

Case Report of a Death Involving Designer Opioid MT-45 Raises the Spectre of Synthetic Opioids in Forensic Casework

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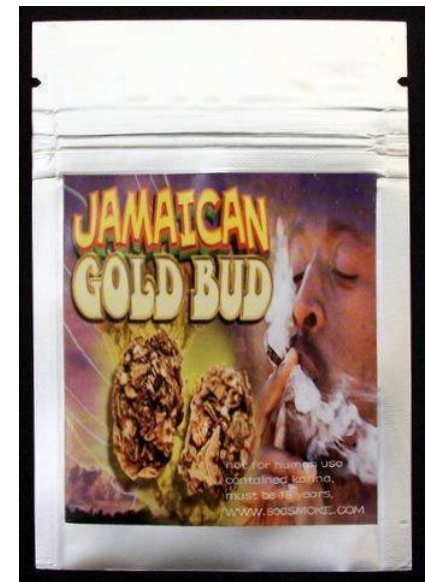
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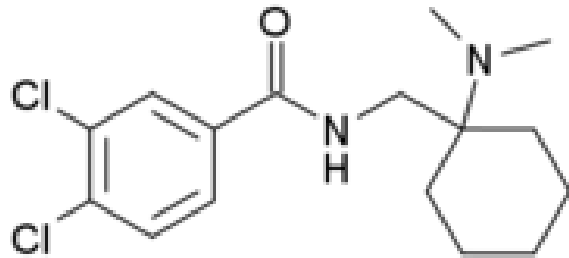
⁵The Center for Forensic Science Research and Education (CFSRE), 2300 Welsh Rd, Willow Grove PA

NPS Movement

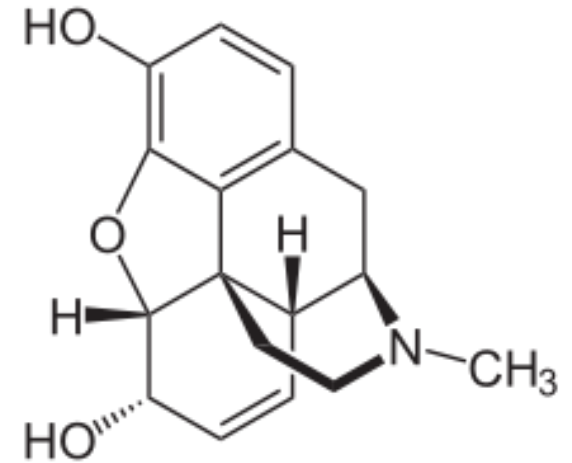
- NPS: Novel Psychoactive Substances
- Started in late 2000s
- Primarily started with synthetic cannabinoids and cathinones
 - Ex. JWH-073, AM-2201, XLR-11
 - Ex. Methylone, MDPV, Alpha PVP
- Market has expanded to include designer benzodiazepines and opioids



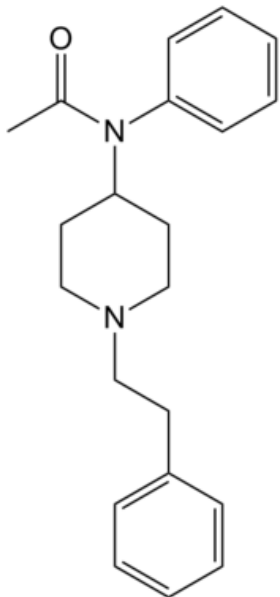
Designer Opioids vs. Morphine



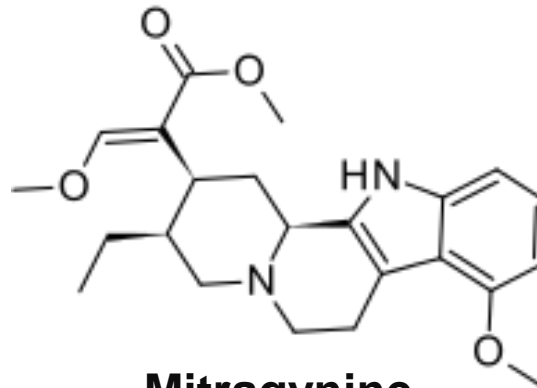
AH-7921



Morphine



Acetyl Fentanyl



Mitragynine

Designer Opioids

- **AH-7921**

- Vorce S, Knittel J, Holler JM et al. A fatality involving AH-7921. *Journal of Analytical Toxicology*. 2014; 38:22-230

- **Acetyl fentanyl**

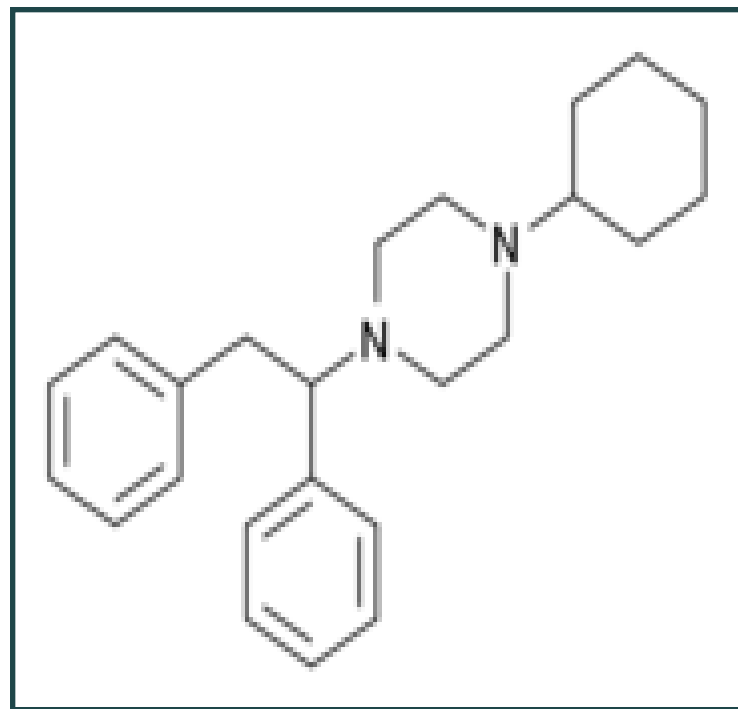
- MMWR Morb Mortal Wkly Rep. Acetyl Fentanyl overdose fatalities—Rhode Island, March-May 2013. 2013 Aug 30; 62(34):703-704

- **MT-45**

- Uchiyama N, Matsuda S, et al. Identification of two new-type designer drugs, piperazine derivative MT-45 and synthetic cannabinoid A-834735, cathinone derivative 4-methoxy alpha-PVP, and phenethylamine derivative 4-methylbuphedrone from illegal products. *Forensic Toxicology*. January 2014; 32(1): 9-18

MT-45

- 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, I-C6
- Invented in 1970s by Dainippon Pharmaceutical Co
- Shared analgesic and CNS depressant properties similar to that of morphine
- Not controlled in the United States



Formula: $C_{24}H_{32}N_2$

Mol. Mass: 348.523 g/mol

Recreational abuse of MT-45

- Typically sold as dihydrochloride salt
- Oral, intranasal, or IV routes of administration
- Doses vary between 15 - 75 mg
- Sometimes found mixed with other substances



The image shows the cover of a joint report. At the top left is the logo of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), which features a blue square with a white arch and stars. To the right of the logo is the text "European Monitoring Centre for Drugs and Drug Addiction". In the top right corner, the words "JOINT REPORTS" are written in orange. The title "MT-45" is prominently displayed in the center in a large, bold, black font, preceded by a vertical orange bar. Below the title, the text reads: "EMCDDA–Europol Joint Report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine ('MT-45')". At the bottom, it states: "In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances".

European Monitoring Centre
for Drugs and Drug Addiction

JOINT REPORTS

MT-45

EMCDDA–Europol Joint Report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine ('MT-45')

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

Adverse side effects (n=7)

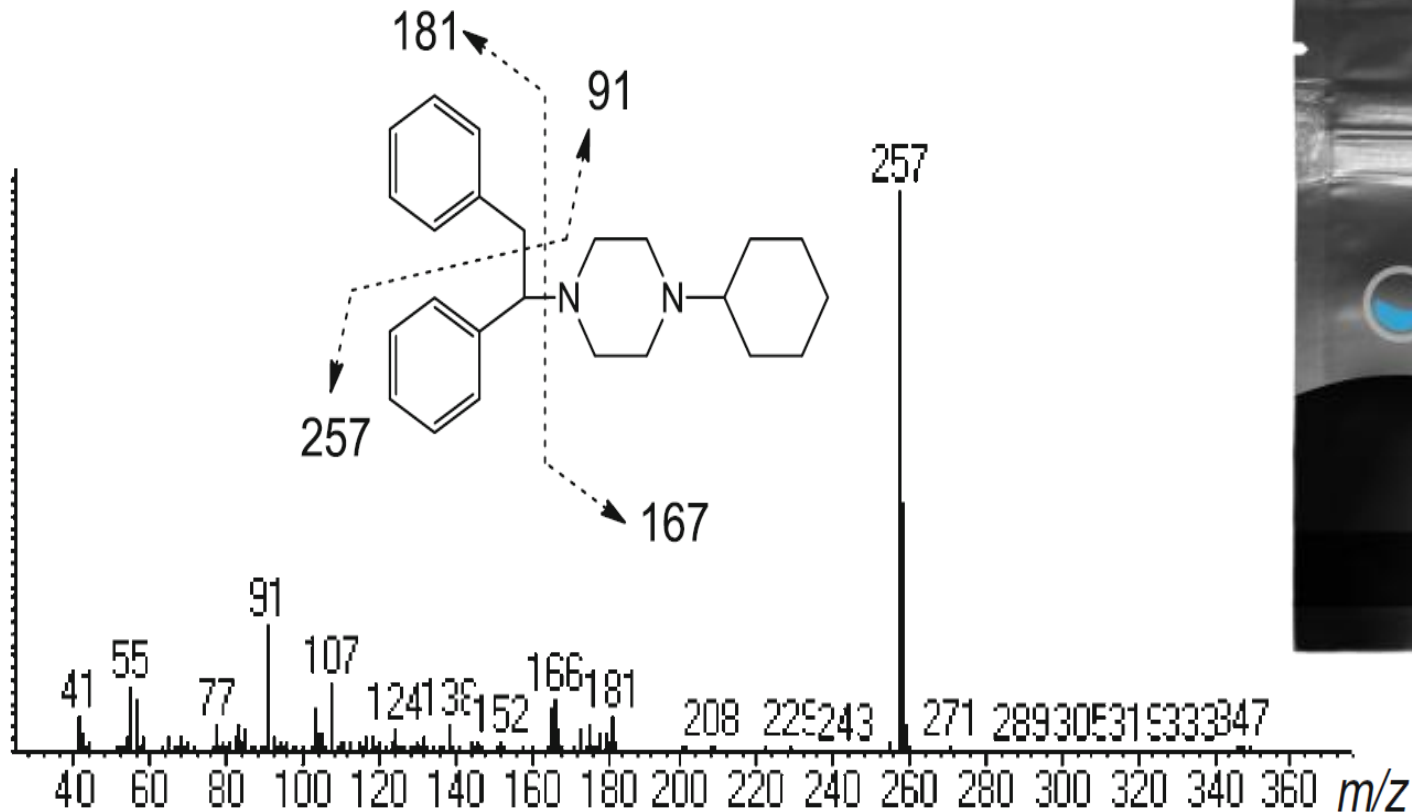
- Somnolence
- Unconsciousness
- Tachycardia
- Decreased respiratory rate
- Hypoxia
- Cyanosis
- Hypotension
- Hypokalemia
- Vomiting



Case Series of MT-45 Hospitalizations

- Patients admitted to hospitals in Sweden from Nov 2013 - Feb 2014 for NPS use
- All patients male, 17-32 y/o
- 9 cases with toxicology testing
 - MT-45 only (n=4): 6 -157 ng/mL in blood
 - MT-45 + other (n=5): 19 - 102 ng/mL in blood
- 3 patients complained of bilateral hearing loss

MT-45 Mass Spectrum



Uchiyama N, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y Identification of two new-type designer drugs, piperazine derivative MT-45 (I-C6) and synthetic peptide Noopept (GVS-111), with synthetic cannabinoid A-834735, cathinone derivative 4-methoxy- α -PVP, and phenethylamine derivative 4-methylbuphedrine from illegal products. *Forensic Toxicology*, January 2014, 32(1):9-18

Case Report

- 35 year old male found deceased by his roommate
- Known history of drug use
- Found collapsed next to the couch
- Scale, spoon, lighter, and two packets of white powder found nearby
- One bag tested positive for MT-45; the other tested positive for Etizolam

Case Report

- One pink punctate mark on dorsum of right foot (possible injection site)
- Cerebral edema and lung congestion
- Specimens collected for toxicology: Femoral and heart blood, urine, vitreous
- Microscopic examination of major organs was performed
- No anatomical cause of death; toxicology requested

Toxicology

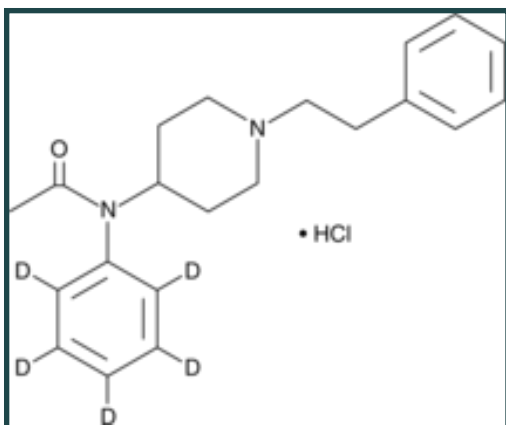
- Routine toxicology performed first with few positive findings
- After identification of materials as MT-45 and etizolam, targeted analyses were developed and samples analyzed
 - Extraction
 - Method parameters
 - Quantitative results
 - Standard addition

LC-MS/MS Analysis

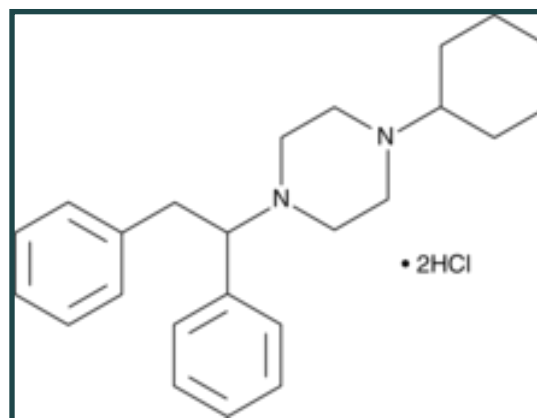
- Liquid-liquid extraction using NH_4OH and n-butyl chloride/acetonitrile (4:1, v/v)
- ISTD = acetyl fentanyl - d5
- Positive electrospray, MRM
- BEH C18, 2.1 x 5.0 mm column for separation
- Mobile phases of 0.1% formic acid in methanol and 0.1% formic acid in diH_2O

Analyte Characteristics

Analyte	Quant Ion	Qual Ion	RT (min)
Acetyl Fentanyl d5	328.3 > 105.1	328.3 > 188.1	1.72
MT-45	349.3 > 181.1	349.3 > 169.2	2.26



Acetyl Fentanyl d5



MT-45

MT-45 Calibration Curve

Compound name: MT-45 Quant

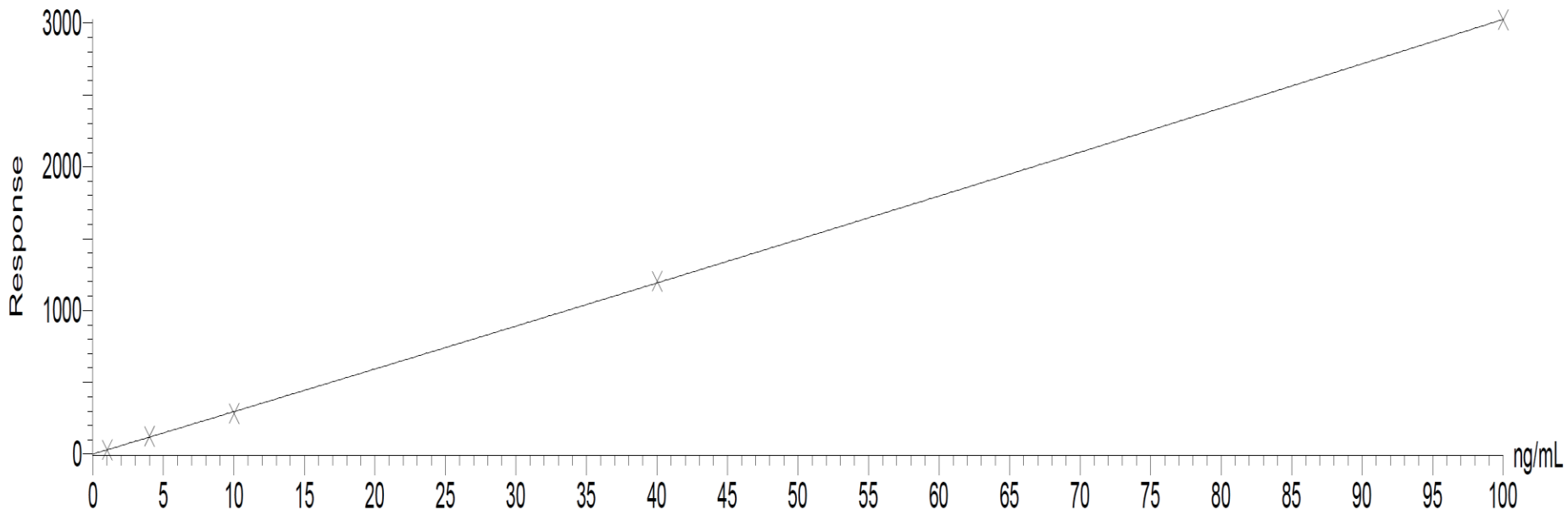
Coefficient of Determination: $R^2 = 0.999795$

Calibration curve: $0.00804825 * x^2 + 29.456 * x + 0.768522$

Response type: Internal Std (Ref 1), Area * (IS Conc. / IS Area)

Curve type: 2nd Order, Origin: Exclude, Weighting: 1/x, Axis trans: None

- **Calibration curve handspikes of 1.0-100 ng/mL**
- **Run in triplicate**
 - **Slope = 0.999**
 - **Bias = 0.05%**



Precision & Accuracy (n=15)

Level	Concentration (ng/mL)	Precision (%CV)		Accuracy (%Difference)	
		Between Run	Total	Between Run	Total
Reporting Limit	1	4.5	8.1	5	5
Low QC	3	5.2	6.9	2	2
Mid QC	30	3.6	4.3	16.7	16.7
High QC	80	3.8	6	3.8	3.8

Toxicology Results

- NMS Expanded Postmortem Toxicology Panel was positive for Diphenhydramine (220 ng/mL) in femoral blood
- Urine presumptively positive for cannabinoids and benzodiazepines
- Targeted analyses in femoral blood
 - MT-45: 520 ng/mL
 - Etizolam: 35 ng/mL

Case Report

- Neither drug is prescribed in the U.S.
 - Etizolam – a benzodiazepine derivative with hypnotic and sedative properties
 - Prescribed in certain Asian and European countries
- Investigation found that decedent had purchased both drugs online from a Canadian company, and had been doing so monthly for some time
- Cause of death – combined toxicity of MT-45 and Etizolam
- Manner of death – accidental

Interpretation of Results

- Etizolam concentration of 35 ng/mL consistent with therapeutic levels

Fracasso C, Confalonieri S, Garattini S, Caccia S. Single and multiple dose pharmacokinetics of Etizolam in healthy subjects. *Eur J Clin Pharmacol.* 1991; 40:181-185.

- MT-45 linked to adverse events and fatalities in Sweden
 - From 21 reported fatalities; 6-1900 ng/g
 - In 6 PM cases attributed to MT-45 intoxication; 200-1900 ng/g



Discussion

- Opiates/opioids are frequently encountered in toxic deaths
- Designer opioids, like MT-45, are starting to hit the market; intoxications by these compounds may look like other opiates/opioids
- MT-45 currently not included in most routine forensic drug screening panels
- MT-45 commonly found in combination with other drugs

Disclaimer

- Work completed on behalf of the Center for Forensic Science Research and Education



Questions?