eppendorf

Reach Your 100%

Your success is our purpose

Your time is precious not only in terms of cost. However, a drug's journey from concept to patient takes years. You need to rely on products and services that ensure maximum efficiency at every step.

Our high-quality solutions are all engineered around the kind of functionality and intuitive performance necessary to speed up workflows, secure reproducibility, and accelerate the desired results.

Let's work together to make our world a better place.

www.eppendorf.com/pharma

Received: 12 April 2022 | Revised: 29 July 2022 | Accepted: 29 July 2022

DOI: 10.1002/dta.3351

SHORT COMMUNICATION

WILEY

Detection of AP-237 and synthetic cannabinoids on an infused letter sent to a German prisoner

Arianna Giorgetti[1,2] | Pietro Brunetti[2,3] | Susi Pelotti[1] | Volker Auwärter[2]

[1]Department of Medical and Surgical Sciences, Unit of Legal Medicine, University of Bologna, Bologna, Italy

[2]Institute of Forensic Medicine, Forensic Toxicology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany

[3]Unit of Forensic Toxicology, Section of Legal Medicine, Department of Excellence of Biomedical Sciences and Public Health, Marche Polytechnic University, Ancona, Italy

Correspondence
Giorgetti A, Department of Medical and Surgical Sciences, Unit of Legal Medicine, University of Bologna, Via Irnerio 49, 40126 Bologna, Italy.
Email: ari.giorgetti@gmail.com; arianna.giorgetti@unibo.it

Funding information
The authors declare no funding.

Abstract

In the past years, new psychoactive substances (NPS) started circulating in prisons, leading to health risks and challenges for the criminal justice system. Seizures of papers and cards impregnated with synthetic cannabinoid (SCs) have been reported. In November 2021, a letter suspected to be drug-infused was sent from a German prison to this laboratory. Toxicological analyses were performed by means of gas chromatography–mass spectrometry (GC–MS) for drug screening and liquid chromatography–tandem mass spectrometry (LC–MS/MS) as well as high-performance (HP) LC with diode-array detection (DAD) for semi-quantification of the compounds. The novel synthetic opioid (NSO) AP-237 was detected on the letter, with an estimated concentration of 1.2 μg/cm^2, together with the SCs MDMB-4en-PINACA (77 μg/cm^2) and 5F-ADB (6.5 μg/cm^2). To the best of the authors' knowledge, this is the first time an NSO was detected on a drug-infused paper seized in a prison. Highly potent NSOs could easily be dissolved in organic solvents to produce impregnated papers and textiles, and this might represent a serious threat to the health of people in prison. Given the inhomogeneity in drug concentrations, health risks might in particular arise from the consumption of highly concentrated areas of the paper—so-called "hot spots"—especially when highly potent NSOs are used for infusion. Laboratories engaged in analyzing such impregnated papers should be aware of the potential presence of NSOs and adapt the respective methods accordingly.

KEYWORDS
drug-infused paper, forensic toxicology, novel synthetic opioids, prison

1 | INTRODUCTION

New psychoactive substances (NPS) make up a wide group of drugs which are not listed in the 1961 and 1971 United Nations Conventions on narcotic drugs and psychotropic substances.[1] They mimic the effect of classical illicit drugs, but are often characterized by higher potency and unknown toxicity, thus posing a serious threat to public health.[2]

So far, more than 830 substances are monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and synthetic cannabinoids (SCs), first detected in herbal plant material in 2008, account for the largest subclass, with 209 compounds monitored by the end of 2020. Novel synthetic opioids (NSOs) represent another subclass of NPS smaller by number (67 so far reported), but of particular concern given the high risk for fatal intoxication.[2,3] In 2020, 10 new NSOs were detected on the NPS market, with seizures

mostly consisting of powders, liquids, tablets, capsules, or, more rarely, smoking mixtures.[3]

In recent years, the use of NPS has started circulating in prisons among other vulnerable populations (e.g., homeless people with long drug careers or young and inexperienced drug users), exacerbating health risks and violence connected to drug misuse in custodial settings.[4] The use of NPS in prisons has been accompanied by a rise of aggressive behavior, violence, bullying, and debts, causing serious safety problems in prisons.[5] NPS are often cheaper than other drugs and may not be detected by routine drug screening methods, being attractive to prisoners who might want to avoid positive drug testing results. Only small amounts of the drugs are needed due to their high potency, and it is almost impossible to train drug tracking dogs to detect them, both facilitating smuggling these substances beyond prison walls.[2,4,6] Moreover, the market for NPS is highly dynamic, so that an additional challenge for screening methods is the need to frequently update databases.

Among NPS, the presence of SCs, colloquially referred to as "Spice," in prisons has increased to such an extent that they were described as "endemic" in England and Wales.[7–9] Seizures mostly included herbal blends sprayed or soaked with SCs (64% of submitted samples), powders, and liquids for e-cigarettes. More recently, in order to facilitate the entry of SCs into prisons and to escape the routine drug screening programs, papers and cards were found to be impregnated with liquids consisting of SCs dissolved in organic solvents like acetone or ethanol, dried, and then sent to prisoners via mail.[6–8,10,11]

Among 354 papers seized in three Scottish prisons, 41% contained at least one SC, with high detection rates for 5F-MDMB-PICA (IUPAC name: methyl 2-{[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl] amino}-3,3-dimethylbutanoate), 4F-MDMB-BINACA (IUPAC name: methyl 2-{[1-(4-fluorobutyl)-1*H*-indazole-3-carbonyl]amino}-3,-3-dimethylbutanoate), and 5F-MDMB-PINACA, also called 5F-ADB (IUPAC name: methyl 2-{[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl] amino}-3,3-dimethylbutanoate).[7] In the separately published studies, among 98 and 392 samples collected in Scotland, 46–64% contained SCs, and it was shown that drug-infused cards/papers seized in prisons mostly reflected the evolution of the SCs market outside of prison.[8,11] Similar results were obtained in a transnational study comprising samples from Germany, the United Kingdom (Scotland and Wales), and the United States.[12]

In November 2021, a letter suspected to be drug-infused was sent to this laboratory in Freiburg from a German prison for toxicological analysis. To the best of the authors' knowledge, this is the first detection of a NSO in combination with SCs in a drug-infused paper coming from a prison.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

The reference standards (RSs) (MDMB-4en-PINACA, 5F-ADB, AP-237 and carfentanil) and the internal standards (IS) (*O*-desmethyltramadol-D_6, pentobarbital-D_5, MDMA-D_5, codeine-D_3, diazepam-D_5) were purchased from Cayman Chemical (Ann Arbor, MI, USA). Ammonium formate solution 10-M solution was purchased from Sigma Aldrich (Steinheim, Germany) and formic acid (Rotipuran® ≥ 98%, p.a.) from Carl Roth (Karlsruhe, Germany). Acetonitrile (HiPerSolvCHROMANORM®) was purchased from VWR Chemicals (Darmstadt, Germany) and methanol (Chromasolv™ LC–MS grade) from Honeywell (Seelze, Germany). Deionized water was freshly prepared using a cartridge deionizer from Memtech (Moorenweis, Germany). Phosphate buffer (13.6 g/l potassium dihydrogenphosphate in deionized water, pH adjusted to 6) was freshly prepared prior to use. Mobile phase A consisted of an aqueous solution of 0.1% formic acid, 2 mM ammonium formate, and 1% acetonitrile. Mobile phase B consisted of 2 mM ammonium formate, 0.1% formic acid in acetonitrile.

2.2 | Toxicological screening of the letter

After careful documentation, the letter and the envelope were cut into pieces of approximately 5 cm^2 each to facilitate handling. All pieces were placed in a single glass vial, and 9 ml of methanol were added. The sample was then extracted by soaking with methanol and gentle mixing for 10 min. The recovered volumes of solvent were measured, then to 50 µl of the resulting extracts 10 µl of internal standards mix (containing pentobarbital-D_5, MDMA-D_5, codeine-D_3, diazepam-D_5) were added; afterwards, 1 µl was injected into the gas chromatography–mass spectrometry (GC–MS) system and screened for drugs in full-scan mode. A 7890A gas chromatograph coupled to a 5975C mass spectrometer from Agilent Technologies, Santa Clara, CA, USA, was used. Data evaluation was carried out using MSD ChemStation D.03.00.611 (Agilent Technologies, Santa Clara, CA, USA). In brief, 1 µl sample was injected using a 25:1 split ratio, injection port temperature was 250°C, and carrier gas flow (He) was 1 ml/min. Column: HP-5MS, 0.25 µm, 0.25 mm × 30 m from Agilent Technologies, Santa Clara, CA, USA. GC oven: 100°C held for 3 min; 30°C/min to 310°C held for 10 min; transfer line: 280°C. The mass spectrometer was operated in electron ionization (EI) mode. Ionization conditions: 70 eV (50–600 Da), ion source: 230°C, quadrupole: 150°C. Analytes in the paper sample extracts were identified by comparison of the obtained spectra to Wiley/NIST (Wiley registry® 11th edition, 2017), MPW (Wiley-VCH, 5th edition, 2016), Cayman Chemical (version 21.05.2020) spectra libraries, and to an in-house library of previously identified SCs. For a positive identification, a library hit of >90% and a critical review by an experienced toxicologist was required. In addition, retention times and ion ratios (for LC–MS/MS) were checked for consistency. No semi-quantification was attempted by GC–MS.

To check the sensitivity on papers impregnated with low doses of highly potent opioids, 1 cm^2 of a blank paper was impregnated with carfentanil (final concentration 1 µg/cm^2), extracted with 0.25 ml methanol and analyzed under the same GC–MS conditions.

2.3 | Methods for semi-quantification

The extraction procedure described above was repeated four times, using 9 ml of methanol each and measuring the recovered solvent volumes (3.1–3.8 ml). Each extract was analyzed separately, and the final concentration was obtained by summing up individual concentrations determined for each extract. The letter and the envelope were left to complete dry in between extractions. Semi-quantification was achieved by LC–MS/MS for AP-237 (see Supporting Information) and by high-performance liquid chromatography (HPLC) with diode-array detection (DAD) for SCs.

For NSO analysis, a previously validated LC–MS/MS method for serum analysis, accredited under ISO/IEC 17,025 for forensic purposes, was used.[13] To reach concentrations in the calibrated range and to avoid matrix effects from coextracted substances, paper extracts were diluted 1:100 with methanol, and a volume of 10 µl was then spiked into 100 µl of blank serum before sample work-up and LC–MS/MS analysis. Retention times, target ion transitions, IS, and limits of detection (LOD) and quantification (LOQ) of the analyte of interest are shown in Table 1.

For SCs, extracts were analyzed by HPLC-DAD,[14] after a 1:1, 1:100, or 1:1000 dilution in methanol. The HPLC-DAD system was a Nexera XR HPLC system (Shimadzu, Duisburg, Germany) consisting of an LC-20AD XR Liquid Chromatograph Pump, a DGU-20A3R degassing unit, a WPS-3000TRS autosampler, a CTO-10AS column oven, and a SPD-M20A diode array detector. Chromatographic separation was performed on a Kinetex® 2.6 µm C18 100 Å, 100 × 2.1 mm^2 (Phenomenex Ltd., Aschaffenburg, Germany) and a corresponding guard-column. A flow rate of 0.5 ml/min and the following gradient elution was applied: starting with 20% of solvent B, held for 1 min, increased to 60% within 1.5 min and to 65% within another 1.5 min, held for 1.5 min; increased to 90% within 2.5 min, and held for 2 min. The initial conditions were then restored within 0.1 min and held for 1.9 min to re-equilibrate the system. The autosampler and column oven temperature were set to 6 and 40°C, respectively. DAD-UV spectra were recorded from 200 to 400 nm, and the chromatogram (detection wavelength 207 nm) was used for semi-quantification. First, 10 µg/ml of 5F-ADB and MDMB-4en-PINACA were injected to exclude co-elution. Then, a 3-point calibration curve (0.5, 5 and 10 µg/ml) was prepared for both analytes on two different days. Injection volume was 10 µl. Full details on the analytical methods can be found as Supporting Information.

3 | RESULTS AND DISCUSSION

The letter consisted of an A4 (21.0 × 29.7 cm, 623.7 cm^2) handwritten paper, which was sent to this laboratory in Freiburg in an

TABLE 1 Retention time (RT), monitored ion transitions (Q1, Q3) corresponding internal standard (IS), limit of detection (LOD) and quantification (LOQ) of the analyte of interest with the LC–MS/MS method validated for serum

Analyte	RT (min)	Q1 (*m/z*)	Q3 (*m/z*)	IS	LOD (ng/ml)	LOQ (ng/ml)
AP-237	10.1	273.2	117.0	D_6-O-Desmethyltramadol	0.3	1
			155.2			
			91.1			

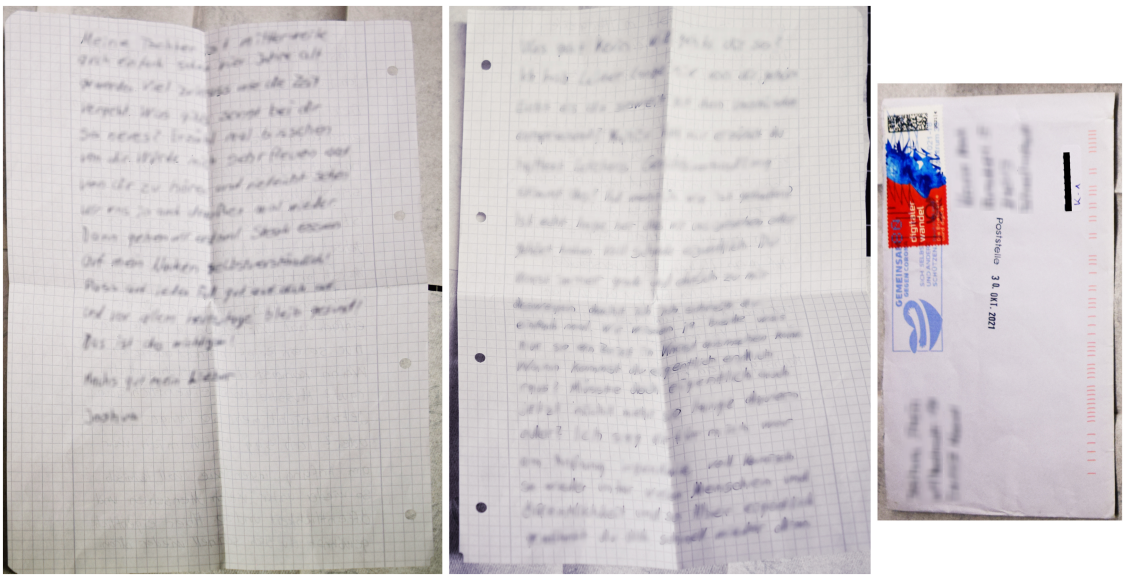

FIGURE 1 Letter and envelope received from a German prison. Handwriting has been blurred to maintain anonymity [Colour figure can be viewed at wileyonlinelibrary.com]

envelope (16.0 × 11.0 cm, 352 cm^2) inside a plastic bag (Figure 1), and contained no visible staining. The GC–MS analysis allowed the detection of MDMB-4en-PINACA (97% match to the library entry), 5F ADB (97% match to the library entry), and AP-237 (99% match to the library entry)[15,16] (Figure 2). Two additional cannabinoids, 5F-MDMB-P7AICA and ADB-4en-PINACA, were detected by GC–MS but not confirmed by further analyses, probably due to relatively low amounts being present. The sensitivity of the GC–MS screening method proved to be sufficient to detect carfentanil in an infused paper with a final concentration of 1 μg/cm^2 (Supporting Information).

The LC–MS/MS method used for semi-quantification of AP-237 revealed a concentration of 1.2 μg/cm^2 on the letter. Concentrations, as estimated from LC–MS/MS and HPLC-DAD analysis, for both letter and envelope are shown in Table 2.

AP-237 (IUPAC name: 1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone), also known as bucinnazine, is a synthetic opioid originally developed as an analgesic drug, still used for the treatment of cancer pain in China, and is not scheduled in Germany, Italy, or the United States.[16–18] The compound recently re-emerged on the market, likely in response to the Chinese inclusion of all fentanyl-related drugs within the list of controlled narcotics,[19] leading to a shift towards more varied chemical structures of synthetic opioids. The scientific knowledge regarding bucinnazine and its effects in humans is still very limited.[17,20–22] AP-237 was classified as an NSO due to its potential for abuse, and even though its analgesic effect is thought to be approximately 1/3 compared to morphine, it seems to be one of the more potent piperazine type opioids.[15,18] The efficacy (EC_{50}) at the μ opioid receptor was estimated in vitro in the range of 3 × 10^4 to 8 × 10^3 nM, but results remained ambiguous.[20]

To the best of the authors' knowledge, the detection of an NSO in combination with SCs on drug-infused paper has never been reported before and represents a matter of concern. NSOs could be easily dissolved in solvents to produce impregnated papers and textiles,[4] which might represent a simple method of smuggling NSOs into prisons. Once smuggled into the prison, impregnated paper (like letters, greeting cards, photographs, drawings, printouts from catalogues or puzzles[2]) are likely consumed by smoking in a cigarette or by vaping with e-cigarettes.[7] In this case, it is likely that the letter, regardless of the infused substances, would have also been consumed in this way, even though other routes of administration are

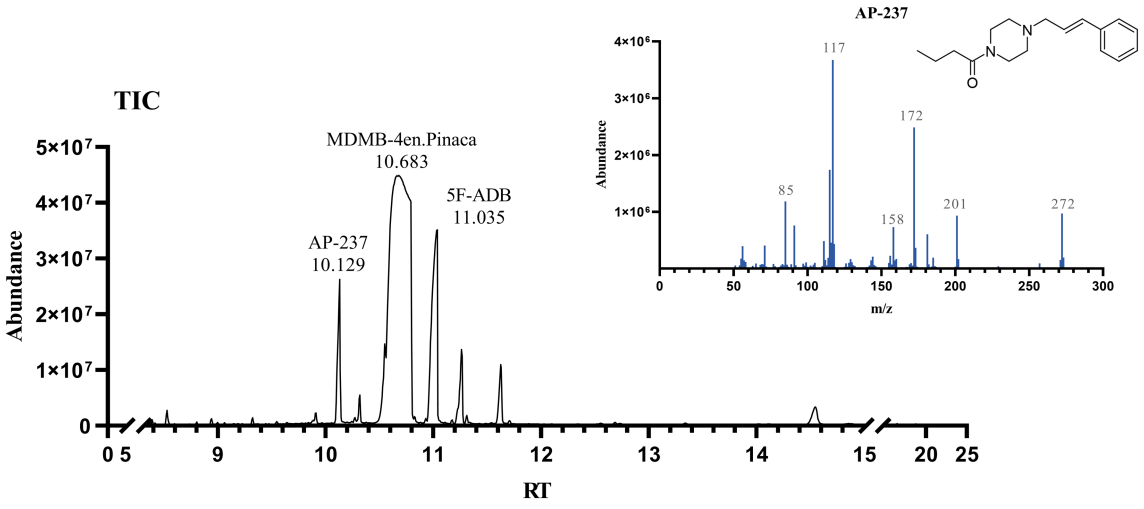

FIGURE 2 GC–MS total ion chromatogram (TIC) obtained from letter extract (lower left corner) and the mass spectrum of AP-237 (right upper corner) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Peak areas of the analytes of interest from GC–MS analysis (only used for screening) and concentrations as estimated by LC–MS/MS and HPLC-DAD analysis

	Letter			Envelope	
Analyte	Concentrations estimated by LC–MS/MS or HPLC-DAD	Concentration in relation to MDMB-4en-PINACA	Estimated total mg	Concentration estimated by LC–MS/MS or HPLC-DAD	Relative concentration envelope/letter
AP-237	1.2 μg/cm^2[a]	1.6%	0.75 mg	0.08 μg/cm^2[a]	6.7%
MDMB-4en-PINACA	77 μg/cm^2[b]	100%	48 mg	1.7 μg/cm^2[b]	2.2%
5F-ADB	6.5 μg/cm^2[b]	8.4%	4.1 mg	0.12 μg/cm^2[b]	1.8%

[a]LC–MS/MS.
[b]HPLC-DAD.

conceivable. Beside the perceived legal status of NSOs and the easy smuggling into prisons, the technical difficulties of detecting impregnated papers seems to be one of the main drivers for using these drugs in prison,[4] and a spreading of opioid-infused papers in this setting might evolve.

In addition to AP-237, MDMB-4en-PINACA (IUPAC name: methyl 2-{[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino}-3,-3-dimethylbutanoate) and 5F-ADB were detected. These are highly potent SCs, which have been commonly detected on infused papers and cards from prisons in concentrations ranging from 0.05 to 1.17 mg/cm^2. The amount of MDMB-4en-PINACA estimated on the letter investigated in the present study was consistent with the range of values reported in the literature (<0.07–0.58 mg/cm^2),[7] although not being in the upper range. The concentrations of 5F-ADB and AP-237 were relatively low, accounting for 8.4% and 1.6% of the main compound (MDMB-4en-PINACA). Although the concentrations here reported should be taken only as rough approximations and a precise quantification was beyond the scope of our analysis, 5F-ADB and AP-237 might be regarded as unintentionally applied impurities, although this cannot be deducted from the available results. However, the hypothesis of impurities appears likely with respect to the relative potencies of the compounds, on the basis of which an effective dose of AP-237 can be expected above 10 mg,[20,22] whereas the cannabinoids are believed to produce strong effects from doses as low as 2–4 mg for JWH-018,[23,24] and probably less than 1 mg for more potent compounds like MDMB-4en-PINACA. Moreover, due to the preparation methods for papers illicitly infused with SCs, the drug concentrations might vary widely from one area to another,[4,7] so that it is possible that the compounds here detected were more concentrated in some areas. In the present study, as a further limitation, concentrations were not mapped across the A4 paper. Nevertheless, the literature data suggest that the inhomogeneous distribution of drug concentrations across the paper might increase the risks for overdoses, should users unexpectedly consume paper areas characterized by higher SC concentrations, so-called "hot-spots."[4,7] This possibility could be of particular concern when papers contain a combination of SCs and NSOs, as detected in the present case. However, whether this applied to the paper matrices investigated here remains unknown.

The health risks arising from NPS use derive both from the poly-drug abuse pattern, that is often encountered in SCs users[25] and in NPS consuming people in prison, as well as from the non-uniformity of doses.[7] Concomitant use of NSOs and SCs may exhibit variable severities of intoxication. In a case series, the most common clinical symptoms of opioid and SC co-exposure were marked by a typical initial opioid toxidrome, consisting of central nervous system (CNS) and respiratory depression. In some cases, hallucinations and adrenergic stimulation with severe tachycardia appeared after treatment with naloxone.[26–28] Since both SCs and NSOs can exert a depressant effect on the CNS, their combination might lead to a synergistic toxicity. Just recently, in April 2022, two samples of paper sent from a German prison and submitted to a GC–MS toxicological screening to this laboratory tested positive for buprenorphine. This is a confirmation of the potential spreading of papers impregnated with opioids in prisons.

4 | CONCLUSIONS

Although in the presented case the opioid AP-237 might be regarded as an impurity not intentionally added (although this remains ultimately unknown), other NSOs with higher potencies would pose a serious threat to people in prison. In the present study, the GC–MS analysis was able to detect concentrations of carfentanil as they could be expected in impregnated paper intended for misuse. Still, it has to be noted that the detection of highly potent compounds might not (always) be achieved by applying standard GC–MS procedures due to the low concentrations expected.

ACKNOWLEDGEMENTS

Open Access Funding provided by Universita degli Studi di Bologna within the CRUI-CARE Agreement.

CONFLICT OF INTEREST

Nothing to disclose.

ETHICS STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data are openly available in a public repository that issues datasets with DOIs.

ORCID

Arianna Giorgetti https://orcid.org/0000-0002-0441-9787
Pietro Brunetti https://orcid.org/0000-0001-5271-7773
Volker Auwärter https://orcid.org/0000-0002-1883-2804

REFERENCES

1. United Nations Office on Drugs and Crime (UNODC). UNODC Early Warning Advisory (EWA) on New Psychoactive Substances (NPS). Published 2020. https://www.unodc.org/LSS/Home/NPS. Accessed April 11, 2022.
2. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). New psychoactive substances: global markets, glocal threats and the COVID 19 pandemic: an update from the EU early warning system. Publications Office; 2020. https://data.europa.eu/doi/10.2810/921262. Accessed April 11, 2022.
3. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European drug report 2021: trends and developments. Publications Office; 2021. https://data.europa.eu/doi/10.2810/18539. Accessed April 11, 2022.
4. European Monitoring Centre for Drugs and Drug Addiction. Publications Office; 2018. https://data.europa.eu/doi/10.2810/7247. Accessed April 11, 2022.
5. HM Prison and Probation Service. Prison drugs strategy. Published online 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/792125/prison-drugs-strategy.pdf. Accessed April 11, 2022.

6. Ford LT, Berg JD. Analytical evidence to show letters impregnated with novel psychoactive substances are a means of getting drugs to inmates within the UK prison service. *Ann Clin Biochem*. 2018;55(6):673-678. doi:10.1177/0004563218767462
7. Norman C, Walker G, McKirdy B, et al. Detection and quantitation of synthetic cannabinoid receptor agonists in infused papers from prisons in a constantly evolving illicit market. *Drug Test Anal*. 2020;12(4):538-554. doi:10.1002/dta.2767
8. Antonides LH, Cannaert A, Norman C, et al. Shape matters: the application of activity-based in vitro bioassays and chiral profiling to the pharmacological evaluation of synthetic cannabinoid receptor agonists in drug-infused papers seized in prisons. *Drug Test Anal*. 2021;13(3):628-643. doi:10.1002/dta.2965
9. Ralphs R, Williams L, Askew R, Norton A. Adding spice to the porridge: the development of a synthetic cannabinoid market in an English prison. *Int J Drug Policy*. 2017;40:57-69. doi:10.1016/j.drugpo.2016.10.003
10. Kronstrand R, Norman C, Vikingsson S, et al. The metabolism of the synthetic cannabinoids ADB-BUTINACA and ADB-4en-PINACA and their detection in forensic toxicology casework and infused papers seized in prisons. *Drug Test Anal*. 2020;14(4):634-652. doi:10.1002/dta.3203
11. Norman C, McKirdy B, Walker G, Dugard P, NicDaéid N, McKenzie C. Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons. *Drug Test Anal*. 2021;13(3):644-663. doi:10.1002/dta.2945
12. Norman C, Halter S, Haschimi B, et al. A transnational perspective on the evolution of the synthetic cannabinoid receptor agonists market: comparing prison and general populations. *Drug Test Anal*. 2021;13(4):841-852. doi:10.1002/dta.3002
13. Müller D, Neurath H, Neukamm MA, et al. New synthetic opioid cyclopropylfentanyl together with other novel synthetic opioids in respiratory insufficient comatose patients detected by toxicological analysis. *Clin Toxicol (Phila)*. 2019;57(9):806-812. doi:10.1080/15563650.2018.1554187
14. Halter D, Mogler L, Auwärter V. Quantification of herbal mixtures containing Cumyl-PEGACLONE - is inhomogeneity still an issue? *J Anal Toxicol*. 2020;44(1):81-85. doi:10.1093/jat/bkz028
15. NMS Lab. Ap-237 report. Published online 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/09/AP-237_091619_NMSLabs_Report.pdf. Accessed April 11, 2022.
16. National Forensic Laboratory (NFL), Slovenia. Analytical report. AP-237. Published online 2019. https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/AP-237-ID-2048-19_report.pdf. Accessed April 11, 2022.
17. Carrano RA, Kimura KK, McCurdy DH. Analgesic and tolerance studies with AP-237, a new analgesic. *Arch Int Pharmacodyn Ther*. 1975;213(1):41-57.
18. UNODC. Global Smart update. The growing complexity of the opioid crisis. Published online 2020. https://www.unodc.org/documents/scientific/Global_SMART-2020-Vol_24_web.pdf. Accessed April 11, 2022.
19. Bao Y, Meng S, Shi J, Lu L. Control of fentanyl-related substances in China. *Lancet Psychiatry*. 2019;6(7):e15. doi:10.1016/S2215-0366(19)30218-4
20. Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. *Arch Toxicol*. 2020;94(11):3819-3830. doi:10.1007/s00204-020-02855-7
21. Resnik K, Brandão P, Alves EA. DARK classics in chemical neuroscience: bucinnazine. *ACS Chem Nerosci*. 2021;12(19):3527-3534. doi:10.1021/acschemneuro.1c00522
22. Fogarty MF, Vandeputte MM, Krotulski AJ, et al. Toxicological and pharmacological characterization of novel cinnamylpiperazine synthetic opioids in humans and in vitro including 2-methyl AP-237 and AP-238. *Arch Toxicol*. 2022;96(6):1701-1710. doi:10.1007/s00204-022-03257-7
23. Teske J, Weller JP, Fieguth A, Rothämel T, Schulz Y, Tröger HD. Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH-018) in human serum by liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2010;878(27):2659-2663. doi:10.1016/j.jchromb.2010.03.016
24. Theunissen EL, Hutten NRPW, Mason NL, et al. Neurocognition and subjective experience following acute doses of the synthetic cannabinoid JWH-018: a phase 1, placebo-controlled, pilot study. *Br J Pharmacol*. 2018;175(1):18-28. doi:10.1111/bph.14066
25. Joseph A, Lekas HM, Manseau M, Lewis C. A polydrug and psychosocial profile of synthetic cannabinoid use in a New York city community sample, 2016-2017. *Subst Use Misuse*. 2019;54(2):282-287. doi:10.1080/10826084.2018.1517178
26. Ershad M, Dela Cruz M, Mostafa A, Khalid MM, Arnold R, Hamilton R. Heroin adulterated with the novel synthetic cannabinoid, 5F-MDMB-PINACA: a case series. *Clin Pract Cases Emerg Med*. 2020;4(2):121-125. doi:10.5811/cpcem.2020.2.45060
27. Maguire DR, France CP. Interactions between opioids and cannabinoids: economic demand for opioid/cannabinoid mixtures. *Drug Alcohol Depend*. 2020;212:108043. doi:10.1016/j.drugalcdep.2020.108043
28. Alon MH, Saint-Fleur MO. Synthetic cannabinoid induced acute respiratory depression: case series and literature review. *Respir Med Case Rep*. 2017;22:137-141. doi:10.1016/j.rmcr.2017.07.011

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Giorgetti A, Brunetti P, Pelotti S, Auwärter V. Detection of AP-237 and synthetic cannabinoids on an infused letter sent to a German prisoner. *Drug Test Anal*. 2022;14(10):1779-1784. doi:10.1002/dta.3351