

Day 2



OAS | CICAD



# DRUG MONITORING IN THE AMERICAS PROJECT

## Emerging Drugs, Synthetic Opioids, and Early Warning Systems

### Webinar

November 6-7, 2023

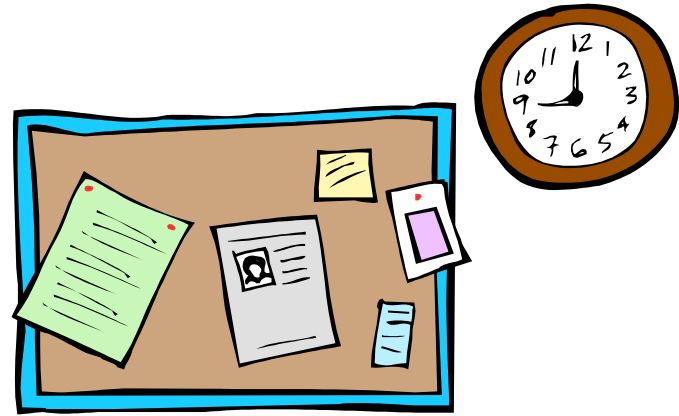
Panelist: Dr. Antonio Pascale, Medical Toxicologist

Organized by: Inter-American Observatory on Drugs (Spanish acronym, OID)

Inter-American Drug Abuse Control Commission (Spanish acronym, CICAD)

# Presentation (day 2)

- Synthetic opioids (part two)
- Fentanyl and its analogues
- Other synthetic opioids
- Early-warning system



# Fentanyl analogues and other synthetic opioids

- 4-fluoroisobutyryl fentanyl
- furanylfentanyl
- acrylfentanyl
- acetylfentanyl
- carfentanyl
- 3-methylfentanyl
- ocfentanyl
- buttrilfentanyl
- beta hydroxythiofentanyl
- **benzylmidazoles:** isotonitazene, etonitazene, etazene, protonitazene.
- U-47700
- Limitations in the analysis for their detection

# Epidemiology and mortality related to opioid use

- In 2020 more than 100,000 overdoses were reported in the US, and about 76,000 were attributed to opioids (39% increase over 2019).
- In Canada, the increase that year stood at 67%, more than 6,200 deaths (*The Lancet*, 2022).

In 2022, the DEA seized more than 59.6 million fentanyl-adulterated pills and nearly 6 kg of fentanyl powder in the U.S. Equal to 395.7 million lethal doses of fentanyl.

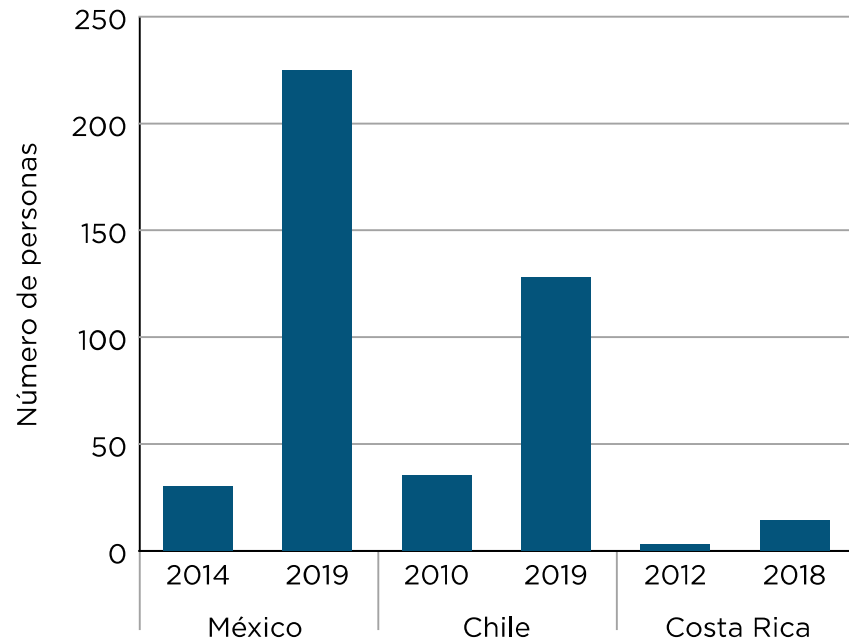
In 2023, more than 287 million lethal doses.

**Table 2. Nitazene opioids identified in 73 samples checked in Toronto, October 10, 2019 – August 31, 2021\***

	Drug name	Estimated strength compared to fentanyl	First identified	Found in how many samples
1	<b>Isotonitazene/Protonitazene</b>	Up to 5x stronger	February 12, 2021	30
2	<b>Etonitazene</b>	10x stronger	May 5, 2021	3
3	<b>Metonitazene</b>	Similar strength	May 31, 2021	38
4	<b>Etodesnitazene</b>	Similar strength	June 24, 2021	2
5	<b>Etonitazepyne</b>	10x stronger	July 13, 2021	5

Source: [www.drugchecking.cdpe.org](http://www.drugchecking.cdpe.org)

*Figure 26: Number of people seeking treatment for non-medical use of opioid drugs in Chile, Costa Rica and Mexico, 2010 to 2019*



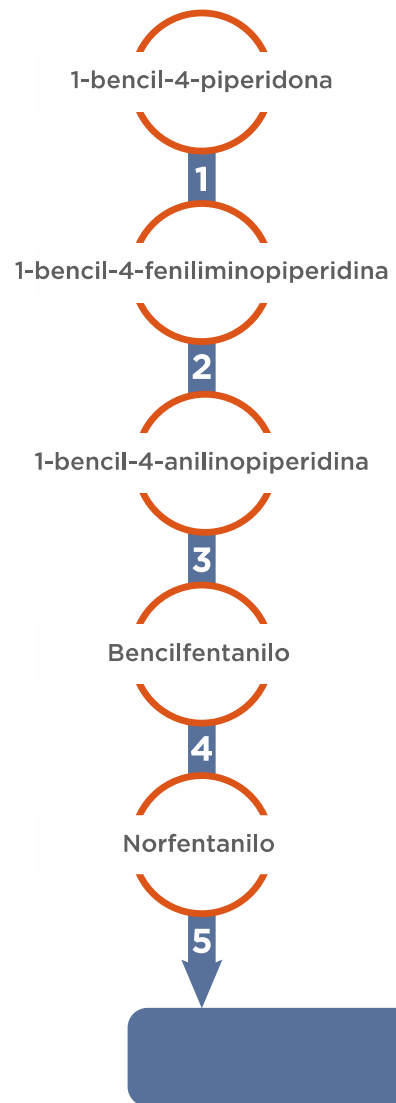
*Fuente:* UNODC, respuestas al cuestionario para los informes anuales.

- Analysis of 89 heroin samples from 3 injection sites (Tijuana, Mexico).
- 93% contained fentanyl (Fleis et al., 2020).

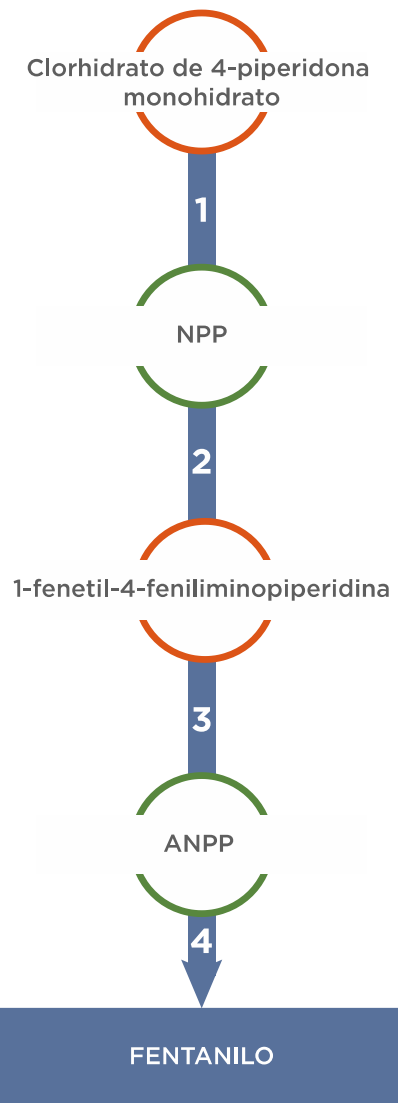
*Source: UNODC Global Smart Programme, 2021*

Figure 27: Selected methods for the synthesis of fentanyl

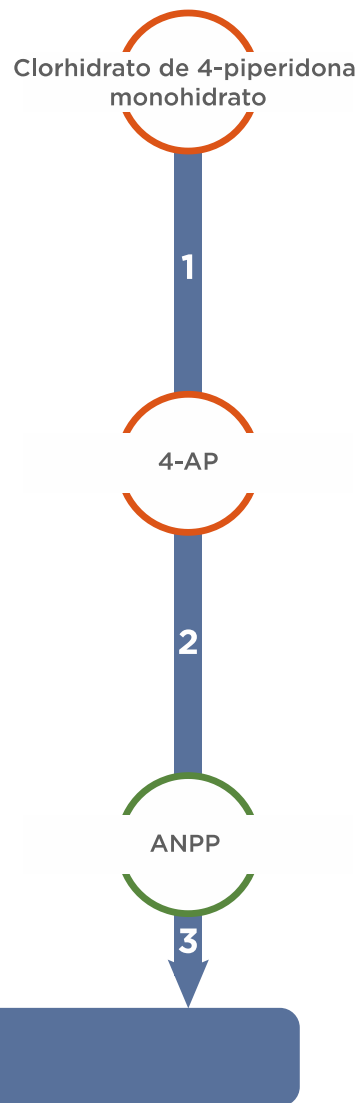
Método "Janssen"



Método "Siegfried"



Gupta et al. (2009)

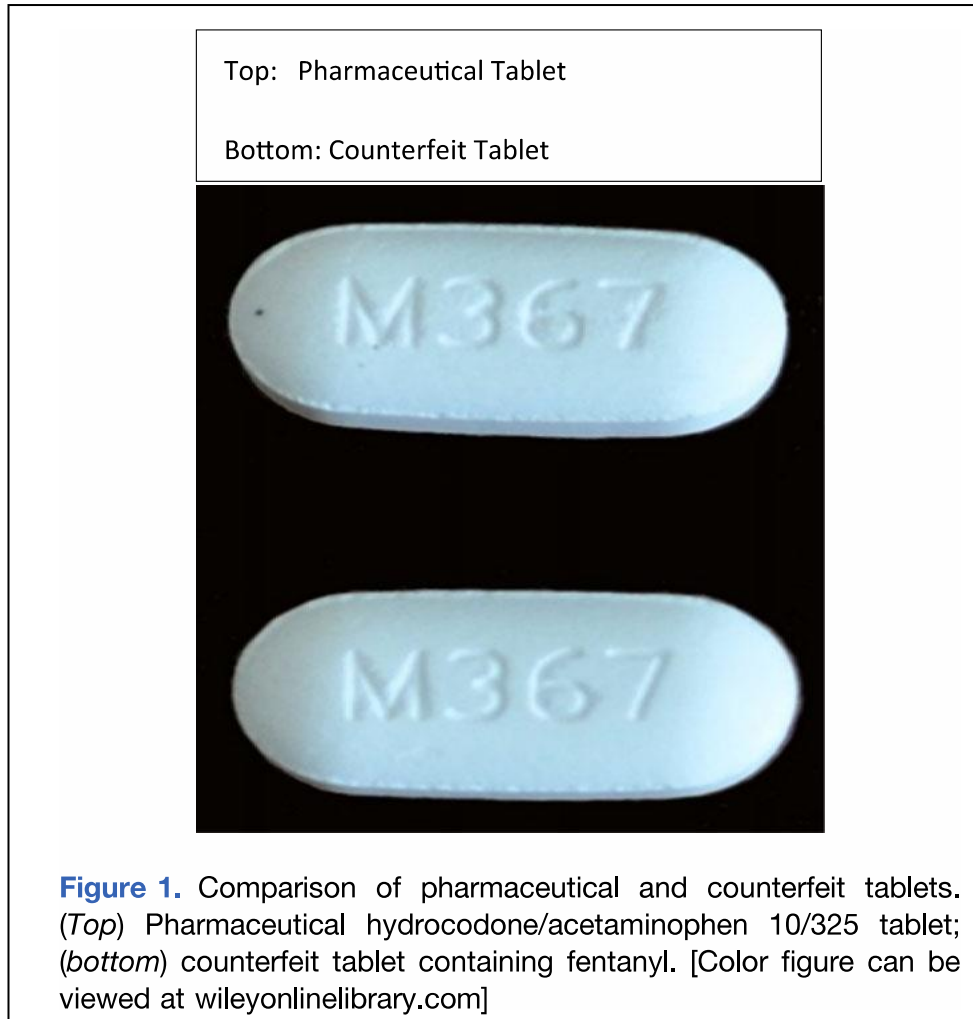


# Fentanyl and derivatives

- Fentanyl: opioid used as an analgesic anesthetic.
- Euphoriant effect: non-medical use by drug users, particularly users of heroin or other opiates, and the development of an illicit market for the sale of fentanyl and its derivatives.
- Heroin adulterants (Carroll et al., 2017).
- Association with heroin (speedballing).
- Opioid drug adulterants or substitutes (oxycodone, hydrocodone, alprazolam) purchased on the illicit market (CDC, 2016).
- Adulterants of other drugs (cocaine, LSD)



# Fatal Fentanyl: One Pill Can Kill

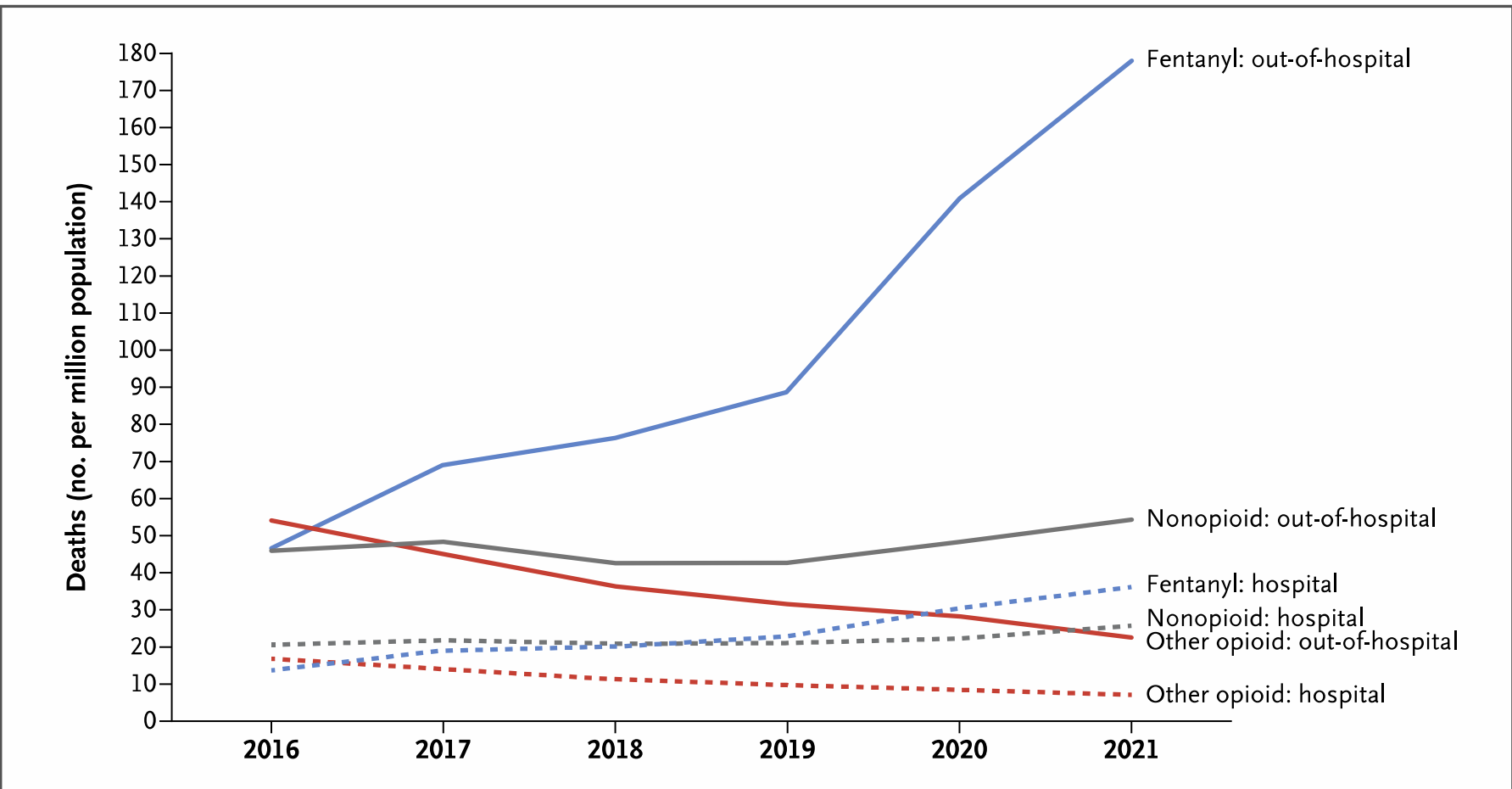


# Acute toxicity - Fentanyl and derivatives

- Fentanyl is 50 to 100 times more potent than morphine and 30 to 50 times more potent than heroin.
- Carfentanyl is 10,000 times more potent than morphine (Misailidi et al., 2018).
- Fentanyl and its analogues can appear as powders, tablets, capsules, liquids or stamps.
- Overdoses with high mortality.
- High requirements of naloxone (antidote).

# Acute intoxication by opioids

- CNS depression → COMA
- Myosis
- Respiratory depression
  
- Bradycardia and hypotension
- Decreased gastrointestinal motility
  
- Acute pulmonary edema (heroin)
- Seizures (meperidine, tramadol)
  
- Severe symptoms (respiratory failure, aspiration pneumonia, shock)
  
- ANTIDOTE treatment with naloxone (i.v., intranasal).



**Figure 1. Trends in Drug-Overdose Deaths, According to Location and Drug Type.**

Shown are the number of deaths from drug overdoses per 1 million U.S. population from 2016 through 2021, a period that encompassed the years immediately before and after the start of the Covid-19 pandemic.

Table 4. Cont.

Series/Case	U-Compound	Case Type	Brief History	Clinical Symptoms/Autopsy Findings	Drug Results (ng/mL unless Specified)	Reference
6.1	U-47700	PM	A 28 y/o M was found deceased at home with dried froth on his mouth and nose. Several plastic baggies labeled as "U-47700", "etizolam", "butyrylfentanyl" and "4-2CO-MET" were found in the room with other drug paraphernalia.	Pulmonary edema, hypertensive-type cardiomegaly, and chronic active hepatitis with steatosis.	Femoral Blood: U-47700 189, oxycodone 67, dextro/levomethorphan 17	[94]
6.2	U-47700	PM	An 18 y/o M was found deceased on his bedroom floor. He had bloody fluid emanating from his nose. Baggies labeled as "U-47700" and "etizolam" were found at the scene with other drug paraphernalia.	Pulmonary edema, cerebral edema, asthma, and focal subgaleal hemorrhage consistent with a terminal fall.	Femoral Blood: U-47700 547, etizolam	[94]
7.1	U-47700	PM	34 y/o M with history of illicit drug use, as well as depression and bipolar disorder, found unresponsive in a bathroom. Drug paraphernalia, including needles and an empty plastic bag labeled "3-FPM", were located near the decedent.	Pulmonary edema and congestion.	Femoral blood: U-47700 360, 3-fluorophenmetrazine 2400, amitriptyline 440, nortriptyline 290 methamphetamine < 40, amphetamine 70, diazepam 200, nordiazepam 180, temazepam 11, flubromazolam, delorazepam	[95]
8.1	U-47700	PM	51 y/o M was found unresponsive in a hotel bathroom. Paraphernalia was found on scene: a spoon, white powder and a syringe.	Brain swelling (1570 g), lung hyperhydration (right lung 905 g and left lung 665 g) and hyperemia of the inner organs (heart 375 g, spleen 185 g, liver 1635 g, right kidney 145 g, left kidney 210 g). Injections site were observed on the right and white crumbs in the gastric contents.	Femoral Blood: U-47700 290, oxycodone 50, noroxycodone 40 Heart Blood: U-47700 1290 Liver: U-47700 9.9 ug/g Urine: U-47700 240 Gastric Contents: U-47700 570 Bile Fluid: U-47700 2300 Cerebrospinal fluid: U-47700 400 Hair: U-47700 0.14 ng/mg	[96]

# Early-warning system

- Multidisciplinary network formed in an interinstitutional way and by key actors that generates and exchanges information for the:
  - Early identification of events that could pose a threat to public health in the area of NPS or emerging drug phenomena.
  - Assessment of risks related to their use.
  - Issuance of rapid alerts for the design of effective responses.

# Toxicovigilance - Early Warning Systems

- Detection: suspicion or knowledge of an NPS or emerging substance.
- Characterization: laboratory identification, study of consumption patterns, health effects.
- Risk assessment: how to disseminate the information?
- Production of alerts.

# Early Warning System Components

- Toxicological databases (by substance or presentation)
- Records of analytical studies
- Case reports





## I) Sellos "Bicycle day"

- Fecha del reporte: 21/7/2017
- Institución: ITF
- Sustancia principal detectada: Fentanilo
- Otras sustancias: no reportadas
- Concentración: s/d

## SUSTANCIA DETECTADA: FENTANILO

- Opiáceo sintético.
- Utilizado por la industria farmacéutica para analgesia, sedación y anestesia.
- Tanto el compuesto original como análogos sintéticos de alta toxicidad se utilizan con fines de abuso.
- Es adulterante de heroína, cocaína y sellos de LSD.
- Forma de consumo: vía oral, transdérmica, y/o por mucosa oral o conjuntival (sellos), vía intravenosa.
- **Sobredosis:** confusión, depresión de conciencia que evoluciona al coma, miosis (constricción de pupilas), depresión respiratoria. Náuseas y vómitos. Bradicardia e hipotensión arterial. Edema pulmonar. Cuadro de alta mortalidad.
- Intoxicación aguda/sobredosis posee antídoto: **NALOXONA.**
- No se detecta con tests de screening de orina habituales.

*Database, May 2018,  
Early Warning System, OUD.*

# SAT Drogas (Uruguay) - NPS Database

- Information based on presentations and substances found.
- Sources: Seizures analyzed by the Forensic Technical Institute and the School of Chemistry.
- Clinical case reports from the Toxicology Center.

<b>Presentations</b>	<b>Substances found</b>
<b>Tablets (ecstasy, pills)</b>	MDMA, methylcathinone, LSD, 2 C-B, MDA, clobenzorex, ethylpentylone.
<b>Crystals, powder</b>	MDMA, ketamine, cocaine, caffeine, tramadol, heroin, DOC.
<b>Stamps</b>	LSD, fentanyl, NBOMe, DOC, DOB, DOI, 2 C-B, 2 C-E, MDMA, ketamine

## Other substances detected in urine of electronic music party attendees (Uruguay, 2016-2019)

- ASRC: JWH-248, JWH-208 (GC/MS)
- ASRC: UR-144/XLR-11, UR-144, XLR-11, A-834735 (ELISA)
- Synthetic cathinones: mephedrone, methedrone, methylone, butphedrone, 4-fluoromethcathinone, 3-fluoromethcathinone, methcathinone (ELISA)
- Fentanyl (ELISA)

# Some public alerts (SAT-LOUD-JND) in Uruguay

- Cocaine adulterated with Levamisole (2016)
- ITF analysis of 575 "LSD stamps" in May 2017
  - Drug detected: fentanyl
- Public health intervention:
  - ✓ public alert
  - ✓ Toxicovigilance (Toxicology Center)
  - ✓ Availability of naloxone at all medical services (including first-level care).
- Public alert in December 2021 (Uruguay)

Tablets, powders and stamps containing various substances (predominantly synthetic drugs, sometimes associated with "classic" drugs).



*LOUD, 2017*

# Final thoughts

- The emergence of NSP means gaps in knowledge about the drugs being consumed and their composition.
- Hospitals must have trained personnel, the necessary material resources, and rapid means of communicating with local laboratories for the identification of adulterants.
- Synthetic opioids are highly addictive substances and their use involves very high mortality rates (potency/acute toxicity, dose).
- Addressing this public health problem effectively involves strengthening networks involving government agencies (e.g. early warning systems), clinical and forensic laboratories, non-governmental organizations with access to users, and universities and toxicology centers.

GRACIAS



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