Alert Regarding 2-Methyl AP-237– June 11, 2021

The US Drug Enforcement Administration (DEA) in collaboration with the University of California San Francisco Clinical Toxicology and Environmental Biomonitoring (CTEB) Laboratory has identified an opioid substance, 2-methyl AP-237 in whole blood samples submitted to our New Psychoactive Substances (NPS) surveillance program1.

**Cohort:** Whole blood samples were recently submitted from an overdose death case in Kansas City, Kansas (January 2021) and a non-fatal overdose case in Omaha, NE (March 2021).

**Drugs Detected:** In the overdose death case (Kansas), 2-methyl AP-237 (141 ng/mL) was confirmed in addition to etizolam (4.5 ng/mL). In the non-fatal overdose case (Nebraska), 2-methyl AP-237 (208 ng/mL) was confirmed in addition to carboxy-THC, cocaine and its metabolites, and methadone and its metabolites.

**2-Methyl AP-237:** Originally patented in 19852, 2-methyl AP-237 is a methyl derivative of the opioid analgesic, bucinnazine (AP-237), a therapeutic drug used as a pain medication in cancer patients in China. Structurally distinct from fentanyl analogues, 2-methyl AP-237 was first identified in Slovenia in 2019 and has since been sold as a designer drug and research chemical.3

**Analysis:** 2-Methyl AP-237 was detected, confirmed and quantified in whole blood samples using liquid chromatography-quadrupole time-of-flight mass spectrometry. Details of the method used along with the chromatogram and mass spectra associated with the compound are presented in the attached supporting documents.

**Reference Standard:** The reference standard for 2-methyl AP-237 is commercially available.

**National Forensic Laboratory Information System (NFLIS)4:** Twenty-seven exhibits submitted to NFLIS confirmed the presence of 2-methyl AP-237 (2019: CA (1), PA (1), SC (2), TN (17); 2020: IA (1), PA (1), TN (2); 2021: FL (2)).

**Additional Cases:** 2-Methyl AP-237 was identified in capsules by the Regional Operations & Intelligence Center (ROIC), Office of Drug Monitoring & Analysis in New Jersey in December 2020. As relayed by the San Diego Medical Examiner’s Office, 2-methyl AP-237 (1,000 ng/mL) was confirmed in a fatal overdose in January 2021. Additional substances confirmed in this case included etizolam, mitragynine, citalopram, and quetiapine.

**Pharmacological Data:** While limited information on 2-methyl AP-237 is available, data demonstrate that it has opioid-like activity5.

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1 This report was prepared by Roy Gerona, Ross Ellison, and Jordan Trecki.
4 NFLIS is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by Federal, State, and local forensic laboratories in the United States. (Query date: 05/27/21)
2-Methyl AP-237

I General Information

Synonyms: 2-methyl Bucinnazine

IUPAC Name: 1-[2-methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one

InChI String: InChI=1S/C18H26N2O/c1-3-8-18(21)20-14-13-19(15-16(20)2)12-7-11-17-9-5-4-6-10-17/h4-7,9-11,16H,3,8,12-15H2,1-2H3/b11-7+

InChI Key: CRSFXYZFNAFVFC-YRNVUSSQA-N

SMILES: CCCCC(O)N1CCN(CC1C)CC=CC2=CC=CC=C2

CAS Number: 98608-61-8

CFR: Not Scheduled

II Physical Properties

Solubility: DMF: 10 mg/mL
DMSO: 15 mg/mL
Ethanol: 30 mg/mL
PBS (pH7.2): 10 mg/mL

III Chemical Characterization

GC-MS: The GC-MS spectrum for 2-methyl AP-237 is available at Cayman Chemical- https://www.caymanchem.com/gcms/26485-0597855-GCMS.pdf

IV LC-QTOF/MS Analysis

Instrument: Agilent 1260 Infinity, Agilent 6550 QTOF-MS/MS

Sample Preparation: Protein precipitation with 95:5 Acetonitrile:Methanol plus zinc acetate followed by phospholipid removal using the Phree column

Chromatography

Column: Phenomenex Kinetex Biphenyl (100 mm x 3.0 mm, 2.6 µm)
Column Temperature: 50 °C
Injection Volume: 10 µL
Mobile Phase: A: Ammonium formate (5 mM) and Formic Acid (12.6 mM) in H2O
B: Formic Acid (12.6mM) in acetonitrile
Flow rate: 0.8 mL/min (0-2 min); 0.7 mL/min (2-9 min)
Elution Profile: Gradient- 100A initially; gradient 70A:30B from 0.5 to 2.0 min; gradient 20A:80B from 2.0 to 6.5 min; 20A:80B, 6.5-8.0 min; 100B from 8.01 to 9.0 min

6 www.caymanchem.com/product/26485
**Run Time:** 11 min

**Mass Spectrometry**

*Ion Source:* Dual Jet Stream Electrospray Ionization  
*Polarity:* Positive  
*TOF MS Scan Range:* 75-1000 Da  
*MS/MS Scan Range:* 50-510 Da  
*Gas Temperature:* 225 °C  
*Drying Gas Flow Rate:* 14L/min  
*Sheath Gas Temperature:* 350 °C  
*Sheath Gas Flow Rate:* 11L/min  
*Nebulizer pressure:* 14psi  
*Capillary Voltage:* 3000 V  
*Nozzle Voltage:* 500 V  
*Skimmer Voltage:* 65 V  
*Octopole RF:* 750 V  
*Fragmentor Voltage:* 380 V  
*Internal Reference Masses:* Purine at m/z 121.0509; HP-921 at m/z 922.0098  
*Data Acquisition:* 2GHz, extended dynamic range  
*Fragmentation:* Auto MS/MS, three maximum precursors (threshold: 500 counts) per cycle with active exclusion after 1 spectrum at a 30s release time

**Extracted Ion Chromatogram**

*Retention Time:* 4.547 min
**TOF-MS Spectrum**

*Exact Mass:* 286.2045 amu

*Accurate Mass:* \([M+H]^+ = 287.2122\) (mass error=-1.73 ppm)

**MS/MS Spectrum**
In response to the ongoing synthetic drug epidemic, the Drug Enforcement Administration (DEA) has initiated a contract with the University of California at San Francisco (UCSF) whereby biological samples generated from overdose victims of synthetic drugs can be further analyzed. In many cases, it can be difficult to ascertain the specific substance responsible for the overdose. In the future, we invite you to contact our program if you encounter an overdose of a suspected synthetic drug and desire to have any leftover biological samples (blood preferred) analyzed further for such synthetic substances.

- **Sample Qualifications:**
  - Patients thought to have ingested a synthetic drug, where the traditional drug screen has produced little or no viable options to explain the symptoms exhibited by the patient (alcohol and THC are exempted).

- **How to Contact Us and Send Your Samples:**
  - Once the above qualifications are satisfied:
    - Email DEATOX@USDOJ.GOV with a brief description of the case (including initial toxicology screen and history) and a request for testing.
    - DEA will respond to each inquiry, and if approved, will send the instructions for packing and shipping of sample(s) to UCSF.
      - The main reason for disapproval of a case would be the identification of substances including methamphetamine, heroin, fentanyl, cocaine, LSD, PCP etc. in a routine toxicology screening at your facility.
      - This program’s goal is to connect symptom causation to abuse of newly emerging synthetic drugs (i.e. synthetic cannabinoids, synthetic cathinones, fentanyl-related substances, other hallucinogens etc.).
    - Ensure that you de-identify and label the sample with a numerical value, sex, date of birth or age, and the date and time the sample was collected in accordance with the labeling instructions (sent with shipping instructions).
    - Keep a master list of the patients and the numerical values you allocated to each sample at your institution.

- **Cost of sample analysis:**
  - The DEA will cover the full cost of testing the patient samples.
  - The sender will only be responsible for paying for packing and shipping samples to UCSF.

- **Turn-around Time:**
  - Results are expected within three weeks of receipt of the sample at UCSF except in rare occurrences when a novel substance is identified.