoing collection of data, information about compounds appearing in the UK should be fed back to coroners / procurators fiscal and toxicology laboratories with, where necessary, information about analytical methods and access to appropriate analytical standards.

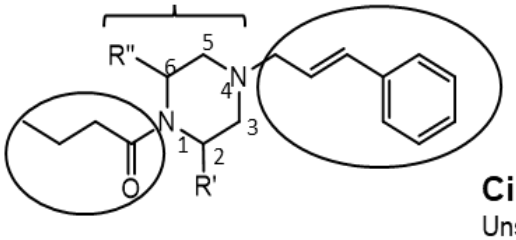
Leads: Office for Health Improvement and Disparities, Public Health Wales, Public Health Scotland, The Crown Office and Procurator Fiscal Service (COPFS), Public Health Agency Northern Ireland, National Crime Agency, Home Office, and the Ministry of Justice.

Measure of outcome: Information on substances used to augment the UK opioid market provided to the ACMD by Government (Synthetic Opioid Taskforce) and Home Office.

Annex A: Acyl Piperazine Chemistry

Acyl Piperazines Chemical Structure:

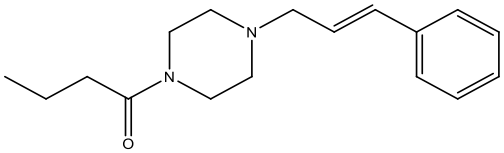
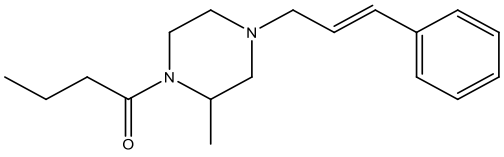
Piperazine core
Unsubstituted (R' and R" = H) and methyl substituted (R' =Me, R" = H or R', R" = Me) variants are known. R' and R" can be joined to form a bridge between position 2 and 6 (e.g. in Azaprocin).
The substitutions/bridge formation can also be at/between positions 3 and 5

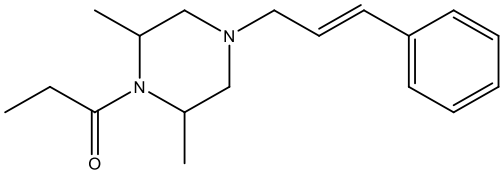
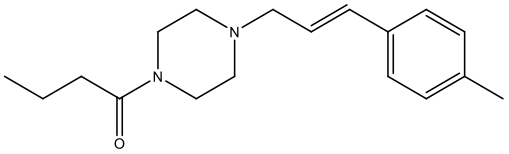
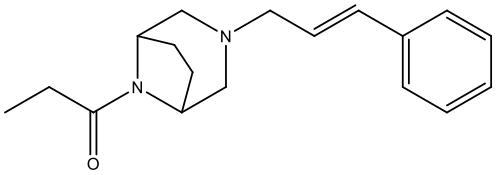
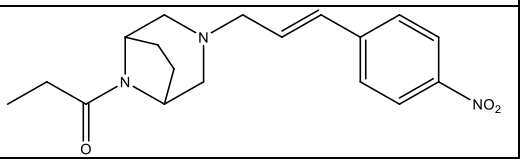


Acyl group
Acyl groups with 4 (as shown) or 3 carbons are preferred. Branching or further elongation of the acyl chain appears to reduce activity

Cinnamyl tail
Unsubstituted (as drawn) appears best for analgesic activity, though substitution with a nitro gives similar activity.
Reduction of the double bond in the tail results in lower activity.

Investigated Acyl Piperazines In The Report:

Name	Synonyms	Structure
AP-237	Bucinnazine BCP 1-{4-[(2E)-3-Phenyl-2-propen-1-yl]-1-piperazinyl}-1-butanone 1-(4-Cinnamylpiperazin-1-yl)butan-1-one 1-Butyryl-4-cinnamylpiperazine	
2-Methyl-AP-237	2-MAP 2-Methyl bucinnazine Methyl-BCP	

	1-{2-Methyl-4-[(2E)-3-phenyl-2-propen-1-yl]-1-piperazinyl}-1-butanone 1-(4-Cinnamyl-2-methylpiperazin-1-yl)butan-1-one	
AP-238	2,6-Dimethyl propionyl AP-237 1-{2,6-Dimethyl-4-[(2E)-3-phenyl-2-propen-1-yl]-1-piperazinyl}-1-propanone 1-(4-Cinnamyl-2,6-dimethylpiperazin-1-yl)propan-1-one	
para-Methyl-AP-237	para-Methyl bucinnazine 1-(4-[(2E)-3-(4-Methylphenyl)-2-propen-1-yl]-1-piperazinyl)-1-butanone 1-(4-(4'-Methyl)-cinnamylpiperazin-1-yl)butan-1-one	
Azaprocin	1-[3-[(E)-3-phenyl-2-propen-1-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]propan-1-one 1-(3-Cinnamyl-3,8-diazabicyclo[3.2.1]octan-8-yl)propan-1-one	
para-Nitroazaprocin	1-[3-[(E)-3-(4-nitrophenyl)- 2-propen-1-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]propan-1-one	

Annex B: Stakeholder Engagement and Data Request

Mortality and Chemical Analysis Data:

- Eurofins
- European-Wide, Monitoring, Analysis and Knowledge Dissemination on Novel/Emerging Psychoactive (EU-MADNESS)
- Forensic Science Northern Ireland (FSNI)
- LGC Standards
- National Programme on Substance Abuse Deaths (NPSAD)
- National Records of Scotland (NRS)
- NHS Grampian
- Northern Ireland Statistics and Research Agency (NISRA)
- Office for National Statistics (ONS)
- SCOOTEC
- Scottish Police Authority (SPA), Criminal Toxicology
- Scottish Police Authority (SPA), Post-Mortem Toxicology
- TICTAC
- Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS)
- Scitegrity Ltd.

Drug Seizure Data:

- Border Force
- Defence Science and Technology Laboratory (DSTL)
- Drugs Team at Public Health Scotland (PHS) (RADAR)
- Forensic Early Warning System (FEWS)
- Manchester Drug Analysis and Knowledge Exchange (MANDRAKE)
- National Crime Agency (NCA)
- Office for Health Improvement and Disparities (OHID)
- Scottish Police Authority (SPA), Drug Detections
- Scottish Prison Service

Drug Poisoning Data:

- Identification of Novel Psychoactive Substances (IONA) Study
- National Poisons Information Service (NPIS)

Legitimate Use:

- Medicines and Healthcare products Regulatory Agency (MHRA)

Annex C: List of Abbreviations Used in This Report

ACMD	Advisory Council on the Misuse of Drugs
CND	The United Nations Commission on Narcotic Drugs
CSFRE	Centre for Forensic Science Research and Education
DHS	Department of Homeland Security
DSTL	Defence Science and Technology Laboratory
ECDD	Expert Committee on Drug Dependence
EDND	European Database on New Drugs
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU-MADNESS	EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS
FEWS	Forensic Early Warning System
FSNI	Forensic Science Northern Ireland
IONA	Identification of Novel Psychoactive Substances
IUPAC	International Union of Pure and Applied Chemistry
MANDRAKE	Manchester Drug Analysis and Knowledge Exchange
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Crime Agency
NFLIS	National Forensic Laboratory Information System
NIHR	National Institute for Health Research
NISRA	Northern Ireland statistics and research agency
NPIS	National Poisons Information Service
NPS	Novel Psychoactive Substances
npSAD	National Programme on Substance Abuse Deaths
NRS	National Records of Scotland
NSO	New Synthetic Opioids
OHID	Office for Health Improvement and Disparities
ONS	Office for National Statistics
PSA	Psychoactive Substances Act 2016
SPA	Scottish Police Authority
UK	United Kingdom
UNODC	United Nations Office of Drugs and Crime

USA	United States of America
WEDINOS	Welsh Emerging Drug & Identification of Novel Substances
WHO	World Health Organization
WHO ECDD	World Health Organization’s Expert Committee on Drug Dependence

Annex D: Chair and Members of ACMD Acyl Piperazine Working Group

Chair of Working Group	
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Members of Working Group	
Dr Caroline Copeland*	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Professor Stephen Husbands*	Professor of Medicinal Chemistry, University of Bath
Professor Simon Thomas	NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble*	Retired Laboratory of the Government Chemist (LGC) expert

*denotes co-opted member of ACMD Novel Psychoactive Substances Committee

Acknowledgements:
In addition to members of the working group listed, significant contributions were made by the following individuals:

- **Dr Emanuele Alves**, Assistant Professor in Forensic Chemistry and Toxicology, Department of Forensic Science at Virginia Commonwealth University
- **Dr Chelsea Shover**, Assistant Professor-in-Residence at UCLA David Geffen School of Medicine

Annex E: ACMD Novel Psychoactive Substances (NPS) Committee Membership, At Time of Publication

Dr Kostas Agath	Consultant psychiatrist (addictions), Change Grow Live Southwark
Mr Paul Bunt**	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Mr Peter Cain**	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Caroline Copeland**	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Mr John Corkery**	Senior Lecturer in Pharmacy Practice at University of Hertfordshire; mortality and epidemiological lead for EU-MADNESS project
Mr Lawrence Gibbons	Head of Drug Threat – National Crime Agency Intelligence Directorate – Commodities
Dr Hilary Hamnett	Associate Professor in Forensic Science, University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Professor Stephen Husbands**	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice at the University of Nottingham
Professor Fiona Measham**	Professor and Chair in Criminology at the University of Liverpool; Co-Founder and Co-Director of the Loop
Mr Harry Shapiro	Director – DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary

Dr Ann Sullivan	Consultant Physician in HIV and sexual health, Chelsea and Westminster Hospital NHS Foundation Trust
Professor Simon Thomas	NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble**	Retired Laboratory of the Government Chemist (LGC) expert
Dr Derek Tracy	Medical Director of West London NHS Trust
Dr David Wood	Consultant Physician and Clinical Toxicologist, Guy's and St Thomas' NHS Foundation Trust and Reader in Clinical Toxicology at King's College London

**denotes co-opted member of ACMD Novel Psychoactive Substances Committee

Annex F: ACMD Membership, At Time of Publication

Dr Kostas Agath	Consultant Psychiatrist (addictions), Change Grow Live, Southwark
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Dr Anne Campbell	Reader in Substance Use and Mental Health, and Co-Director of the Drug and Alcohol Research Network at Queens University Belfast
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a Consultant Psychiatrist for South London and Maudsley NHS Trust
Mr Mohammed Fessal	Chief Pharmacist, Change Grow Live
Mr Lawrence Gibbons	Head of Drug Threat at the National Crime Agency Intelligence Directorate – Commodities
Dr Hilary Hamnett	Associate Professor in Forensic Science at the University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Dr Carole Hunter	Lead Pharmacist at the alcohol And Drug Recovery Services at NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice at the University of Nottingham
Mr Harry Shapiro	Director – DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Reader in Mood Disorders and Psychopharmacology, King's College, London

Dr Ann Sullivan	Consultant Physician in HIV and sexual health, Chelsea and Westminster Hospital NHS Foundation Trust
Professor David Taylor	Professor of Psychopharmacology, King's College, London and Director of Pharmacy and Pathology at the South London and Maudsley NHS Foundation Trust
Professor Simon Thomas	Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Medical Director of West London NHS Trust
Ms Rosalie Weetman	Public Health Lead (alcohol, drugs and tobacco), Derbyshire County Council - (currently on secondment to Office for Health Improvement and Disparities, as Programme Manager, Drug and Alcohol Improvement Support Team)
Dr David Wood	Consultant Physician and Clinical Toxicologist, Guy's and St Thomas' NHS Foundation Trust and Reader in Clinical Toxicology at King's College London

Annex G: Quality Of Evidence

Range of Evidence:
Evidence gathered was considered in line the ACMD's standard operating procedure (SOP) for quality of evidence [ACMD, 2020b].

Evidence relating to the identification and prevalence of acyl piperazines in Europe was taken from the EMCDDA's EDND. Each time a new drug is identified by a participating country in Europe, the EMCDDA produces a formal notification document, which details structural, chemical, and pharmacological information of the substance if available and then set up a page on the EDND. The database then records any further substance notifications in Europe or reporting of adverse effects.

To evidence the identification and prevalence of acyl piperazines in the UK, the ACMD's Novel Psychoactive Substances (NPS) Committee wrote to stakeholders requesting available data on the substances listed in Annex A.

The report also draws on evidence from peer-reviewed literature (UK and international publications) and government reports. The ACMD also considered international approaches when drafting its recommendations.

Quality Of Evidence (Design, Limitations, Bias):
Many agencies and departments returned 'no data held' for most of the acyl piperazines in this report.

It is important to note that owing to the 'novelty' of these substances, forensic testing is limited and inconsistent across the UK and as a result, information being fed into reporting agencies that were approached may underestimate actual use in the UK.

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